THE DEVELOPMENT, CHARACTERIZATION AND EVALUATION OF A NOVEL MULTI-UNIT ERODING MATRIX SYSTEM FOR POORLY SOLUBLE DRUGS

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THE DEVELOPMENT, CHARACTERIZATION AND EVALUATION OF A
NOVEL MULTI-UNIT ERODING MATRIX SYSTEM FOR POORLY SOLUBLE
DRUGS

BY

KETAN ARVIND MEHTA

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
PHARMACEUTICS

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DOCTOR OF PHILOSOPHY DISSERTATION

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KETAN ARVIND MEHTA

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Dissertation Committee

Major Professor

DEAN OF GRADUATE SCHOOL

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1998
ABSTRACT

Mechanisms governing the release of drugs from controlled delivery systems are mainly diffusion, osmosis and erosion. For poorly soluble drugs, the existing mechanisms are limited to osmosis and/or matrix erosion. These mechanisms are commonly employed to control drug release from single unit and multi-unit dosage forms. More recently, multi-unit dosage forms have gained considerable popularity for controlled release technology due to their advantages over single unit dosage forms. However, the mechanism of polymer controlled surface erosion from a multi-unit dosage form has never been reported in the literature. This study describes the development, characterization and evaluation of a matrix pellet system which releases an insoluble drug via polymer controlled surface erosion mechanism. Extrusion/Spheronization method was used to formulate matrix pellets. The effect of various formulation and process parameters affecting the drug release were characterized by analytical techniques such as Differential Scanning Calorimetry, X-Ray Diffractometry, and Mercury Intrusion Porosimetry. Different insoluble drugs were used as model drugs to demonstrate universal applicability of this novel system. The effect of drug solubility was also investigated on the mechanism of drug release from this system. Solid dispersions of the model insoluble drug was formulated to increase its solubility. It was observed that when the drug properties were changed towards increasing solubility in water, the release mechanism and rate also changed from pure surface erosion to erosion/diffusion. Drug release of nifedipine pellets in vivo occurred for more than 24 hours following zero order kinetics in fasted dogs. Thus it was proved that the approach of controlling drug release by polymer
controlled surface erosion mechanism from a multi-unit pellet system is possible and such a system may be beneficial than the current marketed dosage forms of insoluble drugs such as nifedipine.
ACKNOWLEDGMENTS

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endless support, encouragement and willingness to help by devoting extra time besides their current duties on my project work.

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This work has been prepared in accordance with the manuscript format option for dissertation preparation, as outlined in section 11-3 of The Graduate Manual of the University of Rhode Island. Contained within is a body of work divided into three sections.

Included within Section I is Introduction, which introduces the reader to the subject of this dissertation, a statement of the hypothesis tested herein, and the specific objectives of my research.

Section II is comprised of five manuscripts, containing the findings of the research which comprises this dissertation. These five manuscripts are presented in the format required by the journal to which they will, or have been, submitted.

Section III contains appendices containing, ancillary data (information essential to, but not usually included in published manuscripts) and other details pertinent to the understanding of the concepts presented in Section II. This dissertation closes with a complete listing of all the works cited in this dissertation, arranged in alphabetic order by the author’s last name.
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SECTION I

- Introduction. A general introduction followed by compilation of the specific objectives of this research.

- A statement of the hypothesis tested in this dissertation.
INTRODUCTION

Release of poorly soluble drugs in a controlled fashion is a challenging task for the pharmaceutical scientist. The mechanisms that are utilized to control release of drugs are mainly diffusion, osmosis and erosion. Alza Corporation has developed the GITS (Gastro Intestinal Therapeutic Systems) system for the release of nifedipine, a sparingly soluble drug, over a period of 24 hours. This is an “Oros” tablet that delivers drug under osmotic pressure differences between the GI fluids and the drug formulation encapsulated in the semi-permeable membrane surrounding the tablet. The release of the drug occurs as a fine suspension from the laser drilled hole bored in the tablet [1, 2].

Other approaches used are matrix tablets which release the drug in a controlled fashion. Low to moderate viscosity grade hydrophilic polymers such as hydroxy propyl cellulose, hydroxy propyl methyl cellulose hydroxy ethyl cellulose, chitosans, alginates etc, have been used for this purpose. One of the drawback of these matrices is that they are single units and bioavailability from such matrices is dependent on gastric retention [3, 4].

Single unit dosage forms of poorly soluble drugs that release the drug by osmosis or erosion are commercially available. However in vivo drug release from such dosage forms may not be predictable and complete due to physiological variations in the gastric retention time and gastric emptying rates. Additionally, the frequency of bowel movements is also a factor that seriously influences bioavailability of drugs from such systems.
During the past 20 years there has been a growing interest in multi-unit solid dosage forms such as pellets for controlled drug delivery. Pellets offer significant therapeutic advantages over the traditional single unit dosage forms. Since pellets disperse freely in the GIT, they invariably maximize drug absorption, reduce peak plasma fluctuations, and minimize potential side effects without appreciably lowering the bioavailability of the drug. Pellets also reduce variations in gastric emptying rates and overall transit times. Thus, intra and inter subject variations of plasma concentrations of the drug, which are common for the single unit dosage forms, are minimized. Another advantage of pellets over single unit dosage forms is that the high local concentrations of therapeutic agents, which may inherently be irritant to the mucosal membranes, can be avoided. Pellets, when formulated as modified release dosage forms are less susceptible to dose dumping than the reservoir-type single unit formulations [5].

During the early developmental phase of nifedipine GITS system, 20% of the population in the clinical trials taking nifedipine GITS tablet expelled the tablet intact through the GIT via fecal matter. The pellets on the other hand, due to their small size and large number are dispersed rapidly in the GIT and thus avoid dose dumping or loss of dosage form. Pellets also offer technological advantages over single units such as better flow properties and ease of further processing during tablet compaction or coating for controlled release. Table I shows a partial list of pellet products marketed in the US.

Traditionally coated pellets have been used for controlled release applications. Most of the marketed controlled release pellets available today are coated. More recently, matrix
pellets have gained popularity in controlled release technology. Controlled release via matrix pellets avoids the coating process and thus saves time and money. Pellets, manufactured by the pharmaceutical industry, are sized between 500 and 2000 µm. These can be produced in different ways such as spraying a solution or a suspension of a binder and a drug onto an inert core, building the pellet layer after layer, spraying a melt of fats and waxes from the top into a cold tower (spray congealing) forming pellets as the result of the hardening of molten droplets and spraying a binder solution into the whirling powder using fluidized bed [5]. The most popular method of producing pellets is the Extrusion-Spheronization technique. This process was first reported by Reynolds (1970) and by Conine and Hadley (1970) and involves four steps: preparation of the wet mass (granulation), shaping the wet mass into cylinders (Extrusion), breaking up the extrudate and rounding of the particles into spheres (Spheronization) and finally drying of the pellets.

Traditionally, in the Extrusion-Spheronization technique, microcrystalline cellulose (MCC) has been the excipient of choice to prepare matrix pellets. Due to its excellent plasticity, it is widely used as a carrier or filler in the Extrusion-Spheronization process. However, MCC forms a non-disintegrating matrix and thus incorporation of a swelling or disintegrating agent is necessary for drug release to occur from such a system. Drug release from such matrices has been studied extensively by O'Conner et al. [6] and it was concluded that drug release occurred by Higuchi's square root of time equation and followed first order kinetics. Incorporation of a poorly soluble drug in such a matrix system would minimize drug release since the MCC matrix system is non-disintegrating.
Therefore, such a system would be inappropriate to formulate controlled release pellets of a poorly soluble drug. Additionally, since the drug is poorly soluble, diffusional release will be negligible. Thus, the only choice remains is that of an eroding pellet, which is a matrix pellet system that erodes from the surface as a function of time and releases the drug which is homogeneously dispersed in the pellet matrix. There is no such system reported in the literature.

Hellar et al. [7] prepared discs of poly (ortho esters) and studied in vitro and in vivo drug release of the highly water insoluble levonorgestrel. Poly (ortho esters) are polymers that erode due to pendent group hydrolysis of the ester groups, however; it is not generally recognized as safe for pharmaceutical applications. Hellar et al. concluded from his study that levonorgestrel release from surface-eroding polymer discs has three important consequences which are (1) The rate of drug release is directly proportional to drug loading, (2) The lifetime of the delivery device is directly proportional to device thickness, and (3) The rate of drug release is directly proportional to the total surface area of the disc.

The controlled release systems developed by Hellar et al. using poly (ortho esters) showed zero order release for months. Drug released in vitro was analyzed by measuring the drug present in the device after periodic time intervals of dissolution and the polymer erosion was determined by gravimetry. This study demonstrated that an indirect method such as measuring the drug left in the delivery device after dissolution may be employed
to quantify drug released and also the use of gravimetry to determine polymer erosion profiles.

Based on the information given above, the specific objectives of this research were,

1. To search for a surface eroding “GRAS” (Generally Recognized As Safe) polymeric system suitable for Extrusion-Spheronization technique.
2. To develop pellets of poorly soluble drugs for controlled release which releases the drug following zero order kinetics for 12-24 hours.
3. To characterize and evaluate the release mechanisms by analytical techniques such as differential scanning calorimetry, x-ray diffractometry, mercury intrusion porosimetry, particle size distribution, microscopy and in vitro, in vivo analysis.
4. To test the universal application of the system developed initially by using another poorly soluble drug.
5. If circumstances allow, to test the bioavailability in vivo of one of the model drugs from the pellets tested in vitro.

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ischaemic heart disease and peripheral vascular disorders., Drugs, 41 (5), 737-779, (1991).

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6. O’ Connor, Jr., R, E., “The drug release mechanism and optimization of a microcrystalline cellulose pellet systems”, Ph.D. Dissertation, Philadelphia College of Pharmacy and Science, June (1987).

7. Hellar, J., “Controlled drug release from poly (orth-esters) a surface eroding polymer”, Journal of Controlled Release, 167-177, 2 (1985).
Table 1. Partial list of pellet products marketed in the U.S

| Product     | Company                      |
|-------------|------------------------------|
| Sudafed S. A. | Glaxo-Wellcome               |
| Theo-24     | Searle Pharmaceuticals, Inc. |
| Theodur S. R. | Key Pharmaceuticals          |
| Nitrostat S. R. | Parke-Davis                  |
| Bontril SR  | Carnrick Laboratories, Inc.  |
| Compazine   | Smith Kline & French         |
| Hispril     | Smith Kline & French         |
| Nicobid T.S. | U.S. Vitamin                 |
| Papaverine HCL, T.D. | Lederle Laboratories |
| Russ-Tuss   | Boots Pharmaceuticals        |
| Slow-bid    | Rorer                        |
| Theobid S. R. | Glaxo-Wellcome               |
| Inderal L.A. | Ayerst Laboratories          |
| Indocrin S.R. | Merck Sharp & Dohme         |
| Xenical     | Roche Pharmaceuticals        |
| Novafed L.A. | Merrel-Dow                   |
| Fastin      | Beecham Laboratories         |
| Catazyne S  | Organon Pharmaceuticals       |

Source: Sellasie, I. G., "Pharmaceutical Pellitization Technology", Marcell Dekkar, Inc., New York, 12-14, (1989).
HYPOTHESIS TESTED HEREIN

It should be possible to develop a multi-unit controlled release matrix pellet system by Extrusion/Spheronization technique without microcrystalline cellulose (MCC), which can release an insoluble drug by polymer controlled surface erosion mechanism following zero order kinetics for 12-24 hours.
A. Manuscript I  "Development, Characterization and Evaluation of a Novel Multi-
Unit Erosion Matrix for a Poorly Soluble Drug."
(Submitted for publication in International Journal of Pharmaceutics).

B. Manuscript II  "Effect of Formulation and Process Variables on Matrix Erosion
and Drug Release from a Multi-Unit Erosion Matrix of a Poorly Soluble Drug."
(Submitted for publication in Pharmaceutical Research and Developments).

C. Manuscript III  "Effect of Formulation and Process Variables on Porosity
Parameters and Release Rates from a Multi-Unit Erosion matrix of a Poorly
Soluble Drug."
(Submitted for publication in European Journal of Pharmaceutics and
Biopharmaceutics).

D. Manuscript IV  "Multi-Unit Controlled Release Systems of Nifedipine and
Nifedipine:Pluronic® F-68 Solid Dispersions: Characterization of Release
Mechanisms."
(Submitted for publication in the Journal of Controlled Release).

SECTION II
Manuscript V "Nifedipine Bioavailability in Fasted Dogs from an Eroding Multi-Unit Matrix System."

(Submitted for publication in International journal of Pharmaceutics).
DEVELOPMENT, CHARACTERIZATION AND EVALUATION OF A NOVEL MULTI-UNIT EROSION MATRIX FOR A POORLY SOLUBLE DRUG.
Abstract

Mechanisms governing the release of drugs from controlled delivery systems are mainly diffusion, osmosis and erosion. For poorly soluble drugs, the existing mechanisms are limited to osmosis and/or matrix erosion, which are commonly employed via single unit matrix dosage forms. More recently, multi-unit dosage forms have gained considerable popularity for controlled release technology, because their rapid dispersion in the gastrointestinal tract maximizes drug absorption and provides reduced peak plasma fluctuations. Bioavailability from multi-unit dosage forms is affected the least by the presence of food and gastric emptying rate. This study reports the development of a novel multi-unit controlled release system for a model poorly soluble drug (thiazole based leukotriene D4 antagonist, solubility in physiological pH < 1.3 µg/mL) by a polymer controlled, surface erosion drug release mechanism. The drug, rate controlling and pellet forming agents (Eudragit® L 100 55 and Eudragit® S 100) and a binder (polyvinylpyrrolidone, Kollidon® K90F), were wet granulated, extruded and spheronized to form uniform matrix pellets. In vitro matrix erosion and drug release from the pellets were determined using USP Dissolution Apparatus I in pH 6.8 phosphate buffer by gravimetry and UV spectrophotometry, respectively. Results showed that matrix erosion and drug release from the pellets were well correlated. Pellets eroded with a consequent reduction in size without any change in the pellet shape for over 12 hours. Matrix erosion and drug release followed zero order kinetics. Data obtained strongly suggested a polymer controlled, surface erosion drug release mechanism.
KEYWORDS

Extrusion/Spheronization, Eudragit® L 100-55, Eudragit® S 100, polymer controlled surface erosion, controlled release matrix pellets.
1.0 Introduction

Release of poorly soluble drugs from controlled delivery systems is a challenging task for the pharmaceutical scientist. Alza Corporation has developed a gastrointestinal therapeutic system (GITS) for the release of nifedipine, a poorly soluble drug, over a period of 24 hours. The system is an "Oros" tablet which releases the drug under osmotic pressure differences between the GI fluids and drug concentration in the semi-permeable membrane surrounding the tablet. The release of drug occurs as a fine suspension from the laser drilled GITS device (1). Other approaches for the release of poorly soluble drugs from controlled release erosion matrix tablets employing hydrophilic cellulosic polymers are reported (2, 3). These matrices are generally single units and thus may be associated with drawbacks such as irregular bioavailability due to presence of food and dependence on gastric emptying time. Therefore, existing mechanisms for the release of poorly soluble drugs by controlled release are limited to osmosis and/or erosion. Due to their negligible aqueous solubility, diffusion has practically very little or no contribution in the release of such drugs from the controlled delivery system.

More recently, multi-unit dosage forms have gained considerable popularity over conventional single units for controlled release technology. Due to their rapid dispersion in the gastrointestinal tract, they maximize drug absorption, reduce peak plasma fluctuations, minimize potential side effects without lowering drug bioavailability. They also reduce variations in gastric emptying rates and overall transit times. Thus, intra and inter-subject variability of plasma profiles, which are common with single-unit regimens,
are minimized. They are also less susceptible to dose dumping than the reservoir or matrix type, single-unit dosage forms (4).

Controlled release of poorly soluble drugs such as nifedipine, ampicillin and isosorbide dinitrate via pellets have been reported (5-9). All these studies primarily employed microcrystalline cellulose as a pellet forming agent. Due to its excellent pellet forming properties, microcrystalline cellulose offers potential advantage in pellet manufacturing by Extrusion/Spheronization technology. Release from such pellets was extensively studied by O'Connor et al (10). It was concluded that drug release follows first order kinetics as described by Higuchi's square root of time equation from such pellets. Since microcrystalline cellulose forms a non-disintegrating matrix when formulated as pellets, incorporation of a poorly soluble drug in such a matrix would only intensify the problems associated with its release. Such a matrix system would often provide no release of the poorly soluble drug at all.

This paper reports the formulation of pellets which release a poorly soluble drug as a result of surface erosion of the matrix pellet. It was postulated that for drug release to occur in zero order fashion, a matrix pellet must erode slowly as function of time from the pellet surface. This will allow the release of homogeneously dispersed drug in the matrix in constant increments as the erosion progresses in the pellets from the surface thus controlling drug release. A schematic representation of such a delivery system is shown in Figure 1.
2.0 Materials And Methods

The poorly soluble drug used as a model was a thiazole based leukotriene D4 antagonist with a solubility less than 1.3 µg/mL at pH 6.8 (Hoffmann-La Roche Inc., Nutley, NJ). Eudragit® L 100 55 and Eudragit® S 100 (Huls America, Inc., Somerset, NJ) were used as release rate controlling polymers and matrix forming agents. Kollidon® 90 F (BASF Inc., Parsippany, NJ) was used as a binder. Avicel® PH 101 (FMC Corporation, Philadelphia, PA) was employed to prevent inter-pellet sticking during the spheronization stage. Triethyl citrate (Morflex, Inc., Greensboro, NC) was used as a plasticizer for the Eudragit® polymers. All other chemicals were used as received.

2.1 Formulation of Pellets:

Eudragit®L 100 55 and Eudragit®S 100 powders were mixed in a turbula mixer (Turbula Mixer, Impandex Inc., Maywood, NJ, USA) for 30 minutes. Triethyl citrate was added to some formulations (Table-1) as a plasticizer and the resultant mixture was triturated in a mortar for 5 minutes. Drug and polyvinyl pyrrolidone (Kollidon®K90F) as a binder were added and mixed for 30 minutes in turbula mixer. This mixture was then granulated with deionized water in a mortar and later extruded (LCI Xtruder, Model DG-L1, Fuji Paudal Co., Ltd., Japan) at 40 rpm screw speed. The extrudates were immediately transferred into a rotating plate in the spheronizer (G.B. Caleva Ltd, Model 120, Dorset, England, consisting of a stationary vertical cylinder with a friction plate (diameter 32 cm) of 2 mm cross hatched pattern and a rotation speed of 200-3000 rpm).
Spheronization was carried out for 20 minutes at 500-1000 rpm. During this period, 5% w/w of total batch size Avicel® PH 101 was sprinkled over the rotating extrudates to prevent the pellets from sticking. Pellets obtained were dried on trays at 50°C for 12 hours. Dried pellets were later sieved to obtain different particle size fractions (Rotap Sieve Shaker, Model RX-29, W.S. Tyler, Inc., OH, fitted with sieve # 8, 10, 12, 14, 16, 18 and 20). The pellets consisted of drug (10.0% w/w), Eudragit® L 100 55 and Eudragit® S 100 (88.0% w/w) and Kollidon® K90F (2.0% w/w). A flow chart of the manufacturing process is presented in Figure 2. The composition of formulations with different polymer ratios is given in Table 1.

2.2 Characterization of Pellets:

2.2.1 Determination of Glass Transition Temperature (Tg)

Polymer blends (Eudragit® L 100-55 : Eudragit® S 100 in ratio of 1:3) with or without triethyl citrate as a plasticizer were weighed in a DSC aluminium pan. The DSC (Differential Scanning Calorimeter, Seiko Instruments Inc., Japan, Model SSC5200) was programmed to perform a heat-cool-heat cycle from 0 - 200°C. Heating and cooling rates of 10°C/minute was used.

2.2.2 Determination of Matrix Erosion

To study the erosion process of the pellet matrix, three criteria's were monitored, namely; microscopic evaluation of pellets, matrix erosion after dissolution of pellets and volume reduction by erosion of the pellets at different dissolution time intervals.
Pellets were visually inspected, sized and photographed under an optical microscope (Optical Microscope, Nikon HFX,IIA, Japan) before and after matrix erosion and drug release studies. Ten pellets per time interval were evaluated.

Matrix erosion was evaluated by using standard USP dissolution system (Distek, Dissolution System 2100A, USP Apparatus I , Baskets). Matrix erosion was determined by removing the baskets with pellets at intervals of 2, 4, 6, 8, 10, 12 hours and drying them for 12 hours at 50°C to a constant weight. The difference between the initial and final weight was calculated as percent matrix erosion.

Volume reduction due to erosion of pellets was calculated by using Equation 1.

\[ V_s = \frac{1}{6} \pi D^3 \]  
Equation 1

Where, \( V_s \) is volume (mm\(^3\)) of a sphere and \( D \) is the diameter (mm) of a sphere.

Cumulative percent erosion volume was calculated by dividing the change in volume at time 't' by original volume at time zero. The result of this was multiplied by 100 to obtain percentages. Rate of erosion volume (%/hr) was calculated by dividing cumulative percent erosion volume with the time interval.

2.3  Dissolution Studies:
Since the drug is poorly soluble, drug release from the pellets was determined by an indirect procedure which involved determination of drug left in the pellets after dissolution by UV analysis. The difference between initial and final amount of drug present in the pellets after dissolution was calculated as percent drug release.

3.0 Results And Discussion

3.1 Pellet Processing by Extrusion/Spheronization:

Extrusion with Eudragit®L 100 55 and Eudragit®S 100 as pellet forming agents was satisfactory and pellets of uniform shape and size were obtained (Figure 3). Spheronization occurs by rotation of the extrudates at high speeds on a friction plate within a vertical cylinder. During this stage each individual pellet rotates on its own axis due to centrifugal force. This action results in liquid migration from the interstices between particles to the surface of the sphere which may be accompanied by migration of ingredients in the formulation. If the drug is soluble in the granulating liquid, then on drying may lead to non homogeneous distribution of ingredients in the pellets (11).

The drug and the polymers used in this study were insoluble which prevented them from solubilizing or retaining moisture within the pellet matrix, resulting in the migration of moisture alone towards the pellet surface. This action created inter-pellet adherence during the spheronization process. Inter-pellet adherence was eliminated by sprinkling 5% w/w of Avicel®PH 101 on the extrudates during the spheronization step.
3.2 Characterization of Pellets:

Release profiles of the pellets (1.2 mm) prepared with and without triethyl citrate as plasticizer is shown in Figure 4. It was observed that 70 to 100 % drug release was obtained within six hours from these pellets. Pellets with 1:1 and 1:3 ratios of Eudragit® L 100 55 : Eudragit® S 100 were formulated. Pellets within each of the two formulation ratios containing plasticizer showed enhanced drug release rates when compared to pellets without plasticizer. This effect was consistent when the polymer ratio of the pellets were increased. The increased drug release from the pellets containing plasticizer may be the result of increased dissolution rate of the polymers after plasticization.

This effect was investigated by determining the effect of plasticizer on the glass transition temperature of the polymer (Figures 5A thru D). Results obtained are tabulated in Table 2. Polymer blends with plasticizer showed a significant reduction in glass transition temperature and enthalpy. Glass transition temperature of both the polymers were reduced by about 60% indicating that the polymer blend became more amorphous after plasticization, therefore its solubility was increased.

3.3 Characterization of Matrix Erosion and Mechanism of Drug Release:

Microscopic studies showed that the pellets during drug release were reduced in size as a function of time while maintaining a constant surface geometry (Figure 6A thru F). To extend the release period to more than six hours, 2.0 mm pellets were formulated. Figure
7 shows the extent of matrix erosion and drug release from the pellets. Matrix erosion and drug release occurred simultaneously (Figure 7). This correlation of matrix erosion with drug release holds true at stirring rates of 25, 50 and 100 rpm as demonstrated by Figure 8. These findings prove that drug release was a direct consequence of matrix erosion and was stirring rate independent.

Figure 9, shows the correlation of drug released with percent volume reduction by erosion. It indicates a direct relationship between drug release and volume reduction by erosion. Volume reduction depends on the diameter of the pellets. As the pellet erodes with time the pellet diameter reduces due to which erosion volume increases to maintain a constant rate of drug release (Table 3). Table 3 shows the changes in pellet volume, cumulative % erosion volume and rate of erosion volume as a function of dissolution time. The rate of erosion volume from Table 3 was observed to be constant up to 10 hours. This indicated that pellets eroded from the surface with consequent size reduction without affecting the erosion volume. Thus drug release following zero order kinetics was obtained.

These discussions explain the zero order release and matrix erosion profiles achieved from pellets and provide strong evidence for a surface erosion mechanism and for negligible diffusional release of the drug.

4.0 Conclusions
Uniform matrix pellets were obtained by using Eudragit® L 100 55 and Eudragit® S 100 as pellet forming agents. Pellets of satisfactory quality without microcrystalline cellulose in the matrix can be formulated.

As hypothesized, multi-unit pellet system formulated for controlled release of a poorly soluble drug by polymer controlled surface erosion mechanism were developed and characterized. These pellets reduced in size as a result of polymer controlled surface erosion of the drug and provided zero order controlled release up to 12 hours.

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Table 1: Formulation of 1.2 mm and 2.0 mm pellets with different polymer ratios.

| Eudragit® L 100.55 : Eudragit® S 100 ratio | Triethyl citrate (% w/w of total Eudragits®) |
|-------------------------------------------|---------------------------------------------|
| 1.0 : 1.0                                 | 15.0                                        |
| 1.0 : 3.0                                 | -                                           |
| 1.0 : 3.0                                 | 15.0                                        |
| 1.0 : 3.0                                 | -                                           |
Table 2: Effect of plasticizer (triethyl citrate) on Tg and ΔH of Eudragit® L 100 55 and Eudragit® S 100 polymers.

| Polymer blends     | T<sub>g</sub> (°C) | ΔH (mJ/°C mg) |
|--------------------|---------------------|----------------|
| Eudragit® L 100 55 | 93.2                | 0.112          |
| Eudragit® S 100   | 166.4               | 0.189          |
| Eudragit® L 100 55 | 54.5                | 0.050          |
| Eudragit® S 100   | 109.4               | 0.083          |

(a) Ratio of 1:3 unplasticized polymer blend

(b) Ratio of 1:3 plasticized with 15% w/w of triethyl citrate.
Table 3: Determination of the rate of erosion volume reduction from 2.0 mm pellets (n = 10).

| Time (hours) | Pellet Diameter (mm) | Pellet Volume (mm³) | Volume Change (mm³) | Cumulative Percent Erosion Volume (mm³) | Rate of Erosion Volume (%/hr) |
|--------------|----------------------|---------------------|---------------------|-----------------------------------------|-----------------------------|
| 0.0          | 2.08                 | 4.7118              | 0.8889              | 0.0000                                  | 0.0000                      |
| 2.0          | 1.94                 | 3.8229              | 1.8573              | 18.8654                                 | 9.4327                      |
| 4.0          | 1.76                 | 2.8545              | 3.6645              | 39.4180                                 | 9.8545                      |
| 6.0          | 1.26                 | 1.0473              | 4.1392              | 77.7728                                 | 12.9621                     |
| 8.0          | 1.03                 | 0.5721              | 4.6783              | 87.8581                                 | 10.9822                     |
| 10.0         | 0.40                 | 0.0335              | 4.7077              | 99.2890                                 | 9.9289                      |

1: Original Volume – Volume at time 't'.

2: Volume Change divided by 4.7118 (Volume at time zero).

3: Cumulative Percent Erosion Volume divided by the time interval.
Figure 1

Schematic representation of a novel multi-unit erosion matrix for controlled release of a poorly soluble drug.

0 to 24 hours

\textit{in vitro}

matrix pellet

eroding layer

intact matrix pellet
Flow chart of pellet manufacturing procedure.

**Polymer blend (Eud L 100-55 + Eud S 100)**

- mixing in turbula mixer for 30 minutes

**Addition of plasticizer (Triethyl citrate) + binder (PVP K90F) + Drug**

- mixing in turbula mixer for 30 minutes
- granulation with deionized water
- Extrusion at 40 rpm

Sprinkled with Avicel PH 101 to minimize inter-pellet sticking (5% w/w of total batch size)

**Spheronization at 500-1000 rpm**

**Drying at 50 C for 12 hours**

**Pellet screening (Sieve fractions collected 10/12 and 14/16 mesh)**
Figure 3

Photomicrographs of pellets (2.0 mm) viewed under an optical microscope, magnification 5X.
Effect of plasticizer on matrix erosion from pellets (pellet size: 1.2 mm, drug load: 10% w/w, Eud L 100-55: Eud S 100 ratio of 1:1 and 1:3)

Figure 4

Matrix erosion (% w/w) over time (hours) for different plasticizer ratios and conditions.
Figure 5A

DSC thermogram showing the glass transition temperatures of Eudragit® L100-55.
DSC thermogram showing the glass transition temperatures of Eudragit® S100.
Figure 5C

DSC thermogram showing the glass transition temperatures of Eudragit® L100-55 and Eudragit® S100 mixed in ratio of 1:3.
DSC thermogram showing the glass transition temperatures of Eudragit® L100-55 and Eudragit® S100 mixed in ratio of 1:3 and plasticized with 10% w/w triethyl citrate.
Figure 6

Microscopical evaluation of matrix erosion and size reduction of pellets (magnification: 5X).

A. Time: 0 hrs, Size: 2.0 mm  
B. Time: 2 hrs, Size: 1.75 mm  
C. Time: 4 hrs, Size: 1.6 mm  
D. Time: 6 hrs, Size: 1.4 mm  
E. Time: 10 hrs, Size: 0.8 mm  
F. Time: 12 hrs, Size: 0.2 mm
Correlation of matrix erosion (% w/w) with drug release (%) from pellets.
(pellet size: 2.0 mm, drug load: 10% w/w), Eud L100-55: Eud S 100 ratio of 1:3, n = 5±SE.

Matrix Erosion, $r^2 = 0.951$
$y = 8.021 + 7.830x$

Drug Release, $r^2 = 0.964$
$y = 3.110 + 8.214x$
Correlation of matrix erosion (% w/w) with drug release (%) at different stirring speeds.

(pellet size: 2.0 mm, drug load: 10% w/w), Eud L100-55: Eud S 100 ratio of 1:3, \( n = 4 \pm \text{SE} \).

![Graph showing correlation between matrix erosion and drug release at different stirring speeds](image)
Correlation of drug release (%) with volume reduction by erosion (%) of pellets. (pellet size: 2.0 mm, drug load: 10% w/w), Eud L100-55: Eud S 100 ratio of 1:3, n = 4±SE for drug released and n = 10±SE for volume reduction by erosion).

![Graph showing correlation between drug release and volume reduction by erosion over time.](image_url)
MANUSCRIPT II

EFFECT OF FORMULATION AND PROCESS VARIABLES ON MATRIX EROSION AND DRUG RELEASE FROM A MULTI-UNIT EROSION MATRIX OF A POORLY SOLUBLE DRUG.
KEYWORDS

Extrusion/Spheronization, Eudragit® L 100-55, Eudragit® S 100, Drug Loading,
Granulation Water Requirement, Polymer Ratio, Pellet Size, Spheronization Time.
ABSTRACT

A novel multi-unit controlled delivery system for the release of a poorly soluble drug by a polymer controlled, surface erosion mechanism was reported earlier. The present study was undertaken to determine the effects of formulation variables (ratio of polymers used, drug loading) and processing variables (water required for granulation, pellet size and spheronization time) on matrix erosion and drug release. Powder mixtures containing drug, different ratios of Eudragit® L 100 55 and Eudragit® S 100 were blended with polyvinylpyrrolidone (PVP) and were extruded/spheronized to obtain homogeneous matrix pellets. Drug release was predicted by matrix erosion studies. Matrix erosion was determined using USP Dissolution Apparatus I in pH 6.8 phosphate buffer by gravimetry and UV spectrophotometry, respectively. Matrix erosion and drug release rates were found to be a function of polymer ratio. Drug loading at 5, 10, and 20% w/w levels demonstrated that drug release was predominantly matrix erosion controlled. At 30 and 40% w/w drug levels, matrix erosion and drug release rates decreased. Pellet size had a profound effect on the total duration of matrix erosion and drug release from the pellets. Thus, by optimizing the formulation and process variables, pellets can be prepared which release a poorly soluble drug for 12-24 hours following zero order kinetics.
1.0 Introduction

The design and evaluation of a novel multi-unit erosion matrix that releases a poorly soluble drug by matrix erosion for 12 hours was reported earlier [1]. Several authors have reported factors such as polymer type, drug concentration, drug solubility, pelletization technique used, influencing drug release rate [2-9]. All these factors were evaluated for osmotically or diffusion controlled pellets employing microcrystalline cellulose as the principal pellet forming agent and release rate governing polymer in the pellet.

The pellets used in this study were manufactured by Extrusion/Spheronization technique, therefore any change in the formulation or process parameters may influence matrix erosion and drug release from the pellets [10]. The aim of this study was to investigate the influence of the most critical formulation variables (ratio of polymers used and drug loading) and process variables (water required for granulation, pellet size and spheronization time) on matrix erosion and drug release from the pellets. Previously, the linear relationship between matrix erosion and drug release at various dissolution stirring rates was described [1]. It was concluded that in such systems, matrix erosion and drug
release occurred simultaneously, thus matrix erosion can be monitored to predict drug release from the pellets.

2.0 Materials and methods

The poorly soluble drug used as a model was a thiazole based leukotriene D4 antagonist with aqueous solubility < 1.3 µg/ml (Hoffmann-La Roche Inc., Nutley, NJ). Eudragit® L 100 55, Eudragit® S 100 (Huls America, Inc., Somerset, NJ) were used as pellet forming and release rate controlling polymers. Kollidon® 90 F (BASF Inc., Parsipanny, NJ) was used as a binder. Avicel® PH 101 (FMC Corporation, Philadelphia, PA) was used in the spheronization stage to prevent inter-pellet sticking. Triethyl citrate (Morflex, Inc., Greensboro, NC) was used as plasticizer for Eudragits®. All other chemicals were used as received.

2.1 Formulation of Pellets:

Eudragit® L 100 55 and Eudragit® S 100 were dry mixed in a turbula mixer (Impandex Inc., Maywood, NJ, USA) for 30 minutes. This dry mixture was triturated in a mortar for
5 minutes with triethyl citrate (plasticizer). Drug and polyvinylpyrrolidone (PVP) as a binder were added and mixed in a turbula mixer for 30 minutes. This mixture was then granulated with deionized water in a mortar and later extruded (LCI Xtruder, Model DG-L1, Fuji Paudal Co., Ltd., Japan) at 40 rpm screw speed. The extrudates obtained were immediately transferred into a rotating plate in the spheronizer (G.B. Caleva Ltd, Model 120, Dorset, England). The spheronizer consisted of a stationary vertical cylinder with a base friction plate (diameter 32 cm) with a 2 mm cross hatched friction pattern and a rotational speed of 200-3000 rpm. Spheronization was carried out for either 2, 10 or 20 minutes at 500-1000 rpm. During this period, 5% w/w Avicel® PH 101 was sprinkled over the rotating extrudates to prevent them from sticking. The pellets obtained were dried on trays as a monolayer at 50°C for 12 hours. Pellets were later subjected to sieve analysis to collect the desired particle size pellets in a Rotap Sieve Shaker, Model RX-29, W.S. Tyler, Inc., OH, USA, fitted with sieve # 8, 10, 12, 14, 16, 18, 20 and 25.

2.2 **Composition of pellets prepared to evaluate formulation variables:**

Pellets of 2.0 mm size were formulated to determine the effects of polymer ratio and drug loading. Pellet compositions are tabulated in Table 1.

2.3 **Composition of pellets prepared to evaluate process variables:**


Pellets of 2.0 mm size were formulated to determine the effects of granulation water level, pellet size and spheronization time. Pellet compositions for granulation water study are tabulated in Table 1. Pellets of 0.8, 1.2 and 2.0 mm size were each formulated at spheronization times of 2, 10 and 20 minutes (Table 2) to determine the effect of pellet size and the spheronization time on drug release and matrix erosion. The formulation parameters maintained constant for this study were drug loading (10% w/w), polymer ratio (Eudragit® L 100 55 : Eudragit® S 100 was 1:3), Kollidon® K 90F (polyvinylpyrrolidone) as a binder (2% w/w), Triethyl citrate as plasticizer for Eudragits (15% w/w of total Eudragit content), deionized water for granulation (70% w/w).

2.4 In vitro release studies:

Drug release was performed using a standard USP Dissolution Apparatus I (Distek, Dissolution System 2100A USP XXII). Pellets (100 mg) were immersed in 500 ml of pH 6.8 phosphate buffer maintained at 37.0 ± 0.5°C and stirred at 50 rpm. The baskets were removed at intervals of 2, 4, 6, 8, 10, 12 hours and were dried for 12 hours at 50°C to achieve constant weight. The difference between the initial and final weight of the
pellets was calculated to determine percent matrix erosion. The matrix erosion was determined to predict percent drug release [1].

3.0 Results and discussions

Several studies report the influence of formulation and process variables on drug release from pellets formulated by Extrusion/Spheronization process [2-9]. However, the results of these studies are specific to the formulation and utilize either microcrystalline cellulose (MCC) or MCC with various hydrophilic or hydrophobic in combination. Drug release from such matrices is predominantly characterized by first order kinetics due to the presence of microcrystalline cellulose used as the matrix [11]. Tapia et. al. [2] studied the effect of chitosan on drug release from matrix pellets manufactured by Extrusion/Spheronization and concluded that drug delivery occurred by gel formation of chitosan through diffusion process. Gel formation was found to be a direct function of polymer ratio.

The rate controlling polymers used in this study were Eudragit® L 100 55 and Eudragit® S 100. These polymers dissolve above pH 5.5 and 7.0 respectively. Some of their popular
commercial uses include tablet and pellet coatings to achieve controlled or sustained release.

The effect of increased Eudragit® S 100 content on drug release from 2.0 mm pellets is shown in Figure 1. It was observed that rate of drug release decreased as the ratio of Eudragit® S 100 increased in the formulation without any significant change in the release kinetics.

Figure 2 shows the effect of drug loading on drug release. Matrix erosion data was used to compare the effects of drug loading with that of placebo pellets. The same figure demonstrates that drug release from pellets with 5, 10 and 20% w/w drug loading was similar to that of placebo pellets which strongly indicated that the drug release mechanism was matrix erosion controlled up to 20% w/w drug loading. However, above 20% w/w drug loading, the release rates were found to decrease as the drug load increased up to 40% w/w. The reason for this finding may be hydrophobicity of the drug incorporated into the matrix.

The influence of the amount of granulation liquid on the drug release rate from pellets made by Extrusion/Spheronization has been the topic of many publications (Baert et al.
Baert et al and his co-workers demonstrated that slower release rate was the result of increasing amounts of granulating liquid. They correlated the effects of granulation liquid with the differences in hardness, density and structure of the pellets, whereas Jerwanska et al and his co-workers, through their study concluded that rate of drug release increased with increasing granulation liquid level due to an increase in porosity obtained after drying. They also correlated these results with differences in hardness of the pellets.

The effect of the granulation water level on the matrix pellets prepared by employing Eudragit® L 100 55 and Eudragit® S 100 as the rate controlling and pellet forming agents is shown in Figure-3. Increased granulation water levels had a direct effect on the drug release rates. These findings are similar to the findings of Jerwanska et al [5]. However, there seemed to be no significant difference in the release rates above 65% w/w granulation water level. This can be explained by the effect of moisture content on the degree of liquid saturation of the extrudates. Jerwanska et al [5], proposed that for a continuous extrusion process, adequate water is required to bridge the particles together until liquid saturation in the granulation is achieved. This is necessary to deform the granulation to form extrudates and consequently shape them into spheres by spherification. If the granulation water level is below the liquid saturation point the
spheres obtained will be hard and less porous leading to decreased drug release rates. Above the liquid saturation point the hardness and porosity of the pellets are not significantly affected.

In order to investigate the most critical spheronization times which would have an effect on drug release, pellets were spheronized for 2, 5, 8, 10, 20 and 40 minutes. The hardness of pellets (n = 10) was measured (Chatillon Force Measurement System, Model TCD-200 attached with a 5 lb load cell, Greensboro, NC, USA). The results of pellet hardness test of 10 pellets per spheronization time are tabulated in Table 3. From Table 3, the pellet hardness changes with spheronization time up to about 10 minutes with maximum hardness recorded for pellets spheronized at 8 minutes, where after the hardness decreases up to 20 minutes. No significant difference in the pellet hardness from 20 to 40 minutes was observed. This may be explained by the densification process occurring during the spheronization step. As spheronization time progresses from zero to time ‘t’, the extrudates are cut into uniform particles and shaped into spheres due to the centrifugal and frictional forces present in the spheronizer during operation. These forces act on each and every particle making them more dense and more spherical with time. However, after a critical period no further densification occurs with increase in spheronization time. Data from Table 3 indicates that the pellet densification process
takes about 10 minutes above which very minor changes in densification occur. Thus a spheronization time of 2, 10 and 20 minutes was selected to study the effects of time on drug release.

Figure 4 shows the effect of spheronization time on the drug release rate from 0.8, 1.2, and 2.0 mm pellets. Spheronization time appears to effect drug release rates at the 2 and 10 minute processing times for 1.2 and 2.0 mm pellets. This effect became less pronounced when the pellet size increased from 0.8 to 2.0 mm. However, there is no significant difference in the drug release profile of 1.2 and 2.0 mm pellets above 10 minute processing time. It was also observed that the duration of drug release increased as the pellet size increased without any change in release kinetics above 1.2 mm pellet size.

4.0 Conclusions

This study shows the effects of various formulation (ratio of polymers used and drug loading) and process (granulation water level, pellet size and spheronization time) parameters on drug release by surface erosion from multi-unit matrix pellets. Each parameter evaluated, demonstrated a change in drug release from the pellets. Increased
amounts of Eudragit® S 100 retarded the rate of matrix erosion and drug release from the pellets. The drug loading had no influence on drug release mechanism up to the 20% w/w level above which increasing levels of drug up to 40% w/w retarded matrix erosion. Granulation water level at 65% w/w had a significant effect on the rate of matrix erosion and drug release as compared to the formulation with 60% w/w granulation water level. Above 65% w/w, there was no significant effect on the rate of matrix erosion and drug release.

Matrix erosion and drug release rates can be optimized by processing the pellets at different spheronization times. Thus, by optimizing the formulation and process variables pellets that can release a poorly soluble drug by polymer controlled, surface erosion mechanism for 12 hours following zero order kinetics.
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Table 1.  Composition of pellets formulated with different polymer ratios, drug loadings and granulation water levels.

| Ingredients (% w/w) | Pellet Compositions with Different Polymer Ratios | Pellet Compositions with Different Drug Loadings | Pellet Composition with different Granulation Water |
|---------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
|                     | Drug                                          | Drug                                          | Drug                                          |
|                     | 10.00                                         | 0.00                                          | 0.00                                          |
|                     | 10.00                                         | 5.00                                          | 5.00                                          |
|                     | 10.00                                         | 10.00                                         | 10.00                                         |
|                     | 20.00                                         | 20.00                                         | 20.00                                         |
|                     | 30.00                                         | 30.00                                         | 30.00                                         |
|                     | 40.00                                         | 40.00                                         | 40.00                                         |
| Kollidon® 90F       | 2.00                                          | 2.00                                          | 2.00                                          |
| Eudragit®L 100-55   | 35.20                                         | 22.00                                         | 22.00                                         |
| Eudragit®S 100      | 52.18                                         | 66.00                                         | 66.00                                         |
| * Plasticizer       | 15.00                                         | 15.00                                         | 15.00                                         |
| Granulation Water   | 60.00                                         | 77.90                                         | 77.90                                         |

* Trichy citrate (% w/w based on total Eudragit®L 100 55 + Eudragit®S 100 contents in the formulation).
Table 2. Pellets of different size prepared at different spheronization times.

| Pellet Size (mm) | Spheronization Time (minutes) |
|------------------|------------------------------|
| 0.8              | 2.0  |
|                  | 10.0 |
|                  | 20.0 |
| 1.2              | 2.0  |
|                  | 10.0 |
|                  | 20.0 |
| 2.0              | 2.0  |
|                  | 10.0 |
|                  | 20.0 |
Table 3. Effect of spheronization time on pellet hardness.

| Spheronization Time (minutes) | Pellet Hardness (grams) (Mean ± SD) |
|-------------------------------|-------------------------------------|
| 2.00                          | 1091 ± 139.39                       |
| 5.00                          | 1383 ± 177.14                       |
| 8.00                          | 1511 ± 157.12                       |
| 10.00                         | 1259 ± 170.25                       |
| 20.00                         | 1034 ± 177.40                       |
| 40.00                         | 1110 ± 146.06                       |
Figure 1

Effect of varying polymer ratios on drug released (%) from pellets.

(pellet size: 2.0 mm, drug load: 10% w/w, n = 3±SE)
Figure 2

Effect of different drug loading (% w/w) on drug released (%) from pellets.
(pellet size: 2.0 mm, n = 4±SE)
Figure 3

Effect of granulation water level (% w/w) on drug released (%) from pellets.

(pellet size: 2.0 mm, drug load: 10% w/w, n = 4±SE)
Effect of pellet size and spheronization time on drug release rate from pellets.

(drug load: 10% w/w, n = 4±SE)
EFFECT OF FORMULATION AND PROCESS VARIABLES ON POROSITY PARAMETERS AND RELEASE RATES FROM A MULTI UNIT EROSION MATRIX OF A POORLY SOLUBLE DRUG
KEYWORDS

Porosity Parameters, Extrusion/Spheronization, Controlled Release Matrix Pellets, Eudragit® L 100-55, Eudragit® S 100, Polymer Controlled Surface Erosion.
ABSTRACT

Controlled release erosion matrix pellets were prepared by a Extrusion/Spheronization technique. The effect of drug loading, water required for granulation and spheronization time on porosity parameters (intrusion-extrusion isotherms, pore size distribution, total pore surface area, mean pore diameter, shape and morphology of pores) and drug release rates were investigated. Porosity parameters were determined by using mercury intrusion porosimetry. *In vitro* release was performed in phosphate buffer pH 6.8 using USP XXII Apparatus I (baskets, at 50 rpm) by UV spectrophotometry. The drug loading was found to have a profound effect on the porosity parameters. Pellets with low drug loading showed increased pore surface area, with small mean pore diameters and an increased number of total pores. Whereas pellets with high drug loading had decreased pore surface area with bigger mean pore diameters and a decrease in the total number of pores. With high drug loading, drug release rate was found to be decreased. Water required for granulation had a direct effect on the total porosity of the pellets. Dissolution studies showed that release rates were directly related to the water required for granulation. Spheronization time from 2 to 10 minutes had a pronounced effect on porosity parameters and release rates. No changes in porosity parameters and release rates were observed from 10 to 20 minutes of spheronization time. It was shown that each porosity parameter investigated was well correlated with drug release rates and thus it is important to study the effect of porosity parameters in evaluating the *in vitro* performance of multi-unit erosion matrix for controlled release of a poorly soluble drug.
INTRODUCTION

Porosity is a measure of void spaces in a material and can be generally calculated by using a number of techniques such as density, gas adsorption, water displacement and porosimetry (1). Determination of pore structures of solids can provide important information on disintegration, dissolution, adsorption and diffusion of drugs (2). Pore size measurements provide information on the actual pore structures, including pore diameter and volume, and can be determined by gas adsorption and mercury porosimetry. The gas adsorption method is limited to pore diameters smaller than 2000 Angstroms, whereas mercury porosimetry is capable of measuring larger pores and inter-particle spaces (3). Thus mercury porosimetry is a suitable technique to determine a broad range of pores of a sample.

The method is based on intrusion of mercury into the pores of a solid sample and is quantified by the Washburn Equation (4).

\[ P = \frac{-2 \gamma \cos \theta}{r} \]

where \( P \) = pressure (psi), \( r \) = pore radius (µm), \( \gamma \) = surface tension of mercury (dynes/cm) and \( \theta \) = the contact angle of mercury. This equation holds true only when the surface tension and contact angle of mercury are kept constant and shape of the pores is assumed to be circular.
By mercury penetration under pressure, one can determine the size and quantity of void spaces and pores in porous materials. In addition, mercury expelled from pores as a function of decreasing pressure provides information about the shape and structure of the pores (5). In porosimetry, voids are defined as spaces between particles or the several pieces constituting the specimen, whereas cracks, crevices, holes and fissures within the specimen, whether a single piece or a powder, are termed as pores (6).

Mercury porosimetry has been extensively used in porosity determination of granules (7-11), tablets (12-17) and pharmaceutical powders (18,19). The development, characterization and evaluation of a novel multi-unit erosion matrix for a poorly soluble drug was reported in our previous study (20). In which, matrix pellets of a model poorly soluble drug (thiazole based leukotriene antagonist, aqueous solubility < 1.23 µg/mL) was pelletized with Eudragit® L 100 55 and S 100 used as release rate controlling polymers. The pellets were prepared by Extrusion/Spheronization technique and the effect of formulation (drug load, water required for granulation) and process (spheronization time) variables on drug release were studied (21). In this paper we have used mercury intrusion porosimetry to understand the effect of formulation and process variables on drug release behavior relative to the changes in porosity parameters.

MATERIALS AND METHODS

A thiazole based leukotriene D₄ antagonist (Hoffmann-La Roche Inc., Nutley, NJ) was used as a model poorly soluble drug. Eudragit® L 100 55, Eudragit® S 100 (Huls
America, Inc., Somerset, NJ) were employed as matrix forming and release rate governing polymers. Kollidon® 90 F (BASF, Inc., Parsipanny, NJ) was used as a binder in the formulation. Avicel® PH 101 (FMC Corporation, Philadelphia, PA) was used to prevent inter-pellet sticking during the spheronization stage. Triethyl citrate (Morflex, Inc., Greensboro, NC) was used as a plasticizer for Eudragit® polymers. All other chemicals were used as received.

**Preparation of Matrix Pellets by Extrusion/Spheronization:**

Eudragit® L 100 55 and Eudragit® S 100 were dry mixed in a Turbula mixer (Impandex Inc., Maywood, NJ, USA) for 30 minutes. This dry mixture was triturated in a mortar for 5 minutes with triethyl citrate used as a plasticizer. Drug and polyvinylpyrrolidone used as a binder were added to this mixture and were mixed in the Turbula mixer for 30 minutes. The dry blend was transferred to a mortar and was granulated with deionized water for 10 minutes. The wet granulate was later extruded at 40 rpm screw speed (LCI Xtruder, Model DG-L1, Fuji Paudal Co., Ltd., Japan). The instrument used was a single screw extruder capable of extruding at speeds up to 100 rpm. The extrudates were spheronized in a G.B. Calvca Ltd, Model 120, Dorset, England, at 600-800 rpm spheronizer speed. The spheronizer consists of a stationary vertical cylinder which has at the base a friction plate with a 2 mm cross hatched friction pattern and a rotation speed of 200-3000 rpm. Spheronization times used were 2, 10 and 20 minutes. Avicel® PH 101 5% w/w was sprinkled over the rotating extrudates to prevent pellets from sticking. The pellets obtained were dried at 50°C for 12 hours using a tray dryer and were later sieved.
through Rotap Sieve Shaker (Model RX-29, W.S. Tyler, Inc., OH, USA), fitted with sieve number 10 and 12 to obtain 2.0 mm size pellets.

**Drug Loading:**

Composition of pellets formulated to determine the effects of drug loading are given in Table 1.

**Water required for granulation:**

Composition of pellets formulated to study the effects of granulation water level are given in Table 2.

**Spheronization time:**

Pellets were processed at 2, 10 and 20 minutes spheronization times. Formulation composition maintained constant for this study were the drug load (10 % w/w), polymer ratio (1: 3) same as in Table 2, Kollidon® 90F as binder (2 % w/w), triethyl citrate as plasticizer (15 % w/w of total Eudragit® L 100 55 and Eudragit® S 100) and water for granulation (70 % w/w of the total batch size).

**Drug release studies:**
It was shown in our previous study that pellets prepared with the model poorly soluble drug, released the drug as a direct function of matrix erosion (20). *In vitro* drug release was determined by using USP XXII Apparatus I with baskets at 50 rpm (Distek Inc., NJ, USA) in 500 mL of pH 6.8 phosphate buffer at 37.0 ± 0.5° C.

*Mercury intrusion porosimetry:*

Porosity parameters such as intrusion-extrusion isotherms, pore size distribution, total pore surface area, mean pore diameters, shape and morphology of the pores were determined by using a Micromeritics PoreSizer 9320 (Micromeritics Inc., Norcross, GA, USA). Incremental intrusion volumes were plotted against pore diameters which represented pore size distributions. The moisture content of pellets were determined with an infra-red moisture analyzer at 105° C (Computrac, Model Max-50, Arizona Instrument Corp., USA) prior to porosimetry studies. The moisture content of all the pellet samples varied between 2.2-3.0 % w/w. The pore diameter was calculated by using Eq 2.

\[
D = \frac{-4\gamma \cos\theta}{P}
\]

where

\(D\) = pore diameter (µm)

\(\gamma\) = surface tension of mercury (485 dynes/cm).

\(\theta\) = contact angle (130 degrees)

\(P\) = pressure (psi)
The total pore surface area \( (S) \) was calculated by using Eq 3

\[
S = \frac{1}{\gamma \cos \theta} \int_{0}^{V_{\text{tot}}} P dV
\]

where; \( P = \) pressure (psi)

\( V = \) the intruded volume of mercury (mL/g)

\( V_{\text{tot}} = \) total intruded volume of mercury (mL/g)

The mean pore diameter \( (D'\text{mean}) \) was calculated by Eq 4.

\[
D'\text{mean} = 4 \frac{V_{\text{tot}}}{S}
\]

Pore morphology was characterized from the intrusion-extrusion profiles of mercury in the pellets as described by Orr et. al. (6).

**RESULTS AND DISCUSSION**

*Effect of Drug Loading:*
The intrusion volume of mercury is a function of total porosity. In Figure 1 the cumulative intrusion volume was plotted against pore diameters showing the intrusion-extrusion profile of pellets with different drug loading. The intrusion and extrusion curves form a hysteresis indicating that majority of the pores present in the pellets were ink-well type pores that had small openings with broad bases. Although no particular trend was observed in the intrusion profiles with respect to drug loading, the intrusion volume of mercury was significantly lower for 30 and 40% w/w than the 5, 10 and 20% w/w drug loading (Figure 1).

Figure 2 shows the incremental intrusion volume as a function of the pore diameter of the pellets with increasing drug loading. From Figures 1 and 2, the number of pores and mean pore diameters of the pellets can be characterized. The data indicates that as the drug loading increased from 0-10% w/w, the mean pore diameter increased with the total number of pores essentially remaining constant whereas, with 30 and 40% w/w drug loads the mean pore diameters increased and the total number of pores decreased.

Figure 3 shows the effect of drug loading on the total pore surface area and mean pore diameter of pellets; they seem to have an inverse relationship as expected.

Table 3 lists the calculated ranges of pore necks and pore bases as a function of increasing drug loading as characterized from Figures 1 and 2. The data from Table 3 indicates that pore bases were nearly twice the size of pore necks at all levels of drug loading; indicating that all pores have large bases with relatively small necks. This difference
becomes more apparent as drug loading increases above 30% w/w. This interpretation is supported by the relation of drug loading, total pore surface area and the mean pore diameters of the pellets as shown in Figure 3. The results indicate that with increasing drug concentration the pores became wider with larger necks and thus reduced in number. These changes are illustrated schematically in Figure 4.

Figure 5 shows the dissolution profiles of the pellets with different drug loading. Drug release from these pellets occurred via surface erosion. Therefore theoretically, the nature of pores present at the surface of the pellet must influence the erosion rate rather than the total porosity of the pellet matrix during the dissolution process. In pellets with high drug loads, the total polymer content is relatively low. Since the weight fraction of drug per unit weight of the drug-polymer mixture is high, the drug particles associate to form drug agglomerates (22) and this agglomeration tendency of the drug at high drug loads will reduce the number of pores and thus total pore surface area is reduced. Such a system during dissolution will have a low contact surface area with the dissolution media. However, in pellets with low drug loads, the weight fraction of polymer per unit weight of the drug-polymer mixture is high, therefore chances of drug agglomeration are less resulting in more pores with smaller mean pore diameters and increased total pore surface area. Thus, the increase in mean pore diameter and decrease in total pore surface area of pellets with high drug loading were primarily due to agglomeration of the drug particles. As it is discussed above, because of the existence of larger pores, the surface area of contact between the dissolution medium and pellets with high drug load is reduced, which
reduces pellet hydration and consequently the erosion rates. This was confirmed by the
dissolution profiles given in Figure 5.

**Effect of Water Required for Granulation:**

The intrusion-extrusion profiles of mercury for the percent water added to the granulation
are shown by plotting cumulative intrusion volume against pore diameter in Figure 6.
The total intrusion volume was found to be a direct function of granulation water level.
This indicated that total porosity of the pellets increased with the addition of water for
granulation from 60-70% w/w. These findings are similar to the results obtained by other
researchers (23-26).

Figure 7 is a plot of incremental intrusion volume against pore diameter which shows the
pore size distribution of pellets with different granulation water levels. All pores present
are between 0.01-0.1 µm in size. Table 4 summarizes the results of granulation water
level on the range of pore necks and pore bases. The pore base being the average width
of the ink-well type pores inside the pellet matrix. From Figure 7 and Table 4 it is
evident that increasing the granulation water level from 60 to 65% w/w increased the total
number of pores, but the pore necks and bases were not affected indicating that the water
levels used in the study increases the porosity without affecting the morphology of pores.
When the granulation water level was increased from 65 to 70% w/w, the pore neck and
pore base ranges remain narrow but the number of pores increase, resulting in overall
increase in the porosity of the pellets.
Figure 8 shows the effect of total pore surface area and mean pore diameters against granulation water levels. The data indicate that the total pore surface area increases without any significant change in the mean pore diameter as a function of increased granulation water levels. This finding also strongly supports the fact that with the addition of more granulation water, the number of pores increased without any change in the mean pore diameters. These changes are illustrated schematically in Figure 9. Fujiwara and Kato et al. reported similar findings with the increase in granulation water level on pore structure and porosity of sucrose and lactose granules prepared by wet granulation (9).

The dissolution profile of pellets formulated at different granulation water levels are given in Figure 10. The dissolution rates increase with the increase in porosity and total pore surface area of the pellets with 60, 65 and 70% w/w water for granulation. This increase in the porosity and total pore surface area of the pellets increased the dissolution contact area of the medium with the pellet surface resulting in faster hydration and consequently caused higher erosion rates.

*Spheronization Time:*

The sphericity of a pellet is a function of spheronization time. The longer they are spheronized more spherical pellets are produced. The circular motion of the friction plate in the spheronizer, shape the sphagetti like extrudates into smaller and uniform granules.
Eventually, the collision of these granules with the friction plate and the walls of the spheronizer change their shape into small spheres or pellets as a function of time. This transformation may be analogous to tablet compaction. “The term compactability is the ability of the bed of particles to cohere into or form a compact of a defined mechanical strength”(26). In compacting a tablet, the force applied by the upper punch has a direct relation with the compactability of the tablet. It is also generally observed that after a critical force no further increase can change the degree of compaction. Similarly, during spheronization, the pellet is compacted up to a critical strength above which no more compaction is observed. The change in porosity parameters of tablets as a function of compaction force are reported (12-17). However, for pellets no information showing the changes in porosity parameters as a function of spheronization time is reported. Therefore, it was important to elucidate this process with respect to the change in porosity parameters, particularly because the dissolution rates of the pellet were a function of spheronization time.

To understand the changes occurring in porosity with spheronization, the pellets were processed at three different spheronization times, 2, 10 and 20 minutes. Figure 11 shows the total intrusion volume against pore diameters as a function of spheronization time. The data indicate that porosity was not significantly affected by spheronization at 2, 10 and 20 minutes.

Figure 12 shows the plot of incremental intrusion volume against pore diameters which demonstrates that the pores increased with 2 to 10 minute spheronization time. However,
after 10 minutes, no change in the pore size distribution was observed up to 20 minutes. Figure 13 confirms these findings by demonstrating no change in the total pore surface area and mean pore diameter from 10 to 20 minutes.

In summary, following the argument given earlier, processing period from 2 to 10 minutes increased the pores, total pore surface area and decreased pore diameters, beyond this time up to 20 minutes none of the porosity parameters changed. Figure 14 shows the effect of spheronization time on dissolution profiles of pellets which were processed for 2, 10 and 20 minutes. The dissolution rates of pellets processed at 10 and 20 minutes were same. However, pellets processed at 2 minutes spheronization time showed faster dissolution rates. Figure 15 shows a schematic representation of the effect of spheronization time on the porosity of the pellets.

CONCLUSIONS

This study demonstrated that the changes in porosity parameters (intrusion-extrusion isotherms, pore size distribution, total pore surface area, mean pore diameter, pore shape and morphology) of pellets made with insoluble drug substance is affecting drug release rates with erosion controlled mechanism when the drug loading, granulation water level and spheronization time are modified.

By increasing the granulation water level, the number of pores are increased without affecting the mean pore diameter. The total porosity of the pellets was increased with
higher granulation water level. This increases the erosion rate of pellets leading to faster dissolution of the drug.

With spheronization time, the porosity parameters are affected depending on the time. Up to 10 minutes of spheronization time, the number of pores increased with total increase in surface area and decrease in pore diameter. No significant increase in porosity parameters was observed when the spheronization time was further increased from 10 to 20 minutes. This difference is reflected by erosion rate and dissolution profiles.

Thus, the study of porosity parameters is important in characterizing and predicting the in vitro performance of multi-unit matrix pellets.

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Table I: Formulations prepared to determine the effects of drug loading.

| Drug Load (% w/w) | Kollidon®90F (% w/w) | Eudragit®L 100 55 (% w/w) | Eudragit®S 100 (% w/w) | *Plasticizer (% w/w) |
|-------------------|----------------------|---------------------------|------------------------|----------------------|
| 0.00              | 2.00                 | 24.50                     | 73.50                  | 15.00                |
| 5.00              | 2.00                 | 23.25                     | 69.75                  | 15.00                |
| 10.00             | 2.00                 | 22.00                     | 66.00                  | 15.00                |
| 20.00             | 2.00                 | 19.50                     | 58.50                  | 15.00                |
| 30.00             | 2.00                 | 17.00                     | 51.00                  | 15.00                |
| 40.00             | 2.00                 | 14.50                     | 43.50                  | 15.00                |

* Triethyl citrate (% w/w based on total Eudragit®L 100 55 + Eudragit®S 100 contents in the formulation).
Table II: Formulations prepared to determine the effect of granulation water levels.

| Drug Load (%) w/w | Kollidon®90F (% w/w) | Eudragit®L 100 55 (% w/w) | Eudragit®S 100 (% w/w) | * Plasticizer (%) w/w | Granulation Water Level (%) w/w |
|-------------------|----------------------|--------------------------|------------------------|-----------------------|-----------------------------|
| 10.00             | 2.00                 | 22.00                    | 66.00                  | 15.00                 | 60.00                       |
| 10.00             | 2.00                 | 22.00                    | 66.00                  | 15.00                 | 65.00                       |
| 10.00             | 2.00                 | 22.00                    | 66.00                  | 15.00                 | 70.00                       |

* Triethyl citrate (% w/w based on total Eudragit®L 100 55 + Eudragit®S 100 contents in the formulation).
Table III: Effect of drug loading on the size of pore necks and pore bases as characterized from the intrusion-extrusion profiles.

| Drug Load (% w/w) | Pore Necks (nm) | Pore Bases (nm) |
|-------------------|-----------------|-----------------|
| 0.00              | 15 - 90         | 50 - 200        |
| 5.00              | 18 - 60         | 70 - 150        |
| 10.00             | 18 - 60         | 70 - 150        |
| 20.00             | 18 - 70         | 40 - 150        |
| 30.00             | 18 - 90         | 40 - 150        |
| 40.00             | 15 - 180        | 50 - 300        |
Table IV: Effect of water required for granulation on pore necks and pore bases as characterized from intrusion-extrusion curves of mercury.

| Granulation Water Level (%) w/w | Pore Necks (nm) | Pore Bases (nm) |
|--------------------------------|----------------|-----------------|
| 60.00                          | 15 - 90        | 50 - 110        |
| 65.00                          | 15 - 90        | 50 - 110        |
| 70.00                          | 20 - 60        | 60 - 100        |
Figure 1
Cumulative intrusion volume vs pore diameter of pellets with different drug loading (\% w/w). (pellet size: 2.0 mm, spheronization time: 10 minutes, n = 4±SE)
Figure 2

Pore size distribution of pellets with different drug loading (% w/w). (pellet size: 2.0 mm, spheronization time: 10 minutes, n = 3±SE)
Figure 3
Effect of drug loading (% w/w) on total pore surface area and mean pore diameter of pellets. (pellet size: 2.0 mm, sphericization time: 10 minutes, n = 3±SE)
Figure 4

Schematic surface representation of the effect of drug loading on the pore diameters and total number of pores.

Drug Load: 0 - 10% w/w

20 - 30% w/w

40% w/w
Figure 5

Effect of drug loading (% w/w) on drug released (%) from pellets. (pellet size: 2.0 mm, spheronization time: 10 minutes, n = 4±SE)
Effect of granulation water level (% w/w) on cumulative intrusion volume of pellets.

(pellet size: 2.0 mm, drug load: 10% w/w, spheronization time: 20 minutes, n = 3±SE)
Figure 7

Effect of granulation water level (% w/w) on pore size distribution of pellets. (pellet size: 2.0 mm, drug load: 10% w/w, spheronization time: 20 minutes, n = 3±SE)
Figure 8

Effect of granulation water level (% w/w) on total pore surface area and mean pore diameter of pellets. (pellet size: 2.0 mm, drug load: 10% w/w, spheronization time: 20 minutes, n = 3±SE)
Figure 9

Schematic representation of the effect of increasing water required for granulation on the pore diameters and total number of pores.

Water for granulation: 60% w/w

65% w/w

70% w/w
Effect of granulation water level (% w/w) on drug released from pellets. (pellet size: 2.0 mm, drug load: 10% w/w, spheronization time: 20 minutes, n = 4±SE)

Figure 10

Effect of granulation water level (% w/w) on drug released from pellets. (pellet size: 2.0 mm, drug load: 10% w/w, spheronization time: 20 minutes, n = 4±SE)
Figure 1

Effect of spheronization time on cumulative intrusion volume of pellets. (pellet size: 2.0 mm, drug load: 10% w/w, n = 3 ± SE)
Figure 12

Effect of spheronization time on pore size distribution of pellets. (pellet size: 2.0 mm, 
drug load: 10% w/w, n = 3±SE)
Figure 13

Effect of spheronization time on total pore surface area and mean pore of pellets. (pellet size: 2.0 mm, drug load: 10% w/w, n = 3±SE)
Figure 14

Schematic representation of the effect of spheronization time on the pore diameters and total number of pores.

Spheronization time: 2 minutes

Pores

10 minutes
Figure 15

Effect of spheronization time on drug released (%) from pellets. (pellet size: 2.0 mm, drug load: 10% w/w, n = 4±SE)
MANUSCRIPT IV

MULTI-UNIT CONTROLLED RELEASE SYSTEMS OF NIFEDIPINE AND NIFEDIPINE:PLURONIC® F-68 SOLID DISPERSIONS: CHARACTERIZATION OF RELEASE MECHANISMS
KEYWORDS

Nifedipine, Pluronic® F-68, Solid Dispersions, Extrusion/Spheronization, Controlled Release Matrix Pellets, Erosion, Diffusion, Eudragit® L100-55, Eudragit® S100.
Abstract

Nifedipine (N) and nifedipine:Pluronic® F-68 solid dispersion (SD) pellets were characterized for drug release mechanisms from a multi-unit erosion matrix system for controlled release. N was micronized using a jet mill. SD with Pluronic® F-68 was prepared by the fusion method. N and SD were characterized by particle size analysis, solubility, DSC and XRD studies. Samples were subsequently processed into matrix pellets by Extrusion/Spheronization using Eudragit® L 100 55 and Eudragit® S 100 as release rate controlling polymers. Drug release mechanisms from pellets were characterized by microscopy and mercury intrusion porosimetry. DSC and XRD studies indicated no polymorphic changes in N after micronization and also confirmed the formation of SD of N with Pluronic® F-68. Pellets of N showed a 24 hour drug release profile following zero order kinetics. Pellets of SD showed a 12 hour release profile following first order kinetics. Aqueous solubility of N after SD formation was found to be increased by 10 folds. Due to increased solubility of N in SD, the drug release mechanism was found to be changed from pure surface erosion to erosion/diffusion mechanism thereby altering the release rate/kinetics.
1.0 Introduction

Nifedipine is a poorly water-soluble drug and when administered orally in the crystalline form has poor bioavailability. For poorly soluble drugs, dissolution is the rate-limiting step for gastrointestinal absorption of the drug from solid dosage forms. Since dissolution rate is directly proportional to surface area, decreased particle size may increase the dissolution rate. Numerous attempts have been made to modify the dissolution characteristics of drugs to attain more rapid and complete absorption (1-5).

Controlled release Oros® tablets of nifedipine are commercially available. The drug releases in the form of a microfine suspension through a laser drilled hole in the tablet via osmosis following zero order kinetics for 24 hours. Osmotic controlled release multi-unit pellets and granules of nifedipine have also been reported (6).

The mechanism of polymer controlled surface erosion that provides a constant delivery of a poorly soluble drug via multi-unit erosion matrix was reported in our previous study (7). In such a system the drug release was found to be proportional to matrix erosion. Hence, matrix erosion could be used to predict drug release. This system consisted of Eudragit® L 100 55 and Eudragit® S 100 which were used as matrix forming and release rate controlling polymers. These are anionic polymers based on methacrylic acid and methacrylic acid esters. The ratio of carboxyl groups to ester units is about 1:1 in Eudragit® L 100 55 and about 1:2 in Eudragit® S 100. These polymers are soluble above pH 5.5 and 7.0 respectively. The model drug (nifedipine), Eudragits® and
polyvinylpyrrolidone (binder) were wet granulated and later pelletized using an Extrusion/Spheronization technique. The effects of dissolution stirring rate, polymer ratio, granulation water requirement, drug loading, pellet size and spheronization time on the release patterns were reported earlier (8).

Solid dispersions of poorly soluble drugs provide alternatives to increasing drug solubility and bioavailability. Law et al. (9) showed increased oral absorption and bioavailability of nifedipine-polyethylene glycol and nifedipine-phosphatidylcholine-polyethylene glycol solid dispersions in rats. Solid dispersions of nifedipine with different carriers such as urea, lactose, PEG 4000, 6000, 10000 and PVP K-30, K-90 have been studied by Sumnu et al. (10). However none of these solid dispersions were evaluated for their release patterns from the final controlled drug delivery system, and there are no studies determining the influence of solid dispersions on drug release mechanisms via solid dosage forms.

Release mechanisms of a drug from solid dosage forms may be related to the porosity. Porosity is a result of the presence of voids and pores in a sample where voids are the inter particulate spaces and pores are typically the crevices, cracks and fissures located in the particle (11). The porosity can be characterized by mercury porosimetry. The pore structure of a solid can provide valuable information regarding its dissolution and diffusion properties (12). Therefore, porosity and pore size distribution measurements have been extensively used to study tablets (13-18), granules (19-23) and pharmaceutical powders (24,25). Void porosity can be characterized by low pressure mercury
porosimetry (upto 30 psi) and is determined by calculating the pore volume diameter. In contrast, pores are analyzed by high pressure mercury porosimetry (upto 30,000 psi). According to this method, the cumulative volume of mercury intruded is a function of porosity, increased volumes indicate an increased porosity.

The present study was undertaken to develop, characterize and evaluate the multi-unit erosion matrix as described previously (7) with nifedipine and nifedipine:Pluronic® F-68 solid dispersion. A physical characterization of nifedipine solid dispersion by particle size analysis, aqueous solubility, DSC and XRD studies were conducted before they were pelletized. Later, pellets containing nifedipine or nifedipine:Pluronic® F-68 solid dispersions were prepared by a Extrusion/Spheronization technique. The effect of porosity parameters (cumulative intrusion volume, pore size distribution, pore volume diameter, total intrusion volume and total pore surface area) on dissolution time of the pelletized nifedipine and nifedipine:Pluronic® F-68 solid dispersion were determined to better explain the mechanism of drug release from controlled release matrix pellets and to determine the differences that were introduced by the nifedipine:Pluronic® F-68 solid dispersions.

2.0 Materials and methods

Nifedipine (USP/BP) was purchased from Vinchem, Inc, (Chatham, NJ, USA) and was micronized by using a Fluid Energy Aljet Mill (Plumsteadville, PA, USA). Inlet air pressure of 60 psig and grinding air pressure of 80 psig for micronization were used.
Eudragit® L 100 55, Eudragit® S 100 (Huls America, Inc., Somerset, NJ, USA), Kollidon® 90 F (BASF, Inc., Parsippany, NJ, USA), Avicel® PH 101 (FMC Corporation, Philadelphia, PA, USA), Triethyl Citrate (Morflex, Inc., Greensboro, NC, USA) and Pluronic® F-68 (BASF, Inc., Parsippany, NJ, USA). All other chemicals were used as received. Since nifedipine is sensitive to light, all experiments were performed under yellow light.

2.1 Particle size determination

Particle size determination was carried out with Master Sizer X, Malvern Instruments Inc., Southborough, MA, USA. An excess amount of drug was suspended in 1.0 % v/v Tween 80 in 100 mL of distilled water and was sonicated for 30 seconds for a thorough dispersion. This suspension was circulated at medium speed for particle size distribution studies.

2.2 Preparation of nifedipine: Pluronic® F-68 solid dispersions

Solid dispersion with different drug:pluronic ratios were prepared by the fusion method (26). The required amount of Pluronic® F-68 was weighed accurately and heated to 100° C until it formed a transparent melt. Nifedipine (mean particle size: 2.31 µm) was added to this melt in small portions with a constant stirring rate of 750 rpm. The temperature of the mixture was kept constant at 100° C. This mixture was stirred for 45 minutes until a clear transparent melt was formed. The melt was then poured on to a glass plate and was
allowed to solidify at room temperature. The solid mass was powdered and uniformly mixed in a mortar and 80/100 mesh (150-180 µm) particles were used for pelletization.

2.3 Solubility of nifedipine and nifedipine in Pluronic® F-68 solid dispersion

Solubility of nifedipine alone and nifedipine in the Pluronic® F-68 solid dispersion (1:1) was determined by placing an excess amount of sample in amber glass vials with 10 mL deionized water. The samples were then subsequently allowed to equilibrate at 25° C in an incubator shaker for 24 hours. Samples were filtered and the filtrate was analyzed for nifedipine by an HPLC method. A Waters 600E multi solvent delivery system (Waters Corporation, Milford, MA, USA) connected with a variable wavelength absorbance detector (Model Spectra 100, Spectra-Physics, USA) and a Waters 717 plus auto sampler (Waters Corporation, Milford, MA, USA) was used. The stationary phase consisted of a micro bondapak C18 reverse phase column (3.9 x 300 mm, Waters Corporation, Milford, MA, USA). Mobile phase used was acetonitrile : methanol : distilled water (2 : 3 : 5) and the flow rate was 1.0 mL/min with 30 minutes of total run time per injection. Nifedipine was detected at a retention time of 15.8 minutes. The sensitivity of the assay was 1 µg/mL. All studies were performed in triplicate.

2.4 Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies

DSC was carried out with a Seiko Instruments Inc., Japan, Model SSC5200 system. Approximately 10 mg of sample was placed in a hermetically sealed aluminium pan and
was scanned at the rate of 10° C/min from 0 to 200° C. Qualitative powder X-ray diffraction was performed by a Scintag X-Ray Diffractometer System, CA, USA by using nickel filtered copper potassium alpha radiation.

2.5 Preparation of pellets

Eudragit® L 100 55 and Eudragit® S 100 were mixed in a Turbula mixer (Impandex Inc., Maywood, NJ, USA) for 30 minutes. Triethyl citrate was added to this mixture as a plasticizer by triturating in a mortar. Nifedipine or nifedipine solid dispersion was then added followed by Kollidon® 90F used as a binder and they were mixed for 30 minutes in a Turbula mixer. The resultant mixture was then granulated with deionized water in a mortar. The granulate obtained was then fed through an extruder (LCI Xtruder, Model DG-L1 by Fuji Pauda Co., Ltd., Japan) which was equipped with a single screw and a screen of 2.0 mm size. Extrusion was conducted at 40 rpm. Extrudates obtained were immediately processed into pellets by spheronization (Spherizer: Model 120, G.B. Caleva Ltd, Dorset, England attached with a 2.0 mm cross hatched friction plate). The spheronization speed was maintained within 800-1000 rpm and spheronization time was limited to 10 minutes. During this process Avicel® PH 101 (5% w/w of total batch size) was sprinkled on to the pellets to prevent inter pellet sticking. Pellets thus obtained were dried on trays in a hot air convection oven for 12 hours at 50° C. They were then sieved (Rotap Sieve Shaker, Model RX-29, W.S. Tyler, Inc., OH, USA) to obtain 2.0 mm sieve fractions. The quantitative composition of the pellets formulated is given in Table I.
2.6 Determination of In Vitro drug release

In vitro dissolution was performed using USP XXII Apparatus I in 500 mL of pH 6.8 phosphate buffer with ionic strength of 0.05 M, at 50 rpm and 37.0 ± 0.5°C (Distek Inc., NJ, USA). Pellets obtained after dissolution were characterized for their shape and structure by an optical microscope by Nikon HFX, IA, Japan. Transverse sections of pellets obtained after 2 and 4 hour dissolution times were analyzed for the distribution of drug in the matrix.

2.7 Determination of porosity parameters

Pellet dissolution time as a function of cumulative intrusion volume of mercury, pore size distribution, pore volume diameter, total intrusion volume and total pore surface area were determined by mercury intrusion porosimetry. A Micromeritics PoreSizer Model 9320, Micromeritics Inc., Norcross, GA, USA was used for the determinations. Each sample was measured in triplicate.

3.0 Results and discussion

Results of particle size determination are tabulated in Table II. The solubility of nifedipine and nifedipine in the nifedipine:Pluronic® F-68 (1:1) solid dispersion was found to be 9.72±0.13 and 103.06±0.07 µg/mL respectively demonstrating that Pluronic® F-68 increased the solubility of nifedipine by approximately ten fold.
DSC thermograms and XRD pattern of micronized nifedipine indicated no changes in its thermodynamic and crystalline behaviour (Figures 1a and 1b). Data obtained indicates that nifedipine remained the same after micronization. Figures 2a and 2b are the thermograms of nifedipine:Pluronic® F-68 solid dispersions that were prepared in ratios of 1:0.5 w/w drug to polymer (T_m = 167.8° C, ΔH = 50.7 mJ/mg) and 1:1 w/w (T_m = 152.6° C, ΔH = 24.2 mJ/mg) respectively. From these thermograms it was clear that the melting point of nifedipine was reduced in the solid dispersion with consequent reduction in enthalpy. Figures 3a and 3b are XRD patterns of nifedipine:Pluronic® F-68 solid dispersions in ratios of 1:0.5 w/w and 1:1 w/w respectively. The characteristic nifedipine peaks were found to be reduced with increased concentration of Pluronic® F-68 in the solid dispersion. These results provide evidence of decreased drug crystallinity due to the formation of a solid dispersion. Similar results were reported for nifedipine solid dispersions with various other substances (9,10) such as polyethylene glycol, urea, lactose, polyvinylpyrrolidone etc.

A linear relationship of drug release via matrix erosion of a poorly soluble drug, similar to nifedipine, was described in our earlier study (7). The validity of this matrix erosion hypothesis was tested with nifedipine and nifedipine:Pluronic® F-68 solid dispersion pellets. The in vitro release profiles of nifedipine pellets before and after micronization and nifedipine:Pluronic® F-68 solid dispersion pellets are shown in Figure 4. Pellets prepared with nifedipine of three different particle sizes provided a zero order 24 hour drug release profile. On the other hand, drug release from the pellets prepared with nifedipine:Pluronic® F-68 solid dispersions was changed from zero to first order and the
release rates had significantly increased compared to the pellets prepared with nifedipine alone. Drug release rates from the solid dispersion pellets was increased as Pluronic® F-68 increased from 0.5 to 1.0 part in the solid dispersions. Dissolution from these pellets followed first order kinetics for about 12 hours for both the strengths. From Figure 4 it can also be concluded that particle size differences of nifedipine did not significantly influence the release pattern and rates from nifedipine pellets.

In order to understand the underlying release mechanism, the pellets collected at different time intervals during dissolution testing were analyzed under the microscope. Figure 5 shows pellets prepared with nifedipine:Pluronic® F-68 (1:1) solid dispersion after 12 hours of dissolution. The size of the pellets was decreased due to surface erosion. Nifedipine pellets also eroded in a similar fashion over a period of 24 hours. Both these pellets maintained their geometrical shape but were reduced in size. Furthermore, pellets of nifedipine and nifedipine:Pluronic® F-68 (1:1) solid dispersion that were removed from the dissolution medium on the 2 and 4 hours of dissolution were dried at 50° C for 12 hours and transverse sections of these pellets were investigated. After 4 hours the pellets became very soft which made it impossible to obtain the transverse. Transverse sections of nifedipine pellets (Figures 6a and 6b) showed that the drug remained uniformly distributed in the matrix at 2 and 4 hours, whereas nifedipine:Pluronic® F-68 (1:1) solid dispersion pellets showed release of the drug from the core by diffusion. The increased aqueous solubility of drug in the solid dispersion explains the enhanced erosion and release rates from nifedipine:Pluronic® F-68 solid dispersion pellets as compared to nifedipine pellets. Increased aqueous solubility had also increased the release of drug
from the pellets of solid dispersion which occurred by erosion and simultaneous diffusion from the matrix. Whereas release of drug from nifedipine pellets was purely by erosion mechanism.

To further confirm the release mechanisms of both the pellets, their porosity parameters were measured and determined by mercury intrusion porosimetry. The porosities were determined after the pellets were exposed to 2, 4, 6 and 8 hours of dissolution media. Figures 7a and b show the cumulative intrusion volume of mercury against pore diameters obtained at different dissolution intervals of nifedipine and nifedipine:Pluronic® F-68 solid dispersion pellets, respectively. Figures 8a and b show changes in the pore size distribution during dissolution. Figure 7a shows that the cumulative intrusion volumes of mercury for nifedipine pellets following dissolution at 2 to 8 hours mainly remain constant with minimal changes, whereas from Figure 7b, pellets of nifedipine:Pluronic® F-68 solid dispersion showed increased pores as the dissolution time increased from 2 to 8 hours. Further from Figure 8a, a trimodular pore size distribution is observed with maximum pores lying within the range of 0.1 to 0.01 µm indicating that the voids and fine pores contribute to the overall porosity of the pellets with the pores occupying a much higher volume than the voids. A reverse pore size distribution was observed (Figure 8b) for pellets of nifedipine:Pluronic® F-68 (1:1) solid dispersion indicating that the overall porosity was due to the voids which were increasing with dissolution time. Figure 9 shows the effect of dissolution time on the pore volume diameter of the pellets. No significant changes were observed in the pore volume diameters of nifedipine pellets indicating no increase in void porosity during the
dissolution period of 8 hours, whereas pore volume diameters of pellets formulated with nifedipine:Pluronic® F-68 (1:1) solid dispersions increased with dissolution time indicating an increase in the void porosity which is the result of increased void diameters. This increase may be due to the enhanced solubility of drug in the solid dispersion which diffused out of the matrix. Figure 10 shows the total intrusion volumes that were obtained at different dissolution times that summarizes the overall effect of dissolution time on pellet porosity. From this Figure the porosity of nifedipine:Pluronic® F-68 solid dispersion pellets increased linearly with dissolution time whereas, the porosity of nifedipine pellets did not change significantly. Total pore surface area is the cumulative surface area of all the pores and voids present in a sample. Figure 11 shows the total pore surface area against dissolution time. The total pore surface area of nifedipine:Pluronic® F-68 solid dispersion pellets increased linearly from 2 to 8 hours of dissolution time. This maybe due to the formation of voids and pores as nifedipine and pluronic was diffusing out of the matrix. However, it is postulated that the total pore surface area is being reduced during dissolution because the size of the pellets becomes smaller. Such a phenomenon can only occur if surface erosion is the only mechanism of release which in fact was observed with nifedipine pellets. Their total surface area decreased linearly with dissolution time (Figure 11). This confirms that surface erosion is the release mechanism of nifedipine pellets. In addition, the results demonstrated in Figure 11 strongly indicate that upon incorporation of a poorly soluble drug like nifedipine in erosion matrix pellet systems, a zero order release for 12-24 hours as described previously (7) is obtained. However, a change in the physical properties and solubility of the drug as it occurs with nifedipine:Pluronic® F-68 solid dispersions alters the release profile and kinetics.
4.0 Conclusions

In conclusion, controlled release of nifedipine (poorly soluble drug) following zero order kinetics for 24 hours from a multi-unit erosion matrix was achieved. It was proved that multi-unit erosion matrix systems as described earlier (7) are universal in their application for controlled release of poorly soluble drugs. Drug release from nifedipine pellets occurred by matrix erosion. Whereas for pellets of nifedipine:Pluronic® F-68 solid dispersion, release occurred by a combination of matrix erosion and diffusion mechanisms for 12 hours following first order kinetics. The solubility of nifedipine was increased by 10 times due to solid dispersion formation in 1:1 nifedipine:Pluronic® F-68 ratio. Porosity parameters studied by mercury intrusion porosimetry proved that drug release was not influenced by the porosity for nifedipine pellets, however the drug release was predominantly porosity controlled for nifedipine:Pluronic® F-68 solid dispersion pellets.

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Table 1: Composition of pellets prepared with nifedipine and nifedipine:Pluronic\textsuperscript{®} F-68 solid dispersions.

| Formulation Type | Nifedipine (% w/w) | Kollidon\textsuperscript{®} 90F (% w/w) | Eudragit\textsuperscript{®} L 100 55 : S 100 ratio (% w/w) | * Plasticizer (% w/w) |
|------------------|---------------------|-----------------|-----------------------------|---------------------|
| nifedipine pellets D(\nu, 50) = 7.06 \mu | 20.00 | 2.00 | 1 : 3 | 11.70 |
| nifedipine pellets D(\nu, 50) = 2.66 \mu | 20.00 | 2.00 | 1 : 3 | 11.70 |
| nifedipine pellets D(\nu, 50) = 2.31 \mu | 20.00 | 2.00 | 1 : 3 | 11.70 |
| nifedipine:Pluronic\textsuperscript{®} F 68 SD pellets (1:1) | 20.00 | 2.00 | 1 : 3 | 11.70 |
| nifedipine:Pluronic\textsuperscript{®} F 68 SD pellets (1:0.5) | 20.00 | 2.00 | 1 : 3 | 11.70 |

* Triethyl citrate (15% w/w of Eudragit\textsuperscript{®} L 100 55 + Eudragit\textsuperscript{®} S 100)
Table 2: Results of Particle Size of Nifedipine and Nifedipine in Pluronic F-68 solid dispersions.

| SAMPLE                                      | D(V, 0.5) (µ) | D(V, 0.9) (µ) |
|---------------------------------------------|---------------|---------------|
| Nifedipine                                  | 7.06          | 17.29         |
| Nifedipine micronized once                  | 2.87          | 8.72          |
| Nifedipine micronized twice                 | 2.31          | 6.96          |
| Nifedipine:Pluronic® F-68 (1:1) SD          | 3.10          | 12.93         |
| Nifedipine:Pluronic® F-68 (1:0.5) SD        | 2.66          | 8.40          |

* 50th percentile mean volume particle size.

** 90th percentile volume particle size.
Figure 1a

Melting point endotherms of nifedipine before and after micronization

micronized

Tm = 174.7 °C  ΔH = 103.5 mJ/mg

unmicronized

Tm = 174.7 °C  ΔH = 103.3 mJ/mg
Figure 1b

X-ray diffraction pattern of nifedipine before and after micronization.
Figure 2a

Melting point endotherm of nifedipine:pluronic F-68 solid dispersion (1:0.5)
Figure 2 b

Melting point endotherm of nifedipine:pluronic F-68 solid dispersion (1:1)
Figure 3 a

X-ray diffraction pattern of nifedipine:pluronic F-68 solid dispersion (1:0.5)
Figure 3 b

X-ray diffraction pattern of nifedipine:pluronic F-68 solid dispersion (1:1)
Effect of nifedipine mean particle size and ratio of nifedipine:pluronic F-68 solid dispersion on the release profiles obtained with 2.0 mm pellets.

(spheronization time: 10 minutes, n = 4±SE)
Figure 5

Microscopical evaluation of nifedipine:pluronic F-68 (1:1) solid dispersion pellets after dissolution time intervals.

A. 0 hours  B. 2 hours  C. 4 hours
D. 6 hours  E. 8 hours  F. 10 hours
Figure 6a

Transverse section of nifedipine pellets after 2 and 4 hour dissolution time intervals showing uniform drug distribution in the matrix.
Figure 6 b

Transverse section of nifedipine:pluronic F-68 (1:1) solid dispersion pellets after 2 and 4 hour dissolution time intervals showing drug diffusion through the matrix.
Figure 7
Cumulative intrusion profiles of nifedipine and nifedipine:pluronic F-68 solid dispersion pellets during dissolution.

a. Nifedipine Pellets
- 2 hours
- 4 hours
- 6 hours
- 8 hours

b. Nifedipine:Pluronic Solid Dispersion Pellets (1:1)
- 2 hours
- 4 hours
- 6 hours
- 8 hours

PORE DIAMETER (μm)
Figure 8

Pore size distribution of nifedipine and nifedipine:pluronic F-68 solid dispersion pellets during dissolution. (spheronization time: 10 minutes, n = 4±SE)
Figure 9

Changes in the pore volume diameter of pellets during dissolution.

![Graph showing the changes in pore volume diameter of pellets during dissolution. The graph compares Nifedipine to Nifedipine Pluronic Solid Dispersion (1:1).]
Changes in the total intrusion volume of pellets at various dissolution intervals.

Figure 10

Changes in the total intrusion volume of pellets at various dissolution intervals.

Nifedipine Pluronic F-68 Solid Dispersion (1:1)

0.6

Nifedipine

DISSOLUTION TIME (hours)
Effect of dissolution time on the changes in total pore surface area of the pellets.

Figure 11

Effect of dissolution time on the changes in total pore surface area of the pellets.
MANUSCRIPT V

NIFEDIPINE BIOAVAILABILITY IN FASTED DOGS FROM AN ERODING MULTI-UNIT MATRIX SYSTEM
KEYWORDS

Nifedipine Erosion Matrix Pellet Capsules, Adalat® Soft Gelatin Capsules, In Vivo, Beagle Dogs, Pharmacokinetic Parameters, Bioavailability, Eudragit® L 100-55, Eudragit® S 100.
ABSTRACT

The development, characterization and in vitro evaluation of a novel multi-unit erosion matrix pellet system of nifedipine was described earlier. The purpose of this study was to evaluate in vivo performance of the erosion matrix pellets prepared with nifedipine and compare their bioavailability with nifedipine immediate release soft gelatin capsules (Adalat® 10mg and 20 mg gelcaps administered together as one dosage form) in fasted dogs. A randomized two way comparative cross-over design was employed for bioavailability studies and four dogs were used. Blood samples were collected over predetermined time intervals up to 12 or 24 hours and analyzed for nifedipine plasma concentrations by an HPLC method for both the dosage forms. Data obtained was fitted to a non-compartmental pharmacokinetic model to determine parameters such as C_max, T_max, AUC_0-24 h, and MRT_0-24 h. Results indicated that the bioavailability of nifedipine erosion matrix pellets was four times higher than Adalat® gel caps. Nifedipine was detected in plasma within one hour of administration of erosion matrix pellets, thus no significant lag time was observed. Nifedipine multi-unit erosion matrix pellets showed controlled release for more than 24 hours following zero order kinetics.
1.0 Introduction

Nifedipine is a calcium antagonist which is widely used as a coronary dilator in hypertension. Clinical studies have shown that the hypotensive effect of this drug could be correlated with the plasma nifedipine [1]. It is therefore important to prolong the plasma concentrations so as to control and regulate the therapeutic effects of nifedipine over a longer duration. Nifedipine is a poorly soluble drug and its absorption in GIT is rate limited. It has a short biological half life of about 2.3 hours. When administered orally via solid dosage forms, absorption of nifedipine is poor.

Nifedipine is commercially available as soft gelatin capsules and tablets for short term and extended treatments. Controlled release nifedipine is available as an extended release film coated tablet and also as a GITS system. The extended release film coated tablet contains a tablet core coated by a slow releasing layer comprising of the drug and the hydrophilic polymers such as hydroxypropylcellulose and hydroxypropylmethylcellulose. The outer slow releasing layer provides the initial drug release followed by rapid drug release from the tablet core. Drug release from such a tablet typically follows first order kinetics. One of the most desirable outcome in controlled drug delivery is to achieve zero order kinetics in vivo so as to obtain a constant therapeutic effect of the drug for a maximum duration. This is achieved by the nifedipine GITS system for controlled delivery.
The GITS system releases finely powdered nifedipine in a suspension form into the gastrointestinal lumen at a controlled rate over a 24 hour period. The release mechanism involves a “push-pull” process. As water is absorbed across the semi-permeable membrane surrounding the bilayer tablet, nifedipine particles become suspended in solution and are then “pushed” into the intestinal tract as the osmotically active polymers expand. Hydration of the GITS tablet occurs for approximately 2 hours before substantial amounts of nifedipine is detected in plasma. Dose dumping of nifedipine does not occur from the GITS system however approximately 10% of the total GITS tablet content remains unabsorbed after the tablet is emptied [2]. The dosage forms described above are examples to current nifedipine formulations that are available commercially for controlled delivery.

The development, characterization and evaluation of a novel multi-unit erosion matrix pellet system of nifedipine was described elsewhere [3]. It was designed to release a poorly soluble drug by surface erosion as a consequence of the polymer erosion from the matrix pellets. The drug release mechanism from this system is illustrated schematically in Figure 1. In vitro evaluation of this system in pH 6.8 phosphate buffer demonstrated zero order drug release in 24 hours [4].

The purpose of this study was to determine the bioavailability and pharmacokinetic parameters such as C_{max}, T_{max}, AUC_{0-24 h}, and MRT_{0-24 h} of nifedipine from this novel erosion matrix pellet system and compare the bioavailability with Adalat® immediate
release soft gelatin capsules used as a control in a randomized two way cross over design in four fasted dogs.

2.0 Materials and methods

Nifedipine was purchased from Vinchem Inc., Chatham, NJ. Eudragit® L 100 55 and Eudragit® S 100 (polymethacrylic acid esters) were provided as samples by Huls America Inc., Somerset, NJ. Kollidon® 90 F (polyvinylpyrrolidone) was obtained from BASF Inc., Parsippany, NJ. Avicel® PH 101 (microcrystalline cellulose) was purchased from FMC Corporation, Philadelphia, NJ. Triethyl citrate was provided as a sample by Morflex Inc., Greensboro, NC. Butamben (n-butyl-p-amino benzoate) was provided as a free gift by Abbott Laboratories, North Chicago, IL. Methanol and acetonitrile (HPLC grade), chloroform, acetone, 0-phosphoric acid (80% v/v) were purchased from Fisher Scientific., Springfield, NJ. All the chemicals were used as received.

All work was carried out under yellow light. Turbula mixer (Impandex Inc., Maywood, NJ, USA) was used for mixing dry powders. Extruder utilized was LCI Xtruder, Model DG-L1, Fuji Paudal Co., Ltd., Japan. (Single screw extruder, capable of extruding at speeds upto 100 rpm, with variable screens to obtain extrudates of different size). The Spheronizer used was a G.B. Caleva Ltd, Model 120, Dorset, England. [It consists of a stationary vertical cylinder which has at the base a friction plate (diameter 32 cm) with a 2 mm cross hatched friction pattern and a rotation speed of 200-3000 rpm]. Rotap Sieve Shaker, Model RX-29, W.S. Tyler, Inc., OH (Fitted with sieve # 8, 10, 12, 14, 16, 18 and
20) was utilized to collect pellets of the desired particle size. In vitro analysis of the pellets was performed in a Hewlett Packard 8452A Diode Array Spectrophotometer (Hewlett Packard Company, Paramus, NJ).

A vortex Mixer with 40 test tube holding capacity Model Typ VX 2V (IKA® Works, Inc., Cincinnati, OH) was used to equilibrate the frozen blood samples at room temperature prior to analysis. Fisher Vortex Genie 2™ with 40 micro-centrifuge tube holding capacity (Scientific Industries, Inc., Bohemia, NY) was utilized for sample processing. A Centrifuge, Model HN-S II (International Equipment Company, Needham Heights, MA) for separation of plasma proteins after drug extraction from the blood samples was used. TurboVap® LV Evaporator with nitrogen gas pressure of 1.0 bar (Zymark Corporation, Hopkinton, MA) was used as a sample concentrator for the assay.

2.1 Formulation of pellets

Eudragit®L 100 55 and Eudragit®S 100 powders were mixed in a turbula mixer for 30 minutes. Triethyl citrate was added as a plasticizer and the resultant mixture was triturated in a mortar for 5 minutes. Drug and polyvinyl pyrrolidone (Kollidon®K90F) used as a binder, were added and mixed for 30 minutes in a turbula mixer. This mixture was then granulated in a mortar with deionized water and later extruded at 40 rpm screw speed. The extrudates were immediately transferred into a rotating plate in the spheronizer. Spheronization was carried out for 10 minutes at 800-1000 rpm. During this period, 5% w/w of total batch size Avicel® PH 101 was sprinkled over the rotating
extrudates to prevent pellets from sticking. Pellets obtained were dried on trays at 50°C for 12 hours. The pellets consisted of nifedipine (20.0% w/w), Eudragit®L 100 55 and Eudragit® S 100 (78.0% w/w total in ratio of 1:3 respectively) and Kollidon®K90F (2.0% w/w). Granulation water level used was 58% w/w of the total batch size. Pellets (150 mg) were filled in a size 2 blue colored capsule before they were administered to the animals.

2.2 Assay of nifedipine in pellets

Nifedipine content of the pellets was determined by UV spectrophotometry. The pellets (100 mg) were dissolved in 100 mL of methanol and the resultant solution was diluted to obtain 10 ug/mL nifedipine concentration. This solution was analyzed spectrophotometrically at 237 nm and nifedipine content of 100 mg of pellets was determined.

2.3 In vivo absorption study design and protocol

2.3.1 Test animals

The bioavailability of nifedipine pellets was tested on beagle dogs using a randomized two way comparative cross-over design.

Dogs were supplied by Marshall Farms, North Rose, NY. They were acclimatized for at least two weeks prior to the study and were approximately 9-14 kg in weight and one year
old in age. The study group consisted of two males and two females. Each dog had an ear tattoo for identification and was housed individually in a stainless steel cage. Each cage had an identification card showing the study number, dog number and sex. Room temperature and humidity was maintained at approximately $72^\circ \pm 4^\circ$ F and $50\% \pm 20\%$ respectively. During the experiments, the animal room was kept on an approximate 12 hour light/dark cycle. Each dog was exercised outside its cage at least three times a week for at least 15 minutes.

2.3.2 Dosage forms administered, frequency and method of dosing

The bioavailability of nifedipine erosion matrix pellets, (30 mg capsules, Lot No. KM 280/2) was tested against an immediate release soft gelatin capsule (Adalat®, 10 mg gelcaps, Lot No 6EAB and 20 mg, Lot No 5 HAX, manufactured by Bayer Corporation, West Haven, CT). All the test articles were stored in a locked area at ambient temperature protected from light.

The dogs were fed with Harlan-Teklad certified 25% lab dog diet (W). Approximately 800 grams diet (approximately 400 grams of dry dog food moistened with approximately 400 mL of water) was provided to the dogs 8 hours after dosing. Reverse osmosis (RO) water was available ad libitum by means of an automatic watering system. This RO water supply for the animal room was monitored for bacterial contamination at least once a month by the Department of Laboratory Animal Resources. In addition, chemical analysis of water was performed at approximately quarterly intervals by the
Environmental Monitoring and Support Laboratory. No contaminants expected to interfere with the study were known to be present in the feed or water.

Each dog received one 30 mg nifedipine erosion matrix pellets capsule or 10 plus 20 mg Adalat® soft gelatin capsules in fasted state. Following a one week washout period, each dog received a different formulation in phase two. The experimental protocol details are given in Table I.

2.3.3 Blood sampling

Blood samples (6 mL) were taken from each dog at 0, 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours after dosing for the nifedipine erosion matrix pellets. Blood samples from dogs who received Adalat® soft gelatin capsules were collected at 0, 0.5, 1, 2, 4, 6, 8 and 12 hours after dosing. The samples collected were transferred into test tubes containing lithium heparin, used as an anticoagulant, and to prevent decomposition they were placed in an ice bucket prior to centrifugation. Plasma was separated after cold centrifugation and was frozen in amber glass vials at -20°C under yellow light before analysis.

2.4 Assay of Nifedipine in Plasma

Nifedipine in all samples was assayed using a modified version of the HPLC method described by Miyazaki et al [5].

2.4.1 Processing Blood Samples for HPLC
Methanol (100 µl) containing 2 µg/mL butamben, used as an internal standard and acetonitrile (2 mL) were added to 0.5 mL of plasma in a test tube and were agitated in a vortex mixer for 30 minutes. After centrifugation at 4000 rpm for 20 minutes, 2 mL of the supernatant was transferred into a test tube containing 1 mL of distilled water, to this solution 4.5 mL of acetone-chloroform mixture (1:1 v/v) was added. This mixture was agitated for 1 hour on a vortex mixture to ensure complete extraction of nifedipine into the organic phase and was then centrifuged at 4000 rpm for 20 minutes to separate the organic and aqueous phases. The aqueous phase was discarded and 5 mL of the organic phase was transferred to a fresh test tube, and was reduced to dryness in a sample concentrator under nitrogen at 45° C for 30 minutes. The residue was dissolved in 100 µl of the mobile phase and 20 µl of the solution was injected into the HPLC system.

2.4.2 Chromatographic Conditions

HPLC pump used was a Waters multi-solvent delivery system (Waters Corporation, Milford, MA) with a Waters 717 plus auto-sampler (Waters Corporation, Milford, MA) and a variable wavelength absorbance detector (Model Spectra-Physics, USA). The stationary phase used was a reverse phase Zorbax ODS, 4-6 microns 25 cm x 4.6 mm column (I.D., Dupont Inc., Wilmington, DE). The column was warmed at 55° C using a steel column heater (Model Code 600, Waters Corporation, Milford, MA). The mobile phase consisted of 0.01 M disodium hydrogen phosphate buffer-methanol (45:55). Before mixing, the buffer was brought to pH 6.1 with 50% phosphoric acid. Run time used was 30 minutes and the flow rate was 0.8 mL/min at column pressure of approximately 1200 psi. The wavelength of detection was 237 nm.
2.4.3 Calibration Graph

Standard solutions containing 0.05, 0.1, 0.2, 0.4, 0.6, 0.8, 1.0 and 10.0 μg/mL nifedipine in methanol that contained 2 μg/mL butamben (internal standard) were prepared under yellow light. The standard solution (100 μl) was added to 0.5 mL of drug free plasma and the samples were processed as described above. The ratios of the peak height of nifedipine to that of butamben were used to construct a calibration graph. Stock solutions of both nifedipine and the internal standard (1 mg/mL in methanol) were stored in complete darkness; these solutions were freshly prepared every 2 weeks. Precision obtained using the described technique was ±5%.

2.5 Pharmacokinetic Analysis

The most suitable model to describe the pharmacokinetics of nifedipine was determined by fitting the data to a hierarchy of models using WinNonlin software. The data most appropriately fitted to a non-compartmental model and pharmacokinetic parameters such as $C_{\text{max}}$, $T_{\text{max}}$, $\text{AUC}_{0-24} \text{ h}$ and $\text{MRT}_{0-24} \text{ h}$ (mean residence time) were calculated by a computer using WinNonlin software by Scientific Consulting Incorporated (Lexington, KY).

3.0 Results and Discussion
The UV assay demonstrated that nifedipine erosion matrix pellets administered to the dogs contained 98 - 102 % of the original nifedipine loading. The Adalat® soft gelatin capsules were not assayed for nifedipine content. Nifedipine plasma concentrations obtained after dosing with Adalat® soft gelatin capsules and nifedipine matrix erosion pellets are tabulated in Tables II and III respectively. Table IV shows the mean pharmacokinetic parameters (C\text{\text{max}}, T\text{max}, \text{AUC}_{0-24\ h}, \text{MRT}_{0-24\ h}) determined for both dosage forms. Figure 2 shows the nifedipine plasma concentration profile for 24 hours following administration of the pellets and the immediate release capsules. The mean T\text{max} for nifedipine erosion matrix pellets from Table IV was 15.50 hours whereas for Adalat® capsules was 0.5 hours. This indicated that time taken to reach maximum plasma nifedipine concentrations was 15.5 hours thus providing controlled release of the drug. The MRT_{0-24\ h} was 12.5 hours for the pellets and 1.72 for the Adalat® capsules, indicating the presence of pellets in the GIT was prolonged. The mean AUC_{0-24\ h} of the pellets was four times higher than the conventional immediate release Adalat® soft gel capsules.

Adalat® capsules contain nifedipine in the solubilized form in a polyethylene glycol based co-solvent system. The bioavailability from Adalat® 20 mg soft gelatin capsules was reported earlier by Sallam et.al. [6]. Accordingly, the lower AUC obtained with Adalat® soft gelatin capsules might be due the precipitation of the poorly soluble nifedipine in the gastric fluid. As a result the particle size of nifedipine may also have increased, which can be the cause of reduced nifedipine absorption.
Nifedipine release from the matrix pellets is governed by the polymer controlled surface erosion process. In this mechanism, drug release occurs in a constant fashion in the form of a microfine suspension in the gastrointestinal tract and thus is readily available for a prolonged period. It is also interesting to observe that the nifedipine plasma concentrations were obtained one hour after administration without any significant lag time, Figure 2. The pellet matrix contains Eudragit® L 100 55 and Eudragit® S 100 polymers which dissolve at pH 5.5 and pH 7.0 respectively. Considering that the pellets were very small multi-unit systems (particle size: 2.00 mm), they are expected to have a small gastric residence time after which exposure to pH 5.5 and higher pH's may have caused the pellets to release the drug. The most significant effect that is shown in Figure 2 is that nifedipine release from the multi-unit pellets continued for over 24 hours. Thus, the elimination rate constants could not be calculated for this period.

4.0 Conclusions

Controlled delivery of nifedipine via polymer controlled surface erosion of nifedipine provided zero-order drug release both in vitro and in vivo for 24 hours. Bioavailability from the controlled release pellet system was four times more than the conventional immediate release Adalat® soft gelation capsules of nifedipine.

Thus it was demonstrated that the surface erosion mechanism may be used in pellets to obtain a controlled release system that delivers a poorly soluble drug like nifedipine effectively and in a constant fashion.
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Table I:  In vivo absorption study protocol details

| Dosage Form                        | Condition | Dose (mg/dog/day) | No. of Tablets/Capsules | Males | Females |
|-----------------------------------|-----------|-------------------|-------------------------|-------|---------|
| Phase I                           |           |                   |                         |       |         |
| Nifedipine Erosion Matrix Capsules| Fasted    | 30                | 1                       | 1-2   | 3-4     |
| One week Washout period           |           |                   |                         |       |         |
| Phase II                          |           |                   |                         |       |         |
| Adalat Soft Gelatin Capsules      | Fasted    | 30                | 2                       | 1-2   | 3-4     |
Table II: Nifedipine plasma concentrations (12 hours) obtained in dogs (n = 4) after administration of Adalat® soft gelatin capsules (30 mg/dog/day).

| Time (hours) | Nifedipine Levels (µg/mL) | Plasma Levels (µg/mL) | Mean ± SD |
|--------------|---------------------------|-----------------------|-----------|
| Dog I        | Dog II                    | Dog III               | Dog IV    |               |
| 0.0          | 0.0000                    | 0.0000                | 0.0000    | 0.0000 ± 0.0000 |
| 0.5          | 0.2216                    | 2.2628                | 0.6358    | 1.6288 ± 1.1872 ± 0.9288 |
| 1.0          | 0.2079                    | 0.6548                | 0.2530    | 0.7226 ± 0.4595 ± 0.2666 |
| 2.0          | 0.2097                    | 0.2387                | 0.0940    | 0.3394 ± 0.2204 ± 0.1009 |
| 4.0          | 0.0897                    | 0.0648                | 0.0518    | 0.1293 ± 0.0839 ± 0.3410 |
| 6.0          | 0.0365                    | 0.0321                | 0.0215    | 0.0494 ± 0.0348 ± 0.0115 |
| 8.0          | 0.0243                    | 0.0000                | 0.0307    | 0.0228 ± 0.0194 ± 0.0134 |
| 12.0         | 0.0387                    | 0.0000                | 0.0239    | 0.0000 ± 0.0156 ± 0.0190 |
Table III: Nifedipine plasma concentrations (24 hours) obtained in dogs (n = 4) after administration of matrix erosion pellets capsule (30 mg/dog/day).

| Time (hours) | Nifedipine Levels (µg/mL) | Plasma Levels (µg/mL) |
|-------------|---------------------------|----------------------|
|             | Dog I | Dog II | Dog III | Dog IV | Mean ± SD |
| 0.0         | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 ± 0.0000 |
| 1.0         | 0.0000 | 0.1331 | 0.1536 | 0.3551 | 0.1604 ± 0.1465 |
| 2.0         | 0.1333 | 0.0933 | 0.0699 | 0.4714 | 0.1919 ± 0.1881 |
| 4.0         | 0.0586 | 0.0952 | 0.0867 | 0.3419 | 0.1456 ± 0.1317 |
| 6.0         | 0.1454 | 0.1617 | 0.7161 | 0.0953 | 0.2796 ± 0.2923 |
| 8.0         | 0.0727 | 0.0674 | 0.7945 | 0.1438 | 0.2696 ± 0.3516 |
| 12.0        | 0.1252 | 0.1035 | 0.6778 | 0.0733 | 0.2449 ± 0.2893 |
| 16.0        | 0.1636 | 0.1654 | 0.8409 | 0.0985 | 0.3171 ± 0.3505 |
| 20.0        | 0.1869 | 0.1858 | 0.8629 | 0.1449 | 0.3466 ± 0.3487 |
| 24.0        | 0.1192 | 0.1275 | 0.4665 | 0.0386 | 0.1879 ± 0.1899 |
Table IV: Mean pharmacokinetic parameters of nifedipine matrix erosion pellets and Adalat® soft gelatin capsules obtained by non-compartmental analysis in four beagle dogs.

| Dosage Form            | $C_{max} \pm SE$ ($\mu g/mL$) | $T_{max} \pm SE$ (h) | $AUC_{0-24h} \pm SE$ ($\mu g \cdot h/mL$) | $MRT_{0-24h} \pm SE$ (h) |
|------------------------|-------------------------------|----------------------|---------------------------------------|-------------------------|
| Nifedipine Matrix      | 0.4268 ± 0.1602               | 15.5000 ± 4.5000     | 6.1123 ± 2.8690                       | 12.5561 ± 1.2853        |
| Erosion Pellets        |                               |                      |                                       |                         |
| Adalat® Soft Gelatin   | 1.1873 ± 0.4644               | 0.5000 ± 0.0000      | 1.5049 ± 0.3980                       | 1.7280 ± 0.2959         |
| Capsules               |                               |                      |                                       |                         |
Schematic representation of a novel multi-unit erosion matrix for controlled release of a poorly soluble drug.

Figure 1

0 to 24 hours

in vitro

matrix pellet

eroding layer

intact matrix pellet
SECTION III

- Appendix 1, 2, 3a, 3b, 3c and 4.

- Complete listing of references cited.
APPENDICES

1. Solubility studies of nifedipine and nifedipine:pluronic® F-68 solid dispersion (1:1) in water at 25°C.

2. Particle size determination of nifedipine samples before and after micronization and after formation of solid dispersions with pluronic® F-68.

3. Determination of porosity parameters by mercury intrusion porosimetry.
   (a) Pellets formulated with different drug (D₄ Leukotriene antagonist) loads and spheronized at different times.
   (b) Pellets formulated with different granulation water levels.
   (c) Nifedipine and nifedipine:pluronic® F-68 (1:1) solid dispersion pellets after different dissolution time intervals.

4. Determination of nifedipine in plasma after oral administration of nifedipine erosion matrix pellet capsule and Adalat® soft gelatin capsule in fasted dogs.
Appendix 1

Solubility studies of nifedipine and nifedipine pluronic® F-68 solid dispersion (1:1) in water at 25°C.
HPLC METHOD VALIDATION:

SOLUBILITY DETERMINATION OF NIFEDIPINE AND NIFEDIPINE:PLURONIC®

F-68 SOLID DISPERSION (1:1) IN WATER AT 25°C EQUILIBRATED FOR 24 HOURS

1. SOURCE of STANDARD:

Nifedipine, Lot # 9S1172, was purchased from Vinchem Inc., Chatham, NJ, USA.

Pluronic® F-68, Lot # 22415, was obtained as a gift from BASF Inc., Parsippany, NJ, USA.

2. HPLC METHOD:

System:

Pump: Waters 600E Multi-Solvent Delivery System

Injector: Waters 717 Plus Auto Sampler

Column: Micro Bondapack C<sub>18</sub> Reverse Phase, 3.9 x 300 mm, Waters Corp.

Detector: Model Spectra 100, Spectra-Physics, UV/VIS

Parameters:

Flow Rate: 1.0 mL/min

Injection Vol: 20 µL

Temperature: Ambient

Detector: λ<sub>max</sub> 237 nm, 0.01 AUFS
Solutions:

Mobile Phase:

In a suitable flask combine 200 mL of acetonitrile, 300 mL of methanol and 500 mL of distilled water. Mix well and degas under vacuum for 10 minutes. Filter through a 0.5 µ Millipore filter, or equivalent, before use.

3. REPRESENTATIVE CHROMATOGRAMS:

Figures 1 through 3 are the chromatograms of nifedipine samples after injection. Figures 4 and 5 are the chromatograms of nifedipine:pluronic® F-68 solid dispersion (1:1) samples after injection.

4. LINEARITY:

The linearity of nifedipine in the mobile phase was determined by simple linear regression. Figure 6 depicts the standard curve and linear regression of nifedipine in mobile phase.

The following concentrations were used for linearity determinations.

| Solution # | Concentration in mobile phase (µg/mL) |
|------------|----------------------------------------|
| 1          | 1.0012                                 |
| 2          | 5.0024                                 |
| 3          | 10.0800                                |
| 4          | 100.7600                               |
Correlation coefficient for linearity determinations in mobile phase was 1.0000.

5. PRECISION:

Assay precision was determined by plotting the peak areas of triplicate injections of nifedipine samples of known concentration against the standard curves generated in the previous section. The mean % difference between the actual concentration of the samples and that determined by the standard curve were below 4.0 %.
Figure 1

Chromatogram of nifedipine solubility sample 1

| Peak name | R.T. (min) | T.Diff | mg/mL | Peak Area | Ref Std | BL Group |
|-----------|-----------|--------|-------|-----------|---------|----------|
| Nifedipine| 13.725    |        |       | 376       | BB      |          |
|           | 15.156    | 26.61  | 1.19E-04 | 260738    | S       | BB       |
|           | 17.203    | 139    |       | 309       | BV      | VB       |
|           | 17.601    |        |       |           |         |          |
Figure 2

Chromatogram of nifedipine solubility sample 2

| Peak name | R.T. (min) | T.Diff | mg/mL | Peak Area | Ref Std | Bl | Group |
|-----------|------------|--------|-------|-----------|---------|----|-------|
|           |            |        |       |           |         |    |       |
| 0.939     |            |        |       | 119       | BA      |    |       |
| 1.198     |            |        |       | 169       | BV      |    |       |
| 1.349     |            |        |       | 1006      | BV      |    |       |
| 1.666     |            |        |       | 1638      | BV      |    |       |
| 2.023     |            |        |       | 5482      | BV      |    |       |
| 2.283     |            |        |       | 2734      | BV      |    |       |
| 2.433     |            |        |       | 939       | BV      |    |       |
| 2.999     |            |        |       | 1056      | BV      |    |       |
| 3.444     |            |        |       | 886       | BV      |    |       |
| 4.440     |            |        |       | 270       | BV      |    |       |
| 4.804     |            |        |       | 513       | BV      |    |       |
| 5.713     |            |        |       | 208       | BV      |    |       |
| 6.772     |            |        |       | 1960      | BV      |    |       |
| 8.391     |            |        |       | 273       | BV      |    |       |
| 10.005    |            |        |       | 263       | BV      |    |       |
| 11.665    |            |        |       | 4977      | BV      |    |       |
| 13.023    |            |        |       | 217       | BV      |    |       |
| 13.745    |            |        |       | 227       | BV      |    |       |
| Nifedipine| 15.190     | 24.63  | 1.215E-4 | 2655977 | S       | BA |       |
|           | 16.561     |        |       | 111       | BA      |    |       |
|           | 17.809     |        |       | 1289      | BV      |    |       |
|           | 18.565     |        |       | 322       | BV      |    |       |
|           | 19.634     |        |       | 217       | BV      |    |       |

Conversion factors: 1.0000E+00
Figure 3

Chromatogram of nifedipine solubility sample 3

Date: 25-MAR-1997 17:19:08.56
Raw file: PRG32: [EXHIBIT] AASOA RAW.1
Method file: MALDIOR [EXHIBIT] MALDIPRINANALYSIS154444.MET.2
Last method update: 25-MAR-1997 17:19:06.82
Device: Channel 52A, Model 941 Serial Num: 1133533322
Reprocess number: 2
Acq. date: 25-MAR-1997 15:45:40
Sample name: pure drug-2
Place:

Analysis type: EXTERNAL STANDARD
A/D range: 1.0 volt(s)
Report units: mg/ml
Sample amount: 1.00009
Volume injected: 20.00000
Conversion factor: 1.00000000

EXTERNAL STANDARD ANALYSIS

Calibration sample name: Nifedipine

| Peak name | R.T. (min) | T.Diff | mg/ml | Peak Area | Ref Std | El | Group |
|-----------|------------|--------|-------|-----------|---------|----|-------|
| 1.210     |            |        | 3.23  | 806       | BB      |    |       |
| 1.392     |            |        | 1566  | 4744      | BB      |    |       |
| 1.481     |            |        | 2.35  | 1448      | BB      |    |       |
| 1.496     |            |        | 3.000 | 818       | BB      |    |       |
| 1.461     |            |        | 3.46  | 380       | BB      |    |       |
| 4.110     |            |        | 4.11  | 789       | BB      |    |       |
| 4.366     |            |        | 4.36  | 512       | BB      |    |       |
| 4.766     |            |        | 4.76  | 175       | BB      |    |       |
| 5.248     |            |        | 5.25  | 167       | BB      |    |       |
| 5.714     |            |        | 5.71  | 155       | BB      |    |       |
| 6.798     |            |        | 6.80  | 1723      | BB      |    |       |
| 7.305     |            |        | 7.31  | 200       | BB      |    |       |
| 7.966     |            |        | 7.97  | 120       | BB      |    |       |
| 9.063     |            |        | 9.06  | 377       | BB      |    |       |
| 9.571     |            |        | 9.57  | 139       | BB      |    |       |
| 10.238    |            |        | 10.24 | 160       | BB      |    |       |
| 10.817    |            |        | 10.82 | 338       | BB      |    |       |
| 11.684    |            |        | 11.68 | 5851      | BB      |    |       |
| 12.567    |            |        | 12.57 | 127       | BB      |    |       |
| 13.831    |            |        | 13.83 | 480       | BB      |    |       |
| Nifedipine| 15.234     | 21.96  | 1.385 | 205309    | 5       | BB |       |
|           | 16.398     | 4.98   | 4.98  | 310       | BB      |    |       |

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Figure 4

Chromatogram of nifedipine:pluronic® F-68 solubility sample 1.

| Peak name | R.T. (min) | T.Diff | mg/mL | Peak Area | Ref Std | R L Group |
|-----------|------------|--------|-------|-----------|---------|-----------|
| 0.307     |            |        |       | 149       |         | BB        |
| 1.211     |            |        |       | 517       |         | BV        |
| 1.405     |            |        |       | 2523      |         | W         |
| 1.695     |            |        |       | 3242      |         | W         |
| 2.087     |            |        |       | 19294     |         | W         |
| 2.315     |            |        |       | 5982      |         | W         |
| 2.871     |            |        |       | 5217      |         | W         |
| 3.008     |            |        |       | 6624      |         | V         |
| 3.338     |            |        |       | 1445      |         | VB        |
| 3.563     |            |        |       | 1760      |         | BV        |
| 3.879     |            |        |       | 5010      |         | BV        |
| 4.279     |            |        |       | 4651      |         | W         |
| 4.586     |            |        |       | 3709      |         | W         |
| 4.955     |            |        |       | 3639      |         | W         |
| 5.326     |            |        |       | 5466      |         | W         |
| 5.780     |            |        |       | 19549     |         | W         |
| 6.606     |            |        |       | 15163     |         | V         |
| 7.396     |            |        |       | 32771     |         | VB        |
| 8.181     |            |        |       | 383       |         | BB        |
| 8.815     |            |        |       | 131       |         | BB        |
| 9.646     |            |        |       | 630       |         | BB        |
| 10.461    |            |        |       | 1853      |         | BV        |
| 10.953    |            |        |       | 1091      |         | W         |
| 11.837    |            |        |       | 3817      |         | VB        |
| 12.655    |            |        |       | 2685      |         | BB        |
| Nifedipine| 13.947     |        |       | 274       |         | BB        |
|           | 15.381     | 13.15  | 1.24E+03 | 2724822  | S       | BB        |
|           | 16.403     |        |       | 291       |         | BV        |
|           | 19.152     |        |       | 352       |         | W         |
|           | 19.751     |        |       | 307       |         | VB        |
Figure 5

Chromatogram of nifedipine: pluronic® F-68 solubility sample 2.

Date: 19-MAR-1997 21:06:55.30
Report number: 0
Raw file: PROD: DSCAPE(MAD) RAW1
Method file: NBISUR: (DSC SCRAP/NIKM/NK/RNANLYS195710.MET.2
Last method update: 19-MAR-1997 21:05:57.28
Device: Channel 52A, Model 501 Serial Num: 1133513322
Reprocess number: 2
Acq. date: 19-MAR-1997 19:29:14
Sample name: MPD: F68 disp
Molecule:

Analysis type: EXTERNAL STANDARD
A/D range: 0.0 volt(s)
Report units: mg/mL
Sample amount: 2.0000
Volume injected: 20.0000
Conversion factor: 1.00000E+00

EXTERNAL STANDARD ANALYSIS

Calibration Sample name: Nifedipine

Peaks name | R. T. [min] | T. Diff | mg/mL | Peak Area | Ref Std | RL | Group
--- | --- | --- | --- | --- | --- | --- | ---
0.456 | 1.221 | 1.402 | 1.695 | 2.083 | 2.304 | 2.854 | 3.027 | 3.330 | 3.973 | 4.227 | 4.356 | 4.533 | 5.327 | 5.790 | 6.612 | 7.400 | 8.144 | 8.841 | 9.824 | 10.471 | 10.957 | 13.844 | 12.615 | 14.246 | 15.388 | 17.933 | 18.557 | 19.733

Nifedipine

15.388 | 12.71 | 1.246E-03 | 2727260 | S | BB
17.933 | 539 | BB
18.557 | 279 | BB
19.733 | 315 | BB

N. N.
Figure 6

Standard curve of nifedipine in mobile phase

\[ Y = 52774.56 \times + 5475.077 \]
Appendix 2

Particle size determination of nifedipine samples before and after micronization and after formation of solid dispersions with pluronic® F-68.
Particle size distribution of unmicronized nifedipine

![Graph showing particle size distribution with a histogram and a cumulative distribution curve.]

**Figure 1**

Particle size distribution of unmicronized nifedipine
Particle size distribution of once micronized nifedipine

![Graph of particle size distribution]

**Figure 2**
Particle size distribution of once micronized nifedipine
**Figure 3**

Particle size distribution of twice micronized nifedipine

| Size (L1) | Result in | Size (H1) | Result in | Size (L2) | Result in | Size (H2) | Result in |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| μm        | %         | μm        | %         | μm        | %         | μm        | %         |
| 0.05      | 0.00      | 0.12      | 0.00      | 2.83      | 8.66      | 3.49      | 97.45     |
| 0.12      | 0.00      | 0.15      | 0.00      | 3.49      | 8.06      | 4.30      | 75.53     |
| 0.15      | 0.00      | 0.19      | 0.00      | 4.30      | 7.14      | 5.29      | 62.87     |
| 0.19      | 0.00      | 0.23      | 0.00      | 5.29      | 5.83      | 6.53      | 55.30     |
| 0.23      | 0.00      | 0.28      | 0.00      | 6.52      | 4.26      | 8.04      | 92.76     |
| 0.28      | 0.06      | 0.35      | 0.06      | 8.04      | 2.75      | 9.91      | 95.51     |
| 0.35      | 0.61      | 0.43      | 0.69      | 9.91      | 1.59      | 12.21     | 97.99     |
| 0.43      | 1.45      | 0.53      | 2.14      | 12.21     | 0.81      | 15.04     | 97.90     |
| 0.53      | 2.68      | 0.65      | 4.83      | 15.04     | 0.37      | 18.54     | 98.27     |
| 0.61      | 4.42      | 0.81      | 9.24      | 18.54     | 0.18      | 22.84     | 98.44     |
| 0.81      | 6.39      | 1.00      | 15.63     | 22.84     | 0.17      | 28.15     | 98.62     |
| 1.00      | 7.88      | 1.23      | 23.52     | 28.15     | 0.26      | 34.65     | 98.87     |
| 1.23      | 8.40      | 1.51      | 31.91     | 34.65     | 0.32      | 42.75     | 98.19     |
| 1.51      | 8.82      | 1.86      | 40.73     | 42.75     | 0.32      | 52.68     | 98.31     |
| 1.86      | 9.12      | 2.30      | 49.85     | 52.68     | 0.27      | 64.92     | 98.79     |
| 2.30      | 8.94      | 2.83      | 58.79     | 64.92     | 0.21      | 80.00     | 100.00    |

**Presentation: 2830**

Polydisperse mode

- Residual = 0.141 %
- Concentration = 0.004 %
- Obscuration = 13.53 %
- d (0.5) = 2.31 μm
- d (0.1) = 0.83 μm
- d (0.9) = 6.96 μm
- Sauer Mean (D(2,1)) = 1.74 μm
- Specific Surface Area = 3.4530 sq. m. / gm

**Focus** = 45 mm

**Malvern Instruments Inc.**

Sudbury, MA

**MasterSizer X Ver. 1.2**

Serial No. 6376
Particle size distribution of nifedipine:pluronic® F-68 solid dispersion (1:1).
Figure 5

Particle size distribution of nifedipine:pluronic® F-68 solid dispersion (1:0.5).
Appendix 3a

Determination of porosity parameters by mercury intrusion porosimetry. Pellets formulated with different drug (D4 Leukotriene antagonist) loads and spheronized at different times.
Drug Load: 0 % w/w, Spheronization Time: 2.0 minutes, Run # 1
Drug Load: 0 % w/w, Spheronization Time: 2.0 minutes, Run # 2

FILTERIZER 9320 V2.07

SAMPLE DIRECTORY/MONUER: DATAS  /67
OPERATOR: Ketan Mehta
SAMPLE ID: Placebo2mm2minRUN2
SUBMITTER: Ketan Mehta

PENETROMETER NUMBER: 13-0868
PENETROMETER CONSTANT: 10.79 µl/gf
PENETROMETER WEIGHT: 68.4592 g
STAP VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.6800 ps1
PENETROMETER VOLUME: 3.6991 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5353 g/mL
SAMPLE WEIGHT: 0.4025 g
SAMPLE+PENETRY WEIGHT: 112.0135 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 1.0065 psia
LAST LOW PRESSURE POINT: 25.5541 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.3744 mL/g
TOTAL PORE AREA = 35.847 sq-µm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0463 µm
MEDIAN PORE DIAMETER (AREA) = 0.0340 µm
AVERAGE PORE DIAMETER (AV/A) = 0.0440 µm
BULK DENSITY = 0.8633 g/mL
APPEARENT (SKELETAL) DENSITY = 1.5089 g/mL
POROSITY = 34.06 %
STEM VOLUME USED = 39 %

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Drug Load: 0 % w/w, Spheronization Time: 2.0 minutes, Run #3

PRESIZER V3.0

SAMPLE DIRECTORY/NUMBER: DATAT /M
OPERATOR: Ketan Menta
SAMPLE ID: Placebo20m24evolume3
SUBMITTER: Ketan Menta

LP: 06:35:38 02/25/97
HP: 23:49:16 02/25/97
REP: 23:49:17 02/25/97

PENETROMETER NUMBER: 13-0854
ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT: 10.79 ML/LF
RECEDING CONTACT ANGLE: 130.0 deg
PENETROMETER WEIGHT: 69.00295 g
MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME: 0.4120 ML
MERCURY DENSITY: 13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6000 psi
SAMPLE WEIGHT: 0.4005 g
PENETROMETER VOLUME: 3.5541 ML
SAMPLE+PENETRATING WEIGHT: 111.1867 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 1.0065 psi
LAST LOW PRESSURE POINT: 25.5541 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.3970 ML/g
TOTAL PORE AREA = 35.552 sq-µ/m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0461 µm
MEDIAN PORE DIAMETER (AREA) = 0.03559 µm
AVERAGE PORE DIAMETER (AV/A) = 0.0447 µm
BULK DENSITY = 0.8574 g/mL
APPARENT (SKELETAL) DENSITY = 1.299B g/mL
POROSITY = 56.04 %
STEM VOLUME USED = 39 %

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Drug Load: 0 % w/w, Spheronization Time: 10.0 minutes, Run # 1

| Property                        | Value       |
|---------------------------------|-------------|
| Drug Load                       | 0 % w/w     |
| Spheronization Time             | 10.0 minutes|
| Run #                           | 1           |

**Poresizer 9320 v2.07**

**Sample Directory/Number:** DATA1 /69

**Operator:** Katani Manti

**Sample ID:** Placeholder

**Submitter:** Katani Manti

**Penetrometer Number:** 13-0138

**Penetrometer Constant:** 10.79 μL/pf

**Penetrometer Weight:** 66.0664 g

**Stem Volume:** 0.4120 mL

**Maximum Head Pressure:** 4.0000 psi

**Penetrometer Volume:** 3.5835 mL

**Advancing Contact Angle:** 130.0 deg

**Receding Contact Angle:** 130.0 deg

**Mercury Surface Tension:** 485.0 dyn/cm

**Mercury Density:** 13.5335 g/mL

**Hysteresis:** 68.0

**Mercury Volume:** 0.0000 mL

**Surface Area:** 18.7913 m²

**Pore Volume:** 0.4120 mL

**Sample Weight:** 0.4016 g

**Sample+Penning Weight:** 111.4668 g

**Low Pressure:**
- **Mercury Filling Pressure:** 0.7772 psi
- **Last Low Pressure Point:** 25.3592 psi

**High Pressure:**
- **Run Type:** Automatic
- **Run Method:** Equilibrated
- **Equilibration Time:** 10 seconds

**Intrusion Data Summary**

| Property                        | Value       |
|---------------------------------|-------------|
| Total Intrusion Volume          | 0.3629 mL/g |
| Total Pore Area                 | 40.193 m²/g |
| Median Pore Diameter (Volume)   | 0.0378 μm   |
| Median Pore Diameter (Area)     | 0.0254 μm   |
| Average Pore Diameter (AvA)     | 0.0287 μm   |
| Bulk Density                    | 0.8203 g/mL |
| Apparent (Skeletal) Density     | 1.5505 g/mL |
| Porosity                        | 37.23 %     |
| Stem Volume Used                | 37 %        |
**Drug Load:** 0% w/w. **Spheronization Time:** 10.0 minutes. **Run #2**

| Parameter                                      | Value            |
|------------------------------------------------|------------------|
| Drug Load (%) w/w.                            | 0                |
| Spheronization Time (minutes)                 | 10.0             |

**PORESIZER 9300 V2.07**

| SAMPLE DIRECTORY/NUMBER: DATA1 | LP: 04:05:15 02/26/97 |
|---------------------------------|-----------------------|
| OPERATOR: Ketan Mehta           | HP: 06:19:40 02/26/97 |
| SAMPLE ID: Placebo2mm10minRUN2  | REP: 06:19:41 02/26/97|
| SUBMITTER: Ketan Mehta          |                       |

**PEMETRONOMETER NUMBER:** 13-02641  
**PEMETRONOMETER CONSTANT:** 10.79 µL/g  
**PEMETRONOMETER WEIGHT:** 68.3061 g  
**STER VOLUME:** 0.4120 mL  
**MAXIMUM HEAD PRESSURE:** 4.6000 psi  
**PEMETRONOMETER VOLUME:** 3.5443 mL  
**ADVANCING CONTACT ANGLE:** 130.0 deg  
**RECEIVING CONTACT ANGLE:** 130.0 deg  
**MERCURY SURFACE TENSION:** 485.0 dyn/cm  
**MERCURY DENSITY:** 13.5335 g/mL  
**SAMPLE WEIGHT:** 0.4026 g  
**SAMPLE+PEG BUFFER WEIGHT:** 110.2952 g

**LOW PRESSURE:**  
**MERCURY FILLING PRESSURE:** 0.7772 psi  
**LAST LOW PRESSURE POINT:** 25.5392 psi

**HIGH PRESSURE:**  
**RUN TYPE:** AUTOMATIC  
**RUN METHOD:** EQUILIBRATED  
**EQUILIBRATION TIME:** 70 seconds

**INTRUSION DATA SUMMARY**  
**TOTAL INTRUSION VOLUME:** 0.3791 mL/g  
**TOTAL PORE AREA:** 39.202 sq-µm/g  
**MEDIAN PORE DIAMETER (VOLUME):** 0.03390 µm  
**MEDIAN PORE DIAMETER (AREA):** 0.03317 µm  
**AVERAGE PORE DIAMETER (V/A):** 0.02687 µm  
**BULK DENSITY:** 0.8540 g/mL  
**APPEARANT (SKELETAL) DENSITY:** 1.267 g/mL  
**POROSITY:** 32.37%  
**STER VOLUME USED:** 37%
Drug Load: 0 % w/w, Spheronization Time: 10.0 minutes, Run # 3

POESIZER 9120 V2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /71
OPERATOR: Keta Mehta
SAMPLE ID: Placebo2w10minRUN3
SUBMITTER: Keta Mehta

PENETROMETER NUMBER: 13-0731
PENETROMETER CONSTANT: 10.79 μL/mm Hg
PENETROMETER WEIGHT: 67.807 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAT PRESSURE: 4.6800 psig
PENETROMETER VOLUME: 3.5885 mL

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7640 psia
LAST LOW PRESSURE POINT: 25.6797 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

| Metric                          | Value
|--------------------------------|-------|
| TOTAL INTRUSION VOLUME         | 0.5843 mL/g |
| TOTAL PORO AREA                | 40.188 sq-mm/g |
| MEDIAN PORO DIAMETER (VOLUME)  | 0.0238 μm   |
| MEDIAN PORO DIAMETER (AREA)    | 0.0311 μm   |
| AVERAGE PORO DIAMETER (4V/A)   | 0.0382 μm   |
| BULK DENSITY                   | 0.9408 g/mL |
| APPARENT (SKELETAL) DENSITY    | 1.5231 g/mL |
| POROSITY                       | 36.92 %    |
| STEM VOLUME USED               | 37 %     |

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Drug Load: 0 % w/w, Spheronization Time: 20.0 minutes, Run # 1

PORESIZER 9320 V2.07

SAMPLE DIRECTORY/MEDICINE: DATA1 /72
OPERATOR: Ketan Mehta
SAMPLE ID: Placebo22222run1 RUN
SUBMITT: Ketan Mehta

LP 03:33:56 03/03/97
HP 03:01:05 03/03/97
REP 03:01:06 03/03/97

PORE NUMBER: 13-0068
ADVANCING CONTACT ANGLE: 130.0 deg
PORE CONSTANT: 1.079 µl per cm²
RECEIVING CONTACT ANGLE: 130.0 deg
PORE WEIGHT: 68.9255 g
MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME: 0.4120 ml
MERCURY DENSITY: 13.335 g/ml
MAXIMUM HEAD PRESSURE: 6.6800 psi
SAMPLE VOLUME: 0.4000 g
PORE VOLUME: 3.6991 ml
SAMPLE+PENETRATING VOLUME: 113.7276 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7640 psi
LAST LOW PRESSURE POINT: 25.6757 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.3804 ml/g
TOTAL PORT AREA = 39.534 sq.-cm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0366 µm
MEDIAN PORE DIAMETER (AREA) = 0.0315 µm
AVERAGE PORE DIAMETER (AVG) = 0.0385 µm
BULK DENSITY = 0.8440 g/ml
APPEARANT (SKELETAL) DENSITY = 1.2870 g/ml
POROSITY = 32.87 %
STEM VOLUME USED = 37 %
Drug Load: 0 % w/w, Spheronization Time: 20.0 minutes, Run # 2

PORESIZER 9320 v2.0P

SAMPLE DIRECTORY/NUMBER: Data1
OPERATOR: Ketan Rentsa
SAMPLE ID: Placebo2mm-20minRun2
SUBMITTER: Ketan Rentsa

LP 05:00:46 03/03/97
HP 05:39:49 03/03/97

PENETROMETER NUMBER: 13-0854
PENETROMETER CONSTANT: 10.79 µL/g
PENETROMETER WEIGHT: 68.8376 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.6800 psi
PENETROMETER VOLUME: 3.5541 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5335 g/mL
SAMPLE VOLUME: 0.4000 g
SAMPLE-PENETRATING WEIGHT: 111.0813 g
MERCURY FILLING PRESSURE: 0.7587 psi
LAST LOW PRESSURE POINT: 25.5617 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.3831 mL/g
TOTAL PORE AREA = 42.21 % sq-o/a
MEDIAN PORE DIAMETER (VOLUME) = 0.0328 µm
MEDIAN PORE DIAMETER (AREA) = 0.0354 µm
AVERAGE PORE DIAMETER (4V/A) = 0.0363 µm
BULK DENSITY = 0.8654 g/mL
APPARENT (SKELETAL) DENSITY = 1.2945 g/mL
POROSITY = 33.15 %
STEM VOLUME USED = 37 %
Drug Load: 0 % w/w, Spheronization Time: 20.0 minutes, Run # 3

POESIZER 9320 V2 07

SAMPLE DIRECTORY/MODEL: DATA1 /74
OPERATOR: Ketan Mehta
SAMPLE 10: Plasbo2440winRUN3
SUBMITTER: Ketan Mehta

LP 05:00 46 03/05/97
HP 06:38:55 03/05/97
REP 07:06:47 03/05/97

PENETROMETER NUMBER: 13-0247
ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT: 10.79 μL/pF
RECORDING CONTACT ANGLE: 130.0 deg
PENETROMETER WEIGHT: 68.6664 g
MERCURY SURFACE TENSION: 485.0 dyn/cm
ST杀 VOLUME: 0.1200 mL
MERCURY DENSITY: 13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi
SAMPLE WEIGHT: 0.4212 g
PENETROMETER VOLUME: 3.5443 mL
SAMPLE+PEN+Hg WEIGHT: 110.731 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7587 psi
LAST LOW PRESSURE POINT: 25.1611 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.3700 mL/g
TOTAL PORE AREA = 39.224 sq-μm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0353 μm
MEDIAN PORE DIAMETER (AREA) = 0.0351 μm
AVERAGE PORE DIAMETER (4V/A) = 0.0377 μm
BULK DENSITY = 0.8699 g/mL
APPARENT (SKELETAL) DENSITY = 1.2827 g/mL
MOISTURY = 32.19%
STER VOLUME USED = 36 %
Drug Load: 5.0% w/w, Spheronization Time: 2.0 minutes, Run #1

Spheres: 9320 v2.07

Sample Directory/Number: Data1 13
Operator: ketam
Sample ID: 522001=Run1
Submitter: ketam

Penetrometer Number: 15-0'31
Penetrometer Constant: 10.74 uL/pf
Penetrometer Weight: 68.6595 g
Penetrometer Volume: 0.0473 mL
Maximum Liquid Pressure: 6,000 psi
Penetrometer Volume: 3.647 mL
Sample-Ringing Weight: 119.7730 g

Low Pressure:
Mercury Filling Pressure: 0.5788 psi
Last Low Pressure Point: 26.0516 psi

High Pressure:
Run Type: Automatic
Run Method: Equilibrated
Equilibration Time: 10 seconds

Intrusion Data Summary
Total Intrusion Volume = 0.4236 mL/g
Total Pore Area = 39.832 sq.mm/g
Median Pore Diameter (Volume) = 0.0469 um
Median Pore Diameter (Area) = 0.0412 um
Average Pore Diameter (4V/A) = 0.0425 um
Bulk Density = 0.8290 g/mL
Apparent (Skeletal) Density = 1.2777 g/mL
Porosity = 35.12 %
Ster Volume Used = 41 %
Drug Load: 5.0% w/w, Spheronization Time: 2.0 minutes, Run # 2

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PEl'IETltOl'IETU llUlftlEll: 13--0241
05 :46 :40 11 /19/96
07 :22:11 11 /19/96
07 :22:24 11119/96
PenETRMETER NUMBER: 13--0241
PenETRMETER CONSTANT: 10.79 pt/psf
PenETRMETER WEIGHT: 68.0493 g
STER VOLUME: 0.4120 ml
Maximum head Pressure: 4.6800 psia
PenETRMETER VOLUME: 3.5443 ml

Low Pressure:
MERCURY FILLING PRESSURE: 0.3788 psia
LAST LOW PRESSURE POINT: 26.0516 psia

High Pressure:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUIVIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.4200 ml/g
TOTAL PORE AREA = 40.291 sq. ft/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0491 μm
MEDIAN PORE DIAMETER (AREA) = 0.0408 μm
AVERAGE PORE DIAMETER (4V/A) = 0.0417 μm
BULK DENSITY = 0.8280 g/ml
APPARENT (SKELETAL) DENSITY = 1.2695 g/ml
POROSITY = 34.78 %
STER VOLUME USED = 41 %
Drug Load: 5.0 % w/w, Spheronization Time: 2.0 minutes, Run #3

PORESIZER 9720 V2.07

SAMPLE DIRECTORY/NUMBER: DATAT / T5
OPERATOR: ketan minte
SAMPLE ID: 532x1n2sRun3
SUBMITTER: ketan minte

LP 06:39:20 11/24/96
HP 07:23:51 11/24/96
REP 07:23:51 11/24/96

PENETROMETER NUMBER: 13-0139
PENETROMETER CONSTANT: 10.79 μL/°F
PENETROMETER WEIGH: 68.7045 g
STEM VOLUME: 0.420 mL
MAXIMUM HEAD PRESSURE: 4.5800 psig
PENETROMETER VOLUME: 3.5898 mL

ADVANCING CONTACT ANGLE: 130.0°
RECEDING CONTACT ANGLE: 130.0°
MERGY SURFACE TENSION: 48.5° dyn/cm
MERCURY DENSITY: 15.3315 g/mL
SAMPLE WEIGHT: 0.4023 g
SAMPLE+PERM. WEIGHT: 111.8560 g

LOW PRESSURE:
MERURY FILLING PRESSURE: 0.7297 psig
LAST LOW PRESSURE POINT: 25.9601 psig

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.4209 mL/g
TOTAL PORE AREA = 40.245 sq-m/g
MEDIAN PORO DIAMETER (VOLUME) = 0.0044 um
MEDIAN PORO DIAMETER (AREA) = 0.0042 um
AVERAGE PORO DIAMETER (AV/δa) = 0.0042 um
BULK DENSITY = 0.9510 g/mL
APPEARANT (SKELETAL) DENSITY = 1.5312 g/mL
MOBILITY = 39.19 %
STEM VOLUME USED = 41 %
Drug Load: 5.0 % w/w, Spheronization Time: 10.0 minutes, Run # 1

Drug Load: 5.0 % w/w, Spheronization Time: 10.0 minutes, Run # 1
Drug Load: 5.0 % w/w, Spheronization Time: 10.0 minutes, Run # 2
Drug Load: 5.0% w/w, Spheronization Time: 10.0 minutes, Run #3

PORESIZER 9320 v2.07

SAMPLE DIRECTORY/NUMBER: DATA1/1B
OPERATOR: katan mehta
SAMPLE ID: S110aw22aw4m5
SUBMITTER: katan mehta

LP 10:47:16 11/24/96
HP 12:22:24 11/24/96
REP 12:22:25 11/24/96

PELETOMETER NUMBER: 13-0241
PELETOMETER CONSTANT: 10.79 mL/pf
PELETOMETER WEIGHT: 47.8850 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.6800 psi
PELETOMETER VOLUME: 3.5469 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEIVING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5315 g/mL
SAMPLE WEIGHT: 0.4070 g
SAMPLE+POWDER WEIGHT: 109.8288 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7073 psia
LAST LOW PRESSURE POINT: 23.8337 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.3973 mL/g
TOTAL PORE AREA = 42.097 sq-μm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0455 μm
MEDIAN PORE DIAMETER (AREA) = 0.0333 μm
AVERAGE PORE DIAMETER (VOLUME) = 0.0378 μm
BULK DENSITY = 0.8410 g/mL
APPARENT (SKELETAL) DENSITY = 1.2630 g/mL
POROSITY = 33.41%
STEM VOLUME USED = 39%
Drug Load: 5.0% w/w. Spheronization Time: 20.0 minutes. Run # 1

Poresizer 9320 v2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /19
OPERATOR: Ketan Mehta
SAMPLE ID: 5320h12=r=Run1
SUBMITTER: Ketan Mehta

LP 03:52:07 11/25/96
HP 04:39:31 11/25/96
REP 04:49:26 11/25/96

PENETROMETER NUMBER: 13-0131
PENETROMETER CONSTANT: 10.79 +0.007
PENETROMETER WEIGHT: 67.9053 g
MERCURY SURFACE TENSION: 467.0 dyn/cm
FIELD VOLUME: 0.4720 ml
MERCURY DENSITY: 13.5564 g/ml
MAXIMUM HEAD PRESSURE: 4.0000 psig
SAMPLE WEIGHT: 0.4007 g
PENETROMETER VOLUME: 1.5685 ml
SAMPLE PENETRATION WEIGHT: 111.2415 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7293 psig
LAST LOW PRESSURE POINT: 26.1014 psig

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 171 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.3860 ml/g
TOTAL POROSITY = 39.525 ml-w/g
MEDIUM POROSITY VOLUME = 0.0639 µm
MEDIUM POROSITY AREA = 0.0364 µm
AVERAGE POROSITY DIAMETER (4/V/A) = 0.0391 µm
BULK DENSITY = 0.9616 g/ml
APPEARANT (SKELETAL) DENSITY = 1.5290 g/ml
POROSITY = 37.11 %
STEM VOLUME USED = 38 %
Drug Load: 5.0% w/w, Spheronization Time: 20.0 minutes, Run #2

POREZIER 9320 V2.07

SAMPLE DIRECTORY/MEMBER: DATA1 /20
OPERATOR: Ketan Mehta
SAMPLE ID: 5120
SUBMITTER: Ketan Mehta

POREZIER 9320 V2.07

SAMPLE DIRECTORY/MEMBER: DATA1 /20
OPERATOR: Ketan Mehta
SAMPLE ID: 5120
SUBMITTER: Ketan Mehta

 PENETROMETER NUMBER: 13.0241
 PENETROMETER CONSTANT: 10.79 mL/pa
 PENETROMETER WEIGHT: 68.3724 g
 STEM VOLUME: 0.4130 mL
 MAXIMUM HEAD PRESSURE: 4.6800 psi
 PENETROMETER VOLUME: 3.5443 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEIVING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5364 g/mL
SAMPLE WEIGHT: 0.4091 g
SAMPLE+PENNING WEIGHT: 110.3415 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7293 psi
LAST LOW PRESSURE POINT: 26.1014 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.3852 mL/g
TOTAL PORE AREA = 39.491 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0458 µm
MEDIAN PORE DIAMETER (AREA) = 0.0563 µm
AVERAGE PORE DIAMETER (4V/A) = 0.0590 µm
BULK DENSITY = 0.8552 g/mL
APPEARENT (SKELETAL) DENSITY = 1.2752 g/mL
POROSITY = 32.94 %
STEM VOLUME L/D = 58 x
Drug Load: 5.0% w/w, Spheronization Time: 20.0 minutes, Run #3

| Sample Directory/Number: DATA | Page 1 |
|-------------------------------|--------|
| Operator: Ketan Hente         |        |
| Sample ID: 5220mr2mmRUN3      |        |
| Submitter: Ketan Hente        |        |

| Penetrometer Number: 13-Q241  |        |
| Penetrometer Constant: 10.79 µl/pF |        |
| Penetrometer Weight: 68.1909 g |        |
| Stem Volume: 0.4120 ml         |        |
| Maximum Head Pressure: 4.6800 psi |        |
| Penetrometer Volume: 3.5443 ml |        |

Advancing Contact Angle: 150.0 deg
Receding Contact Angle: 150.0 deg
Mercury Surface Tension: 483.0 dyn/cm
Mercury Density: 13.5364 g/ml

Low Pressure:
- Mercury Filling Pressure: 0.7443 psi
- Last Low Pressure Point: 26.0932 psi
High Pressure:
- Run Type: Automatic
- Run Method: Equilibrated
- Equilibration Time: 10 seconds

Intrusion Data Summary:
- Total Intrusion Volume = 0.3862 ml/g
- Total Pore Area = 39.090 sq-µm/g
- Median Pore Diameter (Volume) = 0.0450 µm
- Median Pore Diameter (Area) = 0.0372 µm
- Average Pore Diameter (AV/A) = 0.0395 µm
- Bulk Density = 0.8322 g/ml
- Apparent (Skeletal) Density = 1.2265 g/ml
- Porosity = 32.14 %
- Stem Volume Used = 38 %
Drug Load: 10.0 % w/w, Spheronization Time: 2.0 minutes, Run # 1

Poresizer 9320 V2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /22
OPERATOR: Ketan Mehta
SAMPLE ID: TORZarin2mmRUM
SUBMITTER: Ketan Mehta

LP 08:18:22 11/25/96
HP 11:59:57 11/25/96
REP 11:59:57 11/25/96

PEMTROMETER NUMBER: 13-D131
ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5364 g/ml

PEMTROMETER WEIGHT: 66.6221 g
STEM VOLUME: 0.4120 ml
MAXIMUM HEAD PRESSURE: 4.6800 psi
SAMPLE WEIGHT: 0.4211 g
PEMTROMETER VOLUME: 3.5885 ml
SAMPLE-PENNING WEIGHT: 111.6325 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7443 psi
LAST LOW PRESSURE POINT: 26.0952 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRISATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.4403 ml/g
TOTAL PORE AREA = 37.712 sq.-m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0608 μm
MEDIAN PORE DIAMETER (AREA) = 0.0412 μm
AVERAGE PORE DIAMETER (S/V) = 0.0637 μm
BULK DENSITY = 0.9101 g/ml
APPARENT (SKELETAL) DENSITY = 1.5184 g/ml
POROSITY = 40.07 %
STEM VOLUME USED = 43 %
Drug Load: 10.0 % w/w, Spheronization Time: 2.0 minutes, Run #2

**Poresizer 9320 v2.07**

**Sample Directory/Number:** D:\\axis /22

**Operator:** Kaiten Mehta

**Sample Id:** 1002min2mm Run2

**Submitter:** Kaiten Mehta

**PENETROMETER NUMBER:** 13-0731

**Penetrometer Constant:** 10.79 µl/pf

**Penetrometer Weight:** 67.8749 g

**STEM Volume:** 0.4120 ml

**Maximum Head Pressure:** 6,500 psi

**Penetrometer Volume:** 3.5065 ml

**Advancing Contact Angle:** 130.0 deg

**Receding Contact Angle:** 130.0 deg

**Mercury Surface Tension:** 485.0 dyn/cm

**Mercury Density:** 13.5364 g/ml

**Low Pressure:**

- Mercury Filling Pressure: 0.2510 psia
- Last Low Pressure Point: 25.0979 psia

**High Pressure:**

- Run Type: Automatic
- Run Method: Equilibrated
- Equilibration Time: 10 seconds

**Intrusion Data Summary**

- Total Intrusion Volume: 0.4355 ml/g
- Total Pore Area: 37.098 sq.-µm/g
- Median Pore Diameter (Volume): 0.1606 µm
- Median Pore Diameter (Area): 0.0410 µm
- Average Pore Diameter (V/A): 0.0470 µm
- Bulk Density: 0.9235 g/ml
- Apparent (Skeletal) Density: 1.546 g/ml
- Porosity: 40.23 %
- Stem Volume Used: 42 %
Drug Load: 10.0% w/w, Spheronization Time: 2.0 minutes. Run #3

Poresizer 9320 v2.07

Sample Directory/Number: Data/ #24
Operator: Ketan Mehta
Sample ID: T0122612wineRun3
Submitter: Ketan Mehta

Penetrometer Number: 13-G241
Penetrometer Constant: 10.79 ml/sf
Penetrometer Weight: 68.917 g
Mercury Surface Tension: 483.0 dyn/cm
Ster Volume: 0.4120 ml
Mercury Density: 13.5364 g/ml
Maximum Head Pressure: 4.0800 psi
Sample Weight: 0.4403 g
Penetrometer Volume: 3.5443 ml
Sample+Pen+mg Weight: 110.6957 g

Low Pressure:
MERCURY FILLING PRESSURE: 0.6510 psi
Last Low Pressure Point: 25.8919 psi

High Pressure:
Run Type: AUTOMATIC
Run Method: EQUILIBRATED
Equilibration Time: 10 seconds

Intrusion Data Summary
Total Intrusion Volume = 0.4355 ml/g
Total Pore Area = 37.260 sq-ml/g
Median Pore Diameter (Volume) = 0.0607 μm
Median Pore Diameter (Area) = 0.0409 μm
Average Pore Diameter (4/V:A) = 0.0668 μm
Bulk Density = 0.8211 g/ml
Apparent (Skeletal) Density = 1.2783 g/ml
Porosity = 35.76 %
Ster Volume Used = 42 %
Drug Load: 10.0 % w/w, Spheronization Time: 10.0 minutes, Run # 1

| PENETROMETER NUMBER: | 13-0131  |
| PENETROMETER CONSTANT: | 10.79  μL/gF |
| PENETROMETER WEIGHT: | 67.9940 g |
| STEM VOLUME: | 0.4120 mL |
| MAXIMUM MEAN PRESSURE: | 4.6800 psia |
| PENETROMETER VOLUME: | 3.5685 mL |
| ADVANCING CONTACT ANGLE: | 130.0 deg |
| RECEDING CONTACT ANGLE: | 130.0 deg |
| MERCURY SURFACE TENSION: | 485.0 dyn/cm |
| MERCURY DENSITY: | 13.5364 g/mL |
| SAMPLE WEIGHT: | 0.4072 g |
| SAMPLE+PENETRATING WEIGHT: | 111.1876 g |

LOW PRESSURE:
- MERCURY FILLING PRESSURE: 0.7528 psia
- LAST LOW PRESSURE POINT: 25.9104 psia

HIGH PRESSURE:
- RUN TYPE: AUTOMATIC
- RUN METHOD: EQUILIBRATED
- EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY
- TOTAL INTRUSION VOLUME = 0.4189 mL/g
- TOTAL PORE AREA = 36.994 sq-μm/g
- MEDIAN PORE DIAMETER (VOLUME) = 0.0484 μm
- MEDIAN PORE DIAMETER (AREA) = 0.0428 μm
- AVERAGE PORE DIAMETER (4V/SA) = 0.0430 μm
- BULK DENSITY = 0.9391 g/mL
- APPARENT (SKELETAL) DENSITY = 1.5480 g/mL
- POROSITY = 39.33 %
- STEM VOLUME USED = 41 %
Drug Load: 10.0 % w/w, Spheronization Time: 10.0 minutes, Run # 2

PORESIZER 9320 v2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /ZL
OPERATION: Ketan Mehta
SAMPLE ID: 10G102352AMYTH
SUBMITTER: Ketan Mehta

PENETROMETER NUMBER: 13-0241
ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT: 10.79 µl/cm²
RECEDING CONTACT ANGLE: 130.0 deg
PENETROMETER WEIGHT: 68.7230 g
MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME: 0.4120 mL
MERCURY DENSITY: 13.5364 g/mL
MAXIMUM HEAT PRESSURE: 4.0000 psig
SAMPLE WEIGHT: 0.4020 g
PENETROMETER VOLUME: 3.3443 mL
SAMPLE+PEN+HG WEIGHT: 110.5390 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.1221 psia
LAST LOW PRESSURE POINT: 25.97104 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.4185 mL/g
TOTAL PORE AREA = 39.636 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0682 µm
MEDIAN PORE DIAMETER (AREA) = 0.0629 µm
AVERAGE PORE DIAMETER (44/A) = 0.0625 µm
BULK DENSITY = 0.8291 g/mL
APARENT (SKELETAL) DENSITY = 1.2697 g/mL
POROSITY = 34.70 %
STEM VOLUME USE = 41 %
Drug Load: 10.0% w/w, Spheronization Time: 10.0 minutes, Run #3

**Porosizer 9320 v2.07**

**Sample Directory/Number:** DATAT/27

**Operator:** ketan mehta

**Sample ID:** TOTOMinumRun3

**Submitter:** ketan mehta

**Penetrometer Number:** 13-0241

**Penetrometer Constant:** 10.79 µl/pa

**Penetrometer Weight:** 68.0972 g

**STEM Volume:** 0.4520 mL

**Maximum Head Pressure:** 4,6800 psi

**Penetrometer Volume:** 3.5443 mL

**Low Pressure:**
- Mercury Filling Pressure: 0.6790 psi
- Last Low Pressure Point: 25.9079 psi

**High Pressure:**
- Run Type: Automatic
- Run Method: Equilibrates
- Equilibration Time: 10 seconds

**Intrusion Data Summary**

- Total Intrusion Volume = 0.4170 mL/g
- Total Pore Area = 39.553 µm²/g
- Median Pore Diameter (Volume) = 0.0648 µm
- Median Pore Diameter (Area) = 0.0422 µm
- Average Pore Diameter (AV/A) = 0.0422 µm
- Bulk Density = 0.8569 g/mL
- Apparent (Skeletal) Density = 1.2855 g/mL
- Porosity = 34.90 %
- Stem Volume Used = 41 %
Drug Load: 10.0 % w/w, Spheronization Time: 20.0 minutes. Run #1

PRESIZER 9320 v2.07

SAMPLE DIRECTORY/MONUMBER: DATA1 /28
OPERATOR: ketan mewta
SAMPLE ID: 10240m=20190117
SUBMITTER: ketan mewta

PENETROMETER NUMBER: 13-0131
PENETROMETER CONSTANT: 10.79 µl/pF
PENETROMETER WEIGHT: 68.6338 g
PENETROMETER VOLUME: 3.6417 mL
MAXIMUM HEAD PRESSURE: 6.6800 psi
SAMPLE WEIGHT: 0.4025 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6790 psi
LAST LOW PRESSURE POINT: 25.9379 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 90 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.4026 w/g
TOTAL POROUS AREA = 36.662 sq-mm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0461 µm
MEDIAN PORE DIAMETER (AREA) = 0.0426 µm
AVERAGE PORE DIAMETER (4V/A) = 0.0424 µm
BULK DENSITY = 0.8340 g/mL
APPEAR (SKELETAL) DENSITY = 1.2064 g/mL
POROSITY = 24.74 %

STEM VOLUME USED = 40 %
Drug Load: 10.0 % w/w, Spheronization Time: 20.0 minutes, Run # 2

POMESIZER 9320 V2.07

| Data ID | Value |
|---------|-------|
| Drug Load | 10.0 % w/w |
| Spheronization Time | 20.0 minutes |

| Sample Directory/Number | Data 1 |
|-------------------------|--------|
| OPERATOR               | ketan mehta |
| SAMPLE ID               | 10220run2run2 |
| SUBMITTER              | ketan mehta |

| Penetrometer Number | Penetrometer Constant | Advancing Contact Angle | Receding Contact Angle |
|---------------------|-----------------------|-------------------------|------------------------|
| 13-0131             | 10.79 µL/g            | 130.0 deg               | 130.0 deg              |

| Penetrometer Weight | Stem Volume | Maximum Hexa Pressure | Penetrometer Volume |
|---------------------|-------------|-----------------------|---------------------|
| 67.6550 g           | 0.4120 mL   | 4.6800 psi            | 3.6617 mL           |

| Low Pressure | Mercury Filling Pressure | Last Low Pressure Point |
|--------------|--------------------------|-------------------------|
|              | 0.7958 psi               | 25.8911 psi             |

| High Pressure | Run Type | Run Method | Equilibration Time |
|---------------|----------|------------|-------------------|
|               | AUTOMATIC| EQUILIBRATED| 10 seconds        |

**Intrusion Data Summary**

| Parameter                             | Value |
|---------------------------------------|-------|
| Total Intrusion Volume                | 0.4059 mL/g |
| Total Pore Area                       | 38.266 sq-m/g |
| Median Pore Diameter (Volume)         | 0.0483 µm |
| Median Pore Diameter (Area)           | 0.0426 µm |
| Average Pore Diameter (4V/A)          | 0.0624 µm |
| Bulk Density                          | 0.8377 g/mL |
| Apparent (Skeletal) Density           | 1.2695 g/mL |
| Porosity                              | 34.01 % |
| Stem Volume Used                      | 40 %   |
**Drug Load:** 10.0% w/w, **Spheronization Time:** 20.0 minutes, **Run #3**

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**Poresizer 9320 v2.07**

| Sample Directory/Number: Data | /50 |
|-------------------------------|----|
| Operator: ketan mehta        | LP 06:49:22 12/02/96 |
| Sample ID: 10%20min2mmRUNJ1   | HP 10:02:15 12/02/96 |
| Submitter: ketan mehta        | RP 10:02:46 12/02/96 |

| Penetrometer Number: 13-G0441 | Penetrometer Constant: 10.79 μL/pf |
|-------------------------------|----------------------------------|
| Penetrometer Weight: 69.1096 g | Mercury Surface Tension: 483.0 dyn/cm |
| Ster Volume: 0.4120 mL         | Mercury Density: 13.3413 g/mL |
| Maximum Head Pressure: 4.6600 psi | Sample Weight: 0.6022 g |
| Penetrometer Volume: 3.5443 mL | Sample-Pining Weight: 110.9090 g |

**Low Pressure:**
- Mercury filling pressure: 0.7958 Pa
- Last Low Pressure Point: 25.8911 Pa

**High Pressure:**
- Run Type: Automatic
- Run Method: Equilibrated
- Equilibration Time: 10 seconds

**Intrusion Data Summary**

| Total Intrusion Volume: | 0.4056 mL/g |
|-------------------------|-------------|
| Total Pore Area:        | 38.603 sq-μm/g |
| Median Pore Diameter (Volume): | 0.0569 μm |
| Median Pore Diameter (Area): | 0.0427 μm |
| Average Pore Diameter (V/A): | 0.0460 μm |
| Bulk Density:           | 0.8131 g/mL |
| Apparent (Skeletal) Density: | 1.231 g/mL |
| Porosity:               | 32.98% |
| Ster Volume Used:       | 40% |
Drug Load: 20.0% w/w, Spheronization Time: 2.0 minutes, Run #1

PVERSIS V2 20.07

SAMPLE DIRECTORY/NUMBER: DATA1 /31
OPERATOR: Ketan Mehta
SAMPLE ID: 200220h2um1
SUBMITTER: Ketan Mehta

PENETROMETER NUMBER: 13-0241
PENETROMETER CONSTANT: 10.79 μl/pf
PENETROMETER WEIGHT: 67.8056 g
STEM VOLUME: 0.04720 ml
MAXIMUM HEAD PRESSURE: 4.6800 psi
PENETROMETER VOLUME: 3.5443 ml

ADVANCING CONTACT ANGLE: 130.0 deg
RECEIVING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5364 g/ml
SAMPLE WEIGHT: 0.402 g
SAMPLE+PEN+Hg WEIGHT: 109.8128 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.5768 psi
LAST LOW PRESSURE POINT: 26.3394 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 19 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.3814 ml/g
TOTAL PORE AREA = 32.887 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.05500 μm
MEDIAN PORE DIAMETER (AREA) = 0.00471 μm
AVERAGE PORE DIAMETER (4V/A) = 0.0464 μm
BULK DENSITY = 0.8547 g/ml
APPEARANT (SKELETAL) DENSITY = 1.2679 g/ml
POROSITY = 32.59 %
STEM VOLUME USED = 37 %

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Drug Load: 20.0% w/w, Spheronization Time: 2.0 minute.

PRESIZER 9320 v2.07

Sample Directory/Number: DATA1 /32
Operator: Ketan Mantri
Sample ID: 200211270867
Submitter: Ketan Mantri

Penetrometer Number: 13-0131
Penetrometer Constant: 10.79 mL/0s
Penetrometer Weight: 68.7225 g
Penetration Volume: 0.420 mL
Penetrometer Volume: 5.5695 mL

Maximum Head Pressure: 4.6800 psi
Sample Weight: 0.4278 g
Penetrometer Weight: 112.0378 g

Low Pressure:
M.cury Filling Pressure: 0.5768 psi
Last Low Pressure Point: 26.0094 psi

High Pressure:
Run Type: Automatic
Run Method: Equilibrated
Equilibration Time: 10 seconds

Intrusion Data Summary

Total Intrusion Volume = 0.3655 mL/g
Total Pore Area = 33.729 sq-μm/g
Median Pore Diameter (Volume) = 0.0545 μm
Median Pore Diameter (Area) = 0.0420 μm
Average Pore Diameter (4V/πA) = 0.0455 μm
Bulk Density = 0.9406 g/cm³
Apparent (Skeletal) Density = 1.5210 g/cm³
Pore Size = 36.84 μm

Pore Volume Used = 37 %
Drug Load: 20.0% w/w, Spheronization Time: 2.0 minutes, Run #3

PORESIZER 9320 V2.07

SAMPLE DIRECTORY/NUMBER: DAT1 /33
OPERATOR: Ketan Mehta
SAMPLE ID: 20122413RUN3
SUBMITTER: Ketan Mehta

LP 01:27:16 12/09/96
HP 02:09:50 12/09/96
REP 02:09:51 12/09/96

PENETROMETER NUMBER: 13-0135
PENETROMETER CONSTANT: 10.79 µL/pF
PENETROMETER WEIGHT: 68.1041 g
STER VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.6400 psi
PENETROMETER VOLUME: 3.5885 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 481.0 dyn/cm
MERCURY DENSITY: 13.5564 g/mL
SAMPLE WEIGHT: 0.4015 g
SAMPLE+PERMEATING WEIGHT: 111.2028 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6823 psi
LAST LOW PRESSURE POINT: 25.7469 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.3825 mL/g
TOTAL PORE AREA = 33.843 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0558 µm
MEDIAN PORE DIAMETER (AREA) = 0.0642 µm
AVERAGE PORE DIAMETER (V/A) = 0.0652 µm
BULK DENSITY = 0.9246 g/mL
APPEARANT (SKELETAL) DENSITY = 1.4304 g/mL
POROSITY = 35.36 %
STER VOLUME USED = 37 %
Drug Load: 20.0 % w/w, Spheronization Time: 10.0 minutes, Run # 1

POREZIER 9520 V2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /34
OPERATOR: Keshav Mehta
SAMPLE ID: 202100510211
SUBMITTER: Keshav Mehta

LP 01:27:16 12/09/96
HP 03:23:38 12/09/96
REP 03:23:30 12/09/96

PENETROMETER NUMBER: 13-0241
PENETROMETER CONSTANT: 10.79 µL/dp
PENETROMETER HEIGHT: 68.317 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.6800 psi
PENETROMETER VOLUME: 3.3443 mL
ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5364 g/mL
SAMPLE WEIGHT: 0.4231 g
SAMPLE+STEM WEIGHT: 110.7447 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6823 psi
LAST LOW PRESSURE POINT: 25.7469 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.3522 mL/g
TOTAL PORE AREA = 33.215 sq.-µm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0497 µm
MEDIAN PORE DIAMETER (AREA) = 0.0419 µm
AVERAGE PORE DIAMETER (44/6) = 0.0424 µm
BULK DENSITY = 0.8707 g/mL
APPEARANT (SKELETAL) DENSITY = 1.2557 g/mL
FOREMOST = 30.66 %
STEM VOLUME USED = 34 %
Drug Load: 20.0 % w/w, Spheronization Time: 10.0 minutes, Run # 2

**PORESIZER 9520 V2.07**

| SAMPLE DIRECTORY/NUMBER: DATAT /35 | PAGE 1 |
|-----------------------------------|--------|
| OPERATOR: Ketan Mehta             | LP 05:47:56 12/09/96 |
| SAMPLE ID: 2020Omic/2nnRn2        | HP 06:32:31 12/09/96 |
| SUBMITTER: Ketan Mehta            | REP 06:57:12 12/09/96 |

**Penetrometer Number:** 13-D131  
**Penetrometer Constant:** 10.79 µl/pf  
**Penetrometer Weight:** 68.1160 g  
**Penetrometer Volume:** 0.6720 ml  
**Maximum Head Pressure:** 6,880.0 psi  
**Penetrometer Volume:** 3.5985 ml  
**Advancing Contact Angle:** 150.0 deg  
**Receding Contact Angle:** 150.0 deg  
**Mercury Surface Tension:** 465.0 dyn/cm  
**Mercury Density:** 13.5364 g/ml  
**Sample Weight:** 0.4023 g  
**Sample Penetrometer Weight:** 111.6350 g

**LOW PRESSURE:**  
**Mercury Filling Pressure:** 0.6992 psi  
**Last Low Pressure Point:** 25.7799 psi

**HIGH PRESSURE:**  
**Run Type:** Automatic  
**Run Method:** Equilibrated  
**Equilibration Time:** 10 seconds

**Intrusion Data Summary**

| Parameter                              | Value     |
|----------------------------------------|-----------|
| Total Intrusion Volume                 | 0.3551 ml/g |
| Total Pore Area                        | 33.578 sq-µm/g |
| Median Pore Diameter (Volume)          | 0.0456 µm   |
| Median Pore Diameter (Area)            | 0.0459 µm   |
| Average Pore Diameter (µV/A)           | 0.0423 µm   |
| Bulk Density                           | 0.9973 g/ml |
| Apparent Density (Skeletal) Density    | 1.5440 g/ml |
| Pore Size                               | 35.41 %    |
| Stem Volume Used                       | 35 %      |
Drug Load: 20.0 % w/w, Spheronization Time: 10.0 minutes, Run #3

PORESIZER 9320 v2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /06
OPERATOR: Ketan Mehta
SAMPLE ID: 200710052mmRun3
SUBMITTER: Ketan Mehta

PEMETROMETER NUMBER: 13-0241
PEMETROMETER CONSTANT: 10.79 ml/pa
PEMETROMETER WEIGHT: 66.777 g
STER VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.6800 psia
PEMETROMETER VOLUME: 3.5443 mL
ADVANCING CONTACT ANGLE: 130.0 deg
RECEIVING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5364 g/mL
SAMPLE WEIGHT: 0.4019 g
SAMPLE+WtNg WEIGHT: 110.9042 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6992 psia
LAST LOW PRESSURE POINT: 25.7779 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.3516 mL/g
TOTAL PORE AREA = 32.877 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0496 μm
MEDIAN PORE DIAMETER (AREA) = 0.0425 μm
AVERAGE PORE DIAMETER (4/V/A) = 0.0428 μm
BULK DENSITY = 0.8707 g/mL
APPARENT (SKELETAL) DENSITY = 1.2937 g/mL
POROSITY = 30.59 %
STER VOLUME USED = 34 %
Drug Load: 20.0 % w/w, Spheronization Time: 20.0 minutes, Run # 1

POREZER G200 V2.07

SAMPLE DIRECT/NUMBER: DATA1 /37
OPERATOR: Ketan Mehta
SAMPLE ID: 20220min2amHunt
SUBMITTER: Ketan Mehta

PENETROMETER NUMBER: 13-0641
PENETROMETER CONSTANT: 10.79 μL/μF
PENETROMETER WEIGHT: 67.8050 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 6,000 psi
PENETROMETER VOLUME: 3.5443 mL

ADVANCED CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5364 g/mL
SAMPLE HEIGHT: 0.4258 g
SAMPLE+PENNOMETER WEIGHT: 110.0928 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.8010 psia
LAST LOW PRESSURE POINT: 25.8091 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUIBILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.3259 mL/g
TOTAL PORE AREA = 50.785 sq-μm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0495 μm
MEDIAN PORE DIAMETER (AREA) = 0.0611 μm
AVERAGE PORE DIAMETER (V/A) = 0.0435 μm
BULK DENSITY = 0.8950 g/mL
APPARENT (SKELETAL) DENSITY = 1.2635 g/mL
POROSITY = 29.16 %
STEM VOLUME USED = 32 l
Drug Load: 20.0% w/w, Spheronization Time: 20.0 minutes, Run #2

PORESIZER 9320 V2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /58
OPERATOR: Ketan Khata
SAMPLE ID: 20220M212RUN2
SUBMITTER: Ketan Khata

LP 03-07:26 12/10/96
HP 05:10:52 12/10/96
REP 05:10:53 12/10/96

ADJUSTED CONTACT ANGLE: 130.0 deg
ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
HIGHER SURFACE TENSION: 485.0 dyn/cm
HIGHER DENSITY: 13.536 g/mL
SAMPLE WEIGHT: 0.4008 g
SAMPLE+PEELING WEIGHT: 112.3340 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.8070 psia
LAST LOW PRESSURE POINT: 25.8070 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.5339 mL/g
TOTAL PORE AREA = 31.7858 sq-Å/g
MIDIAN PORE DIAMETER (VOLUME) = 0.0495 μm
MIDIAN PORE DIAMETER (AREA) = 0.0411 μm
AVERAGE PORE DIAMETER (V4/A) = 0.0620 μm
BULK DENSITY = 1.0104 g/mL
APPARENT (SKELETAL) DENSITY = 1.5248 g/mL
POROSITY = 33.73 %
STER VOLUME USED = 32 %
Drug Load: 20.0 % w/w, Spheronization Time: 20.0 minutes, Run # 3

FORESIZER 7220 V2.07

SAMPLE DIRECTORY/NUMBER: DATAT /39
OPERATOR: Ketan Mehta
SAMPLE ID: 20120m-2wRUN3
SUBMITTER: Ketan Mehta

LP 02:25:45 12/16/96
HP 03:06:58 12/16/96
REP 03:06:58 12/16/96

PENETROMETER NUMBER: 13-0241
PENETROMETER CONSTANT: 10.79 pL/psi
PENETROMETER WEIGHT: 67.6530 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.6800 psig
PENETROMETER VOLUME: 3.5443 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5364 g/mL
SAMPLE WEIGHT: 0.4000 g
SAMPLE+PEG-ING WEIGHT: 109.9712 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6844 psig
LAST LOW PRESSURE POINT: 25.8844 psig

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.3377 mL/g
TOTAL PORE AREA = 31.498 sq.-m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0495 μm
MEDIAN PORE DIAMETER (AREA) = 0.0420 μm
AVERAGE PORE DIAMETER (AREA) = 0.0469 μm
BULK DENSITY = 0.8937 g/mL
APPEARANT (SKELETAL) DENSITY = 1.2800 g/mL
POROSITY = 30.18 %
STEM VOLUME USED = 33 %
Drug Load: 30.0 % w/w, Spheronization Time: 2.0 minutes, Run #1
Drug Load: 30.0 % w/w, Spheronization Time: 2.0 minutes. Run #2

Poresizer 9320 v2.07

Sample Directory/Number: Data: /41
Operator: Ketan Manta
Sample ID: 3032min2mmlm2z
Submitter: Ketan Manta

Penetrometer Number: 43-0241
Advancing Contact Angle: 130.0 deg
Penetrometer Constant: 10.79 ml/pa
Penetrometer Weight: 67.0934 g
Penetrometer Volume: 3.5443 ml
Maximum Head Pressure: 4.6000 psi
Sample Weight: 0.4306 g

Low Pressure:
Mercury Filling Pressure: 0.6973 psi
Last Low Pressure Point: 25.6376 psi

High Pressure:
Run Type: Automatic
Run Method: Equilibrated
Equilibration Time: 10 seconds

Intrusion Data Summary

Total Intrusion Volume = 0.3580 ml/g
Total Pore Area = 30.147 sq-um/g
Median Pore Diameter (Volume) = 0.0638 um
Median Pore Diameter (Area) = 0.0460 um
Average Pore Diameter (Av/A) = 0.0475 um
Bulk Density = 0.8754 g/ml
Apparent (Skeletal) Density = 1.2750 g/ml
Porosity = 31.34 %
Sinter Volume Used = 35
Drug Load: 30.0 % w/w, Spheronization Time: 2.0 minutes, Run # 3

PRESIZER V320 V2.07

SAMPLE DIRECTORY/METHOD: DATA1 1/27
OPERATOR: Ketan Mehta
SAMPLE ID: 92522fen-2mmrun3
SUBMITER: Ketan Mehta

LP 07:15:40 12/16/96
DP 08:55:59 12/16/96
EP 08:56:00 12/16/96

PENETROMETER NUMBER: 13-0731
PENETROMETER CONSTANT: 10.79 mL/gf
PENETROMETER WEIGHT: 68.6199 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.5800 psi
PENETROMETER VOLUME: 3.5985 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5364 g/mL
SAMPLE WEIGHT: 0.6006 g
SAMPLE PENETRATION WEIGHT: 112.0818 g

LOW PRESSURE:
MERCUORY FILLING PRESSURE: 0.6933 psi
LAST LOW PRESSURE POINT: 25.8316 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.3595 mL/g
TOTAL PORE AREA = 30.107 sq-µm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0640 µm
MEDIAN PORE DIAMETER (AREA) = 0.0410 µm
AVERAGE PORE DIAMETER (4/πA) = 0.0678 µm
SHELL DIAMETER = 0.0514 µm
APPARENT (SKELETAL) DENSITY = 1.5216 g/mL
POROSITY = 35.56 %
STEM VOLUME USED = 35 %
Drug Load: 30.0 % w/w, Spheronization Time: 10.0 minutes, Run #1
Drug Load: 30.0% w/w, Spheronization Time: 10.0 minutes, Run # 2

POREZIER 9220 V2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /44
OPERATOR: Ketan Mehta
SAMPLE (3): SITONIN2
SUBMITTER: Ketan Mehta

LP 00:43:22 12/17/96
HP 03:32:44 12/17/96
REP 01:32:43 12/17/96

PENETROMETER NUMBER: 13-0241
PENETROMETER CONSTANT: 10.79 µL/pf
PENETROMETER WEIGHT: 68.4200 g
STER VOLUME: 0.6100 mL
MAXIMUM HEAD PRESSURE: 4.6800 psi
PENETROMETER VOLUME: 3.5463 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 48.5 dyn/cm
MERCURY DENSITY: 13.5344 g/mL
SAMPLE WEIGHT: 6.0000 g
SAMPLE+MERGING WEIGHT: 111.0860 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6858 psi
LAST LOW PRESSURE POINT: 25.7189 psi

HIGH PRESSURE:
RUN METHOD: AUTOMATIC
EQUILIBRATION TIME: 19 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.3439 mL/g
TOTAL PORE AREA = 29.707 m²/g
MEDIAN PORE DIAMETER (VOLUME) = 0.00693 μm
MEDIAN PORE DIAMETER (AREA) = 0.0449 μm
AVERAGE PORE DIAMETER (V/A) = 0.0463 μm
BULK DENSITY = 0.8843 g/mL
APPEARANT (SKELETAL) DENSITY = 1.2707 g/mL
POROSITY = 30.41 %
STER VOLUME USED = 33 %
Drug Load: 30.0 % w/w, Spheronization Time: 10.0 minutes, Run #3

PRESIZER 9320 V2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /45
OPERATION: Ketan Patel
SAMPLE ID: SATION=m2awutum3
SUBMITTER: Ketan Patel

PENETROMETER NUMBER: 13-0241
PENETROMETER CONSTANT: 10.79  1/mL
PENETROMETER WEIGHT: 68.0890 g
STEM VOLUME: 0.4720 mL
MAXIMUM HEAD PRESSURE: 4.6800 psi
PENETROMETER VOLUME: 3.5443 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
H当初ERCUY SURFACE TENSION: 485.0 dyn/cm
H当初ERCUY DENSITY: 13.5364 g/mL
SAMPLE WEIGHT: 0.4007 g
SAMPLE+PEN+Hg WEIGHT: 110.3431 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6758 psia
LAST LOW PRESSURE POINT: 25.561 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.367 mL/g
TOTAL PORE AREA = 32.897 sq-um/g
MEDIAN PORE DIAMETER (VOLUME) = 0.00086 µm
MEDIAN PORE DIAMETER (AREA) = 0.0414 µm
AVERAGE PORE DIAMETER (V4/A) = 0.0451 µm
BULK DENSITY = 0.8819 g/mL
APARENT (SKELETAL) DENSITY = 1.2840 g/mL
MOISTURE = 30.92 %
STEM VOLUME USED = 54 %
Drug Load: 30.0% w/w, Spheronization Time: 20.0 minutes, Run #1

Poresizer 9320 V2.07

Sample Directory/Number: Data/M /46
Operator: Ketan Mehta
Sample ID: 303920Mz2amn1
Submitter: Ketan Mehta

Penetrometer Number: 13-0131
Penetrometer Constant: 10.79 μL/df
Penetrometer Weight: 68.3189 g
Ster Volume: 0.4120 mL
Maximum Head Pressure: 4.6000 psi
Penetrometer Volume: 3.5685 mL
Sample Weight: 0.4014 g
Sample Penning Weight: 112.0148 g

Low Pressure:
Mercury Filling Pressure: 0.6758 psia
Last Low Pressure Point: 25.5901 psia

High Pressure:
Run Type: Automatic
Run Method: Equilibrated
Equilibration Time: 10 seconds

Intrusion Data Summary

Total Intrusion Volume = 0.3195 mL/g
Total Pore Area = 28.186 sq-μm/g
Median Pore Diameter (Volume) = 0.0584 μm
Median Pore Diameter (Area) = 0.0406 μm
Average Pore Diameter (4V/A) = 0.0454 μm
Bulk Density = 1.0289 g/mL
Apparent (Skeletal) Density = 1.5327 g/mL
Porosity = 32.87%
Ster Volume Used = 31 L
Drug Load: 30.0 % w/w, Spheronization Time: 20.0 minutes, Run # 2

PORESIZER 9320 v2.07

SAMPLE DIRECTORY/MAXBER: DATA /53
OPERATOR: KETAN MEHTA
SAMPLE ID: 30X20my290fUR2
SUBMITTER: KETAN MEHTA

LP 04:20:19 02/18/97
HP 04:58:40 02/18/97
REP 04:58:40 02/18/97

PENETROMETER NUMBER: 13-0131
PENETROMETER CONSTANT: 10.79 µl/pf
PENETROMETER WEIGHT: 68.0736 g
STER VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.00800 psi
PENETROMETER VOLUME: 3.5865 mL
ADVANCING CONTACT ANGLE: 150.0 deg
RECEDING CONTACT ANGLE: 150.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5335 g/mL
SAMPLE WEIGHT: 0.4036 g
SAMPLE-DRAINING WEIGHT: 111.0464 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.5855 psi
LAST LOW PRESSURE POINT: 25 KWP data

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.3552 mL/g
TOTAL POR D AREA = 28.670 wt-%/g
MEDIAN PORE DIAMETER (VOLUME) = 0.013 μm
MEDIAN PORE DIAMETER (AREA) = 0.044 μm
AVERAGE PORE DIAMETER (G/B) = 0.046 μm
NULL DENSITY = 1.0707 g/mL
APPEARANT (SKELETON) DENSITY = 1.5330 g/mL
POROSITY = 33.94 %
STER VOLUME USED = 33 %
Drug Load: 30.0 % w/w, Spheronization Time: 20.0 minutes, Run # 3
Drug Load: 40.0 % w/w, Spheronization Time: 2.0 minutes, Run #1

PEGRESER 9320 v2.07

SAMPLE DIRECTORY/MONUMBER: DATA/155
OPERATOR: KETAN MEHTA
SAMPLE ID: 420Z61n2mmRUN1
SUBMITTER: KETAN MEHTA

PEMETROMETER NUMBER: 13-0131
PEMETROMETER CONSTANT: 10.79 pL/grad
PEMETROMETER WEIGHT: 67.9856 g
STER VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.0000 psi
PEMETROMETER VOLUME: 3.5085 mL
FILLING PRESSURE: 0.5308 psi
LAST LOW PRESSURE POINT: 25.1334 psi

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.5308 psi
LAST LOW PRESSURE POINT: 25.1334 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.3778 mL/g
TOTAL PORE AREA = 25.804 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0949 um
MEDIAN PORE DIAMETER (AREA) = 0.0364 um
AVERAGE PORE DIAMETER (4V/A) = 0.0588 um
BULK DENSITY = 0.8715 g/mL
APPEARANT (SKELETAL) DENSITY = 1.5350 g/mL
POROSITY = 36.71 %
STER VOLUME USED = 37 %
Drug Load: 40.0 % w/w, Spheronization Time: 2.0 minutes, Run # 2

Sample ID: 40528122 RUPM02
Submitter: Ketan Mehta

Penetrometer Number: 13-0941
Penetrometer Constant: 10.79 mL/dL
Penetrometer Weight: 68.7471 g
Ster Volume: 0.4120 mL
Maximum Head Pressure: 4.6600 psi
Penetrometer Volume: 3.5643 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.1535 g/mL
SAMPLE WEIGHT: 0.4099 g
SAMPLE+Pen Weight: 110.7373 g

Low Pressure:
MERCURY FILLING PRESSURE: 0.5508 psi
LAST LOW PRESSURE POINT: 25.5334 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

Intrusion Data Summary

TOTAL INTRUSION VOLUME = 0.3701 mL/g
TOTAL PORE AREA = 26.0800 sq-nm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0952 μm
MEDIAN PORE DIAMETER (AREA) = 0.0585 μm
AVERAGE PORE DIAMETER (AV/A) = 0.0585 μm
BULK DENSITY = 0.8507 g/mL
APPARENT (SKELETAL) DENSITY = 1.2557 g/mL
POROSITy = 32.25 %
STER VOLUME USED = 37 %
Drug Load: 40.0% w/w, Spheronization Time: 2.0 minutes, Run #3

PORESIZER 9320 V2.07

SAMPLE DIRECTORY/MODEL: DATA1 /S7
OPERATOR: Ketan Patel
SAMPLE ID: 14172m0m2/Run#3
SUBMITTER: Ketan Patel

PENETROMETER NUMBER: 13-0131
ADVANCE CONTACT ANGLE: 130.0 deg
RECEIVING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5335 g/mL

PENETROMETER WEIGHT: 68.9978 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 6.6800 psi
SAMPLE WEIGHT: 0.4238 g
SAMPLE PENETRATING VOLUME: 112.2790 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.8863 psi
LAST LOW PRESSURE POINT: 25.747 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.3756 mL/g
TOTAL MOUNT AREA = 25.762 sq-m/g
MEDIAN MOUNT DIAMETER (VOLUME) = 0.0933 μm
MEDIAN MOUNT DIAMETER (AREA) = 0.0361 μm
AVERAGE MOUNT DIAMETER (4V/A) = 0.0900 μm
BULK DENSITY = 0.9723 g/mL
APPARENT (SKELETAL) DENSITY = 1.5270 g/mL
POROSITY = 36.33 %
STEM VOLUME USED = 37 %
Drug Load: 40.0 % w/w, Spheronization Time: 10.0 minutes, Run # 1

PRESIZER 9120 - 2.07

SAMPLE DIRECTORY/NUMBER: DATAT /S
OPERATOR: Ketan Mania
SAMPLE ID: 40Z2mm(0minrun)
SUBMITTER: Ketan Mania

PENETROMETER NUMBER: 13-Q341
PENETROMETER CONSTANT: 10.79 µL/DF
PENETROMETER WEIGHT: 67.7971 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4,8000 psig
PENETROMETER VOLUME: 3.543 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 481.0 dyn/cm
MERCURY DENSITY: 13.535 g/mL
SAMPLE WEIGHT: 0.4095 g
SAMPLE-PEMMING WEIGHT: 116.0473 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.0005 psia
LAST LOW PRESSURE POINT: 25.7454 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 30 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.3392 mL/g
TOTAL PORE AREA = 25.045 m²/m³
MEDIAN PORE DIAMETER (VOLUME) = 0.0685 µm
MEDIAN PORE DIAMETER (AREA) = 0.0489 µm
AVERAGE PORE DIAMETER (4V/SA) = 0.0562 µm
BULK DENSITY = 0.8661 g/mL
APPARENT (SKELETAL) DENSITY = 1.2668 g/mL
POROSITY = 30.05 %
STEM VOLUME USED = 33 %
Drug Load: 40.0% w/w, Spheronization Time: 10.0 minutes, Run #2

Poresizer 9320 V2.07

Sample Directory/Number: Data 1/61
Operator: Ketan Mente
Sample ID: 40532-109d
Submitter: Ketan Mente

Penetrometer Number: 13-0331
Penetrometer Constant: 19.79 µl/°F
Penetrometer Weight: 67.8919 g
Penetrometer Volume: 3.5885 ml

Maximum Head Pressure: 6.6800 psi
Sample Weight: 0.4005 g
Sample Pen+Hg Weight: 111.2862 g

Low Pressure:
Mercury Filling Pressure: 0.6190 psi
Last Low Pressure Point: 25.6197 psi

High Pressure:
Run Type: Automatic
Run Method: Equilibrated
Equilibration Time: 170 seconds

Intrusion Data Summary

| Total Intrusion Volume | 0.3442 ml/g |
|------------------------|-------------|
| Total Pore Area        | 26.370 sq-µm |
| Median Pore Diameter (Volume) | 0.0639 µm |
| Median Pore Diameter (Area) | 0.0453 µm |
| Average Pore Diameter (µm) | 0.0927 µm |
| Bulk Density           | 0.9778 g/ml |
| Apparent (Skeletal) Density | 1.4664 g/ml |
| Poresity                | 33.64% |
| Stem Volume Used        | 34 x       |
Drug Load: 40.0 % w/w, Spheronization Time: 10.0 minutes, Run # 3

Poresizer 9320 v2 07

Sample Directory/Number: DATA1 /62
Operator: Ketan Mente
Sample ID: 402%10minRUN#3
Submitter: Ketan Mente

Penetrometer Number: 13-0241
Penetrometer Constant: 10.79 µl/pf

Advancing Contact Angle: 130.0 deg
Receding Contact Angle: 130.0 deg

Penetrometer Weight: 68.9310 g
Mercury Surface Tension: 48.50 dyn/cm

Ster Volume: 0.4120 mL
Mercury Density: 13.5355 g/mL

Maximum Head Pressure: 6.6800 psi
Sample Weight: 0.4000 g

Penetrometer Volume: 3.3443 mL
Sample-Penning Weight: 111.1706 g

Low Pressure:
Mercury Filling Pressure: 0.6190 psie
Last Low Pressure Point: 25.6197 psie

High Pressure:
Run Type: Automatic
Run Method: Equilibrated
Equilibration Time: 10 seconds

Intrusion Data Summary

Total Intrusion Volume = 0.3414 mL/g
Total Pore Area = 25.649 sq-m/g
Median Pore Diameter (Volume) = 0.0082 µm
Median Pore Diameter (Area) = 0.0453 µm
Average Pore Diameter (4h/4) = 0.0532 µm
Bulk Density = 0.8055 g/mL
Apparent ( Skeletal) Density = 1.2651 g/mL
Porosity = 30.16 %
Ster Volume Used = 33 %
Drug Load: 40.0 % w/w, Spheronization Time: 20.0 minutes, Run # 1

PENUMETER NUMBER: 13-0854
PENUMETER CONSTANT: 10.79 µL/µF
PEMETER WEIGHT: 68.99000 g
STER VOLUME: 0.41200 ml
MAXIMUM HEAD PRESSURE: 4.68000 psi
PEMETER VOLUME: 3.5541 ml
ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5355 g/ml
SAMPLE WEIGHT: 0.4003 g
SAMPLE-PEMETING WEIGHT: 111.2366 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6003 psi
LAST LOW PRESSURE POINT: 29.7527 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.3615 ml/g
TOTAL PORE AREA = 28.265 sq-µm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0577 µm
MEDIAN PORE DIAMETER (AREA) = 0.0453 µm
AVERAGE PORE DIAMETER (S/V) = 0.0512 µm
BULK DENSITY = 0.6666 g/ml
APPARENT (SKELETAL) DENSITY = 1.2614 g/ml
POROSITY = 31.32 %
STER VOLUME USED = 35 %
Drug Load: 40.0 % w/w, Spherization Time: 20.0 minutes, Run #2

Poresizer 9320 v1.07

Sample Directory/Number: GA312 04
Operator: Ketan Mehta
Sample 12: 45.72mmX200mL
Submitter: Ketan Mehta

Pressure: 00:02:03 02/25/97
Report: 02:33:42 02/25/97

Penetrometer Number: 13-0868
Penetrometer Constant: 10.79 μl/gf
Penetrometer Weight: 68.4436 g
Penetrometer Volume: 3.6999 ml
Maximum Head Pressure: 6.6000 psi
Sample Weight: 0.4205 g
Sample+Penning Weight: 112.6359 g

Low Pressure:
Merkury Filling Pressure: 0.6073 psig
Last Low Pressure Point: 25.7327 psig

High Pressure:
Run Type: Automatic
Run Method: Equilibrated
Equilibration Time: 10 seconds

Intrusion Data Summary

Total Intrusion Volume = 0.3645 ml/g
Total Pore Area = 29.098 sq-m/g
Median Pore Diameter (Volume) = 0.0574 μm
Median Pore Diameter (Area) = 0.0452 μm
Average Pore Diameter (4V/A) = 0.0501 μm
Bulk Density = 0.8645 g/ml
Apparent (Skeletal) Density = 1.3621 g/ml
Porosity = 31.51 %
Ster Volume Used = 35 %
Drug Load: 40.0 % w/w, Spheronization Time: 20.0 minutes, Run # 3

Penetrometer: 3.20 v2.07

Sample Directory/Number: DATA1 /65
Operator: Ketan Mote
Sample ID: 40Z2mzo3mRUNI
Submitter: Ketan Mote

Penetrometer Number: 13-21531
Penetrometer Constant: 10.79 m3/dm
Penetrometer Weight: 67.8074 g
Stem Volume: 0.4720 mL
Maximum Head Pressure: 4.6400 psia
Penetrometer Volume: 3.5895 mL

Advancing Contact Angle: 130.0 deg
Receding Contact Angle: 130.0 deg
Mercury Surface Tension: 485.0 dyn/cm
Mercury Density: 13.5333 g/mL
Sample Weight: 0.4902 g
Sample Forming Weight: 111.2070 g

Low Pressure:
Mercury Filling Pressure: 0.7403 psia
Last Low Pressure Point: 25.5971 psia

High Pressure:
Run Type: Automatic
Run Method: Equilibrated
Equilibration Time: 10 seconds

Intrusion Data Summary

Total Intrusion Volume = 0.3578 mL/g
Total Pore Area = 26.258 m2/g
Median Pore Diameter (Volume) = 0.0580 μm
Median Pore Diameter (Area) = 0.0435 μm
Average Pore Diameter (4n/a) = 0.0507 μm
Bulk Density = 0.9735 g/mL
Apparent (Skeletal) Density = 1.0390 g/mL
Porosity = 34.83 %
Stem Volume Used = 35 %

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Appendix 3b

Determination of porosity parameters by mercury intrusion porosimetry. Pellets formulated with different granulation water levels.
Granulation water level: 60% w/w, Run #1

Poresizer 9320 v2.07

Sample Directory/Number: DATA17/75
Operator: Kean Reheja
Sample ID: 102122591waterRUN1
Submitter: Kean Reheja

Penetrometer Number: 13-0654
Penetrometer Constant: 10.79 µL/g
Penetrometer Weight: 68.5228 g
Stem Volume: 0.4120 mL
Maximum Head Pressure: 6.0000 psig
Penetrometer Volume: 3.5541 mL

Low Pressure:
Mercury filling pressure: 1.0350 psia
Last low pressure point: 25.641 psia

High Pressure:
Run Type: Automatic
Run Method: Equilibrated
Equilibration Time: 150 seconds

Intrusion Data Summary

Total Intrusion Volume = 0.2643 mL/g
Total Pore Area = 24.830 m²/mg
Median Pore Diameter (Volume) = 0.0453 µm
Median Pore Diameter (Area) = 0.0453 µm
Average Pore Diameter (A/V/A) = 0.0426 µm
Bulk Density = 0.9527 g/mL
Apparent (Skeletal) Density = 1.2733 g/mL
Porosity = 25.18%
Stem Volume Used = 26 %
Granulation water level: 60 % w/w, Run #2

PORESIZER 9320 v2.07

SAMPLE DIRECTORY/NUMBER: DATA1
OPERATOR: Ketan Bement
SAMPLE ID: 1020%H2O/Grain/Run#2
SUBMITTER: Ketan Bement

LP 01:09:06 03/05/97
HP 01:45:44 03/05/97
REP 01:45:44 03/05/97

PENETROMETER NUMBER: 13-0854
PENETROMETER CONSTANT: 10.79 ml/g
PENETROMETER WEIGHT: 67.6299 g
MAXIMUM HEAD PRESSURE: 4.4800 psi
PENETROMETER VOLUME: 3.5541 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECESSING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
Hg DENSITY: 13.5255 g/mL
SAMPLE WEIGHT: 0.4007 g
SAMPLE PENETRATION WEIGHT: 110.6407 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7988 psi
LAST LOW PRESSURE POINT: 25.6147 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.2619 mL
TOTAL PORE AREA = 24.981 sq-m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0467 µm
MEDIAN PORE DIAMETER (AREA) = 0.0367 µm
AVERAGE PORE DIAMETER (AV/A) = 0.0419 µm
BULK DENSITY = 0.9538 g/mL
APPROXIMATE (SKELETAL) DENSITY = 1.2715 g/mL
POROSITY = 24.98 %
STEM VOLUME USED = 25 %
Granulation water level: 60% w/w, Run #3

PORESIZER 9320 v2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /BD
OPERATOR: Ketan Mehta
SAMPLE ID: 101120MinOwaterRunF3
SUBMITTER: Ketan Mehta

PEFETROMETER NUMBER: 13-0868
PEFETROMETER CONSTANT: 10.79 μL/pf
PEFETROMETER WEIGHT: 68.929 g
PEFETROMETER VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.8000 psi
PEFETROMETER VOLUME: 3.6991 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 405.0 dyn/cm
MERCURY DENSITY: 13.5335 g/mL
SAMPLE WEIGHT: 0.4003 g
MERCURY FILLING PRESSURE: 0.7988 psi
LAST LOW PRESSURE POINT: 25.6147 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.2665 mL/g
TOTAL PORE AREA = 25.547 sq.μ/m/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0475 μm
MEDIAN PORE DIAMETER (AREA) = 0.0370 μm
AVERAGE PORE DIAMETER (4V/A) = 0.0417 μm
BULK DENSITY = 0.9622 g/mL
APPARENT (SKELETAL) DENSITY = 1.2941 g/mL
POROSITY = 25.64%
STER VOLUME USED = 26%
Granulation water level: 65% w/w, Run #1

**Poresizer ST20 V.2.07**

| Sample Directory/Number: Data | Data 1 | Sample ID: TO2OMin651waterRUN#1 | Sample ID: Ketan Mehta |
|--------------------------------|--------|---------------------------------|------------------------|

| Operator: Ketan Mehta         | LP 08:13:56 03/03/97 | HP 04:04:16 03/04/97 | REP 04:05:31 03/04/97 |

- **Penetrometer Number:** 13-0868
- **Penetrometer Constant:** 10.79 µL/pd
- **Penetrometer Weight:** 67.996 g
- **Step Volume:** 0.6120 mL
- **Maximum Measured Pressure:** 46800 psi
- **Penetrometer Volume:** 3.6991 mL
- **Advancing Contact Angle:** 130.0 deg
- **Receding Contact Angle:** 130.0 deg
- **Mercury Surface Tension:** 485.0 dyn/cm
- **Mercury Density:** 13.5335 g/mL
- **Sample Weight:** 0.4216 g
- **Sample+Pen+Hg Weight:** 112.0299 g

**Low Pressure:**
- **Mercury Filling Pressure:** 0.7065 psi
- **Last Low Pressure Point:** 25.9189 psi

**High Pressure:**
- **Run Type:** Automatic
- **Run Method:** Equilibrated
- **Equilibration Time:** 10 seconds

**Intrusion Data Summary**

| Total Intrusion Volume | 0.3929 mL/g |
| Total Pore Area       | 34.803 sq-µm |
| Median Pore Diameter (Volume) | 0.0453 µm |
| Median Pore Diameter (Area) | 0.0372 µm |
| Average Pore Diameter (4V/4A) | 0.0452 µm |
| Bulk Density          | 0.8856 g/mL |
| Apparent (Skeletal) Dens. | 1.2843 g/mL |
| Porosity              | 33.54 % |
| Step Volume Used      | 38 % |
Granulation water level: 65 % w/w, Run # 2

PORESIZER 9320 V2.07

SAMPLE DIRECTORY/NUMBER: DATA 176
OPERATOR: Ketan Mehta
SAMPLE ID: 10120min65water RUN#2
SUBMITTER: Ketan Mehta

LOW PRESSURE:
MERURY FILLING PRESSURE: 0.7465 pa
LAST LOW PRESSURE POINT: 25.2189 pa

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.3850 mL/g
TOTAL PORE AREA = 32.234 sq-nm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0641 µm
MEDIAN PORE DIAMETER (AREA) = 0.0599 µm
AVERAGE PORE DIAMETER (4V/A) = 0.0473 µm
BULK DENSITY = 0.9465 g/mL
APPEARANT (SKELETAL) DENSITY = 1.4975 g/mL
POROSITY = 36.44 %
STEREO VOLUME USED = 38
Granulation water level: 65% w/w, Run #3

| Sample Directory/Number: DATA1 | PAGE 1 |
|-------------------------------|--------|
| Operator: Ketan Mehta          | LP 06:21:30 05/04/97 |
| Sample ID: 1002001065waterRUNS3 | HP 07:01:01 05/04/97 |
| Submitter: Ketan Mehta         | REP 07:01:02 05/04/97 |

- Penetrometer Number: 13-0241
- Penetrometer Constant: 10.79 mL/ps
- Penetrometer Weight: 66.9028 g
- Steer Volume: 0.4120 mL
- Maximum Head Pressure: 4.4000 psi
- Penetrometer Volume: 3.5443 mL
- Advancing Contact Angle: 150.0 deg
- Receding Contact Angle: 130.0 deg
- Mercury Surface Tension: 485.0 dyn/cm
- Mercury Density: 13.335 g/mL
- Sample Weight: 0.4033 g
- Sample+Pen Weight: 110.6948 g

Low Pressure:

- Mercury Filling Pressure: 1.0350 psia
- Last Low Pressure Point: 29.6341 psia

High Pressure:

- Run Type: Automatic
- Run Method: Equilibrated
- Equilibration Time: 10 seconds

Intrusion Data Summary

- Total Intrusion Volume = 0.3863 mL/g
- Total Pore Area = 34.582 eq-m2/g
- Median Pore Diameter (Volume) = 0.0453 μm
- Median Pore Diameter (Area) = 0.0397 μm
- Average Pore Diameter (4/V) = 0.0366 μm
- Bulk Density = 0.4444 g/mL
- Apparent (Skeletal) Density = 1.2575 g/mL
- Porosity = 32.69 %
- Steer Volume Used = 38 %
Granulation water level: 70% w/w, Run #1

MORRISER R200-12 07

SAMPLE DIRECTORY/NUMBER: DATA 1/28
OPERATOR: Ketan Mehta
SAMPLE ID: T000201999
SUBMITTER: Ketan Mehta

LP 03:09:15 12/02/96
HP 04:41:16 12/02/96
REP 04:41:17 12/02/96

PETROMETER NUMBER: 13-0931
PETROMETER CONSTANT: 10.79 μL/s
PETROMETER WEIGHT: 68.6358 g
STER VOLUME: 0.6120 mL
MINIMUM HEAD PRESSURE: 4.0000 psi
PETROMETER VOLUME: 3.6417 mL
ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5473 g/mL
SAMPLE WEIGHT: 0.4025 g
SAMPLE+PER+WEIGHT: 111.8144 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6790 psia
LAST LOW PRESSURE POINT: 25.9079 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.4094 mL/g
TOTAL PORE AREA = 58.662 sq-μm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0483 μm
MEDIAN PORE DIAMETER (AREA) = 0.0436 μm
AVERAGE PORE DIAMETER (SA/SA) = 0.0424 μm
BULK DENSITY = 0.8540 g/mL
APPEARANT (SKELETAL) DENSITY = 1.2664 g/mL
POROSITY = 34.14 %
STERE VOLUME USED = 40 %
Granulation water level: 70 % w/w, Run # 2

PENETROMETER NUMBER: 13-Q131
PENETROMETER CONSTANT: 10.79 ml/psi
PENETROMETER HEIGHT: 07.650 g
STEM VOLUME: 0.4120 ml
MAXIMUM HEAD PRESSURE: 4.6800 psi
PENETROMETER VOLUME: 5.6178 ml
ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5113 g/ml
SAMPLE WEIGHT: 0.4010 g
SAMPLE-PENETRING WEIGHT: 110.8076 g
LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7958 psi
LAST LOW PRESSURE POINT: 25.8911 psi
HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.6294 ml/g
TOTAL PORE AREA = 38.206 a-m2/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0483 um
MEDIAN PORE DIAMETER (AREA) = 0.0626 um
AVERAGE PORE DIAMETER (VOLUME) = 0.0426 um
AVERAGE PORE DIAMETER (AREA) = 0.0424 um
BULK DENSITY = 0.6377 g/ml
APARENT (SKELETAL) DENSITY = 1.2695 g/ml
PORE DENSITY = 34.07 %
STEM VOLUME USED = 40 %
Granulation water level: 70% w/w, Run #3

SAMPLE DIRECTORY/NUMBER: DATA1 130
OPERATOR: Yetan manta
SAMPLE ID: 1022019-240m3
SUBMITTER: Yetan manta

PETROMETER NUMBER: 13-0241
PETROMETER CONSTANT: 10.79 µL/pa
PETROMETER WEIGHT: 69.1056 g
STER VOLUME: 0.4120 mL
MAXIMUM LOAD PRESSURE: 4.6020 psi
PETROMETER VOLUME: 3.5443 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECORDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.513 g/mL
SAMPLE WEIGHT: 0.4623 g
SAMPLE-PEARING WEIGHT: 110.8000 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.7958 psi
LAST LOW PRESSURE POINT: 25.8991 psi

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY
TOTAL INTRUSION VOLUME = 0.4056 mL/g
TOTAL PORE AREA = 58.620 sq-µm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0420 µm
MEDIAN PORE DIAMETER (AREA) = 0.0627 µm
AVERAGE PORE DIAMETER (4V/A) = 0.0420 µm
BULK DENSITY = 0.8315 g/mL
APPARENT (SKELETAL) DENSITY = 1.2151 g/mL
POROSITY = 42.98 %
STER VOLUME USED = 40 µ
Appendix 3c

Determination of porosity parameters by mercury intrusion porosimetry. Nifedipine and nifedipine: pluronic® F-68 (1:1) solid dispersion pellets after different dissolution time intervals.
Nifedipine pellets, dissolution time: 0 hours

Poresizer 9320 V2.07

Sample directory/number: DATA1 /81
Operator: Ketan Mehta
Sample ID: 20% nifedipine beads 2 mm, 0 hours
Submitter: Ketan Mehta

Penetrrometer number: 13-0866
Penetrrometer constant: 10.79 μL/pF
Penetrrometer weight: 68.1624 g
Stem volume: 0.4120 mL
Maximum head pressure: 4,680 psi
Penetrrometer volume: 3.6991 mL

Advancing contact angle: 130.0 deg
Receding contact angle: 130.0 deg
Mercury surface tension: 485.0 dyn/cm
Mercury density: 13.5335 g/mL

Low pressure:
Mercury filling pressure: 0.7450 psia
Last low pressure point: 25.4604 psia

High pressure:
Run type: Automatic
Run method: Equilibrated
Equilibration time: 10 seconds

Intrusion data summary

Total intrusion volume = 0.2815 mL/g
Total pore area = 27.425 sq-μm/g
Median pore diameter (volume) = 0.0480 μm
Median pore diameter (area) = 0.0330 μm
Average pore diameter (4V/A) = 0.0411 μm
Bulk density = 0.9622 g/mL
Apparent (skeletal) density = 1.3198 g/mL
Porosity = 27.09 %
Stem volume used = 21 %
Nifedipine pellets, dissolution time: 2.0 hours

PORESIZER 9320 V2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /83
OPERATOR: Ketan Mehta
SAMPLE ID: 20%nifedipine beads2hr
SUBMITTER: Ketan Mehta

LP 00:13:47 04/07/97
HP 00:48:22 04/07/97
REP 00:48:23 04/07/97

PENETROMETER NUMBER: 13-0868
PENETROMETER CONSTANT: 10.79 µL/pF
PENETROMETER WEIGHT: 67.9982 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.6800 psi
PENETROMETER VOLUME: 3.6991 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5335 g/mL
MERCURY FILLING PRESSURE: 0.6052 psia
LAST LOW PRESSURE POINT: 25.5137 psia
HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.4650 mL/g
TOTAL PORE AREA = 27.813 sq-μm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.0814 μm
MEDIAN PORE DIAMETER (AREA) = 0.0318 μm
AVERAGE PORE DIAMETER (4V/A) = 0.0669 μm
BULK DENSITY = 0.8086 g/mL
APPARENT (SKELETAL) DENSITY = 1.2960 g/mL
POROSITY = 37.61 %
STEM VOLUME USED = 34 %
Nifedipine pellets, dissolution time: 4.0 hours

PORESIZER 9320 V2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /85
OPERATOR: Ketan Mehta
SAMPLE ID: 20% nifedipine beads 2mm, 4 hours
SUBMITTER: Ketan Mehta

LP 05:42:16 04/07/97
HP 06:18:05 04/07/97
REP 06:18:06 04/07/97

PENETROMETER NUMBER: 13-0868
PENETROMETER CONSTANT: 10.79 µL/pF
PENETROMETER WEIGHT: 68.1666 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAD PRESSURE: 4.6800 psi
PENETROMETER VOLUME: 3.6991 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5335 g/mL
SAMPLE WEIGHT: 0.3017 g
SAMPLE+PEN+Hg WEIGHT: 113.4587 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.8105 psia
LAST LOW PRESSURE POINT: 28.5694 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.4904 mL/g
TOTAL PORE AREA = 26.559 sq-•/g
MEDIAN PORE DIAMETER (VOLUME) = 0.1530 µm
MEDIAN PORE DIAMETER (AREA) = 0.0305 µm
AVERAGE PORE DIAMETER (4V/A) = 0.0739 µm
BULK DENSITY = 0.8051 g/mL
APPARENT (SKELETAL) DENSITY = 1.3303 g/mL
POROSITY = 39.48 %
STEM VOLUME USED = 36 %
Nifedipine pellets, dissolution time: 6.0 hours

PORESIZER 9320 V2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /87
OPERATOR: Ketan Mehta
SAMPLE ID: 20% nifedipine beads 2mm, 6 hrs
SUBMITTER: Ketan Mehta

PENETROMETER NUMBER: 13-0868
ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT: 10.79 µL/pf
RECEDING CONTACT ANGLE: 130.0 deg
PENETROMETER WEIGHT: 67.9340 g
MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME: 0.4120 mL
MERCURY DENSITY: 13.5335 g/mL
MAXIMUM HEAD PRESSURE: 4.6800 psi
SAMPLE WEIGHT: 0.2671 g
PENETROMETER VOLUME: 3.6991 mL
SAMPLE+PEN+Hg WEIGHT: 113.6380 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.5458 psia
LAST LOW PRESSURE POINT: 28.4771 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.5038 mL/g
TOTAL PORE AREA = 25.529 sq-µm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.4056 µm
MEDIAN PORE DIAMETER (AREA) = 0.0296 µm
AVERAGE PORE DIAMETER (4V/A) = 0.0789 µm
BULK DENSITY = 0.7816 g/mL
APPARENT (SKELETAL) DENSITY = 1.2893 g/mL
POROSITY = 39.38 %
STEM VOLUME USED = 33 %
Nifedipine pellets, dissolution time: 8.0 hours

FORESIZER 9320 V2.07

SAMPLE DIRECTORY/NUMBER: DATA1 /89
OPERATOR: Ketan Mehta
SAMPLE ID: 20% nifedipine beads, Zma, 8hours
SUBMITTER: Ketan Mehta

LP 00:04:47 04/09/97
HP 00:39:37 04/09/97
REP 00:39:37 04/09/97

PENETROMETER NUMBER: 13-0866
PENETROMETER CONSTANT: 10.79 μL/pF
PENETROMETER WEIGHT: 68.2047 g
STEM VOLUME: 0.4120 mL
MAXIMUM HEAP PRESSURE: 4.6800 psi
PENETROMETER VOLUME: 3.6991 mL

ADVANCING CONTACT ANGLE: 130.0 deg
RECEDING CONTACT ANGLE: 130.0 deg
MERCURY SURFACE TENSION: 485.0 dyn/cm
MERCURY DENSITY: 13.5335 g/mL
SAMPLE WEIGHT: 0.2549 g
SAMPLE+PEN+Hg WEIGHT: 114.1119 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.6518 psia
LAST LOW PRESSURE POINT: 28.4637 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 1d seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.4950 mL/g
TOTAL PORE AREA = 26.074 sq-μm/g
MEDIAN PORE DIAMETER (VOLUME) = 0.5036 μm
MEDIAN PORE DIAMETER (AREA) = 0.0290 μm
AVERAGE PORE DIAMETER (A/V/A) = 0.0759 μm
BULK DENSITY = 0.7623 g/mL
APPARENT (SKELETAL) DENSITY = 1.2768 g/mL
POROSITY = 38.73 %
Nifedipine: Pluronic® F-68 solid dispersion pellets, dissolution time: 0 hours

| Parameter                                      | Value                        |
|------------------------------------------------|------------------------------|
| Penetrometer number                            | 13-0854                      |
| Penetrometer constant                          | 10.79 µL/µF                  |
| Penetrometer weight                            | 68.3914 g                    |
| STEM volume                                    | 0.4120 mL                    |
| Maximum head pressure                          | 4.6800 psi                   |
| Penetrometer volume                            | 3.5541 mL                    |

Advancing contact angle: 130.0 deg
Receding contact angle: 130.0 deg
Mercury surface tension: 480.0 dyn/cm
Mercury density: 13.5335 g/mL
Mercury filling pressure: 0.7450 psi
Last low pressure point: 25.4604 psi

Low pressure:

- SAMPLE DIRECTOR/NUMBER: DATA1 /02
- OPERATOR: Ketan Mehta
- SAMPLE ID: 1:NFD SD 0.01 hours
- SUBMITTER: Ketan Mehta
- LP 07:42:00 04/06/97

High pressure:

- RUN TYPE: AUTOMATIC
- RUN METHOD: EQUILIBRATED
- EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

- TOTAL INTRUSION VOLUME = 0.1636 mL/g
- TOTAL PORE AREA = 18.159 sq-µ/m²/g
- MEDIAN PORE DIAMETER (VOLUME) = 0.0518 µm
- MEDIAN PORE DIAMETER (AREA) = 0.0164 µm
- AVERAGE PORE DIAMETER (4V/Å) = 0.0360 µm
- BULK DENSITY = 1.0702 g/mL
- APPARENT (SKELETAL) DENSITY = 1.2974 g/mL
- POROSITY = 17.51 %

STEM VOLUME USED = 12 %
Nifedipine: Pluronic® F-68 solid dispersion pellets, dissolution time: 2.0 hours

Poresizer 9320 V2.07

Sample Directory/Number: DATA1 /B4
Operator: Ketan Mehta
Sample ID: 1:Nifedipine SD, 2mm, 2 hrs
Submitter: Ketan Mehta

Penetrometer Number: 13-0854
Penetrometer Constant: 10.79 μL/PF
Penetrometer Weight: 68.3229 g
Penetrometer Volume: 0.4120 mL
Maximum Head Pressure: 4.6800 psi
Penetrometer Volume: 3.5541 mL

Low Pressure:
Merkury Filling Pressure: 0.6052 psi
Last Low Pressure Point: 25.5137 psi

High Pressure:
Run Type: Automatic
Run Method: Equilibrated
Equilibration Time: 10 seconds

Intrusion Data Summary

Total Intrusion Volume = 0.3527 mL/g
Total Pore Area = 12.105 sq-μm/g
Median Pore Diameter (Volume) = 11.4396 μm
Median Pore Diameter (Area) = 0.0109 μm
Average Pore Diameter (4V/A) = 0.1166 μm
Bulk Density = 0.8894 g/mL
Apparent (Skeletal) Density = 1.2960 g/mL
Porosity = 31.37 %
Stem Volume Used = 22 %****
Nifedipine: Pluronic® F-68 solid dispersion pellets, dissolution time: 4.0 hours
Nifedipine: Pluronic® F-68 solid dispersion pellets, dissolution time: 6.0 hours

PORESIZER 9320 V2.07

SAMPLE DIRECTORY/NUMBER: DAT1 /88
OPERATOR: ketan mehta
SAMPLE ID: 1:nifedipine SO, 2mm, 6 hrs
SUBMITTER: Ketan Mehta

PENETROMETER NUMBER: 13-0241 ADVANCING CONTACT ANGLE: 130.0 deg
PENETROMETER CONSTANT: 10.79 µL/pf RECEIVING CONTACT ANGLE: 130.0 deg
PENETROMETER WEIGHT: 69.0044 g MERCURY SURFACE TENSION: 485.0 dyn/cm
STEM VOLUME: 0.4120 ml MERCURY DENSITY: 13.5335 g/ml
MAXIMUM HEAD PRESSURE: 4.6800 psi SAMPLE WEIGHT: 0.1489 g
PENETROMETER VOLUME: 3.5443 ml SAMPLE+PEN+Hg WEIGHT: 114.3570 g

LOW PRESSURE:
MERCURY FILLING PRESSURE: 0.5458 psia
LAST LOW PRESSURE POINT: 28.4/31 psia

HIGH PRESSURE:
RUN TYPE: AUTOMATIC
RUN METHOD: EQUILIBRATED
EQUILIBRATION TIME: 10 seconds

INTRUSION DATA SUMMARY

TOTAL INTRUSION VOLUME = 0.5703 ml/g
TOTAL PORE AREA = 18.161 sq-µm/g
MEDIAN PORE DIAMETER (VOLUME) = 13.7318 µm
MEDIAN PORE DIAMETER (AREA) = 0.0118 µm
AVERAGE PORE DIAMETER (4V/A) = 0.1256 µm
BULK DENSITY = 0.7293 g/ml
APPARENT (SKELETAL) DENSITY = 1.2487 g/ml
POROSITY = 41.59 %
STEM VOLUME USED = 21 %
Nifedipine: Pluronic® F-68 solid dispersion pellets, dissolution time: 8.0 hours

**Sample Directory/Number:** DATA1 /90

**Operator:** Ketan Mehta

**Sample ID:** 1:1 nifedipine SD, 2mm, 8 hours

**Submitter:** Ketan Mehta

**Penetrometer Number:** 13-Q241

**Penetrometer Constant:** 10.79 μL/pF

**Penetrometer Weight:** 68.3024 g

**STEM Volume:** 0.4120 mL

**Maximum Head Pressure:** 4.6800 psi

**Penetrometer Volume:** 3.5443 mL

**Low Pressure:**

- MERCURY FILLING PRESSURE: 0.6518 psia
- LAST LOW PRESSURE POINT: 28.4637 psia

**High Pressure:**

- RUN TYPE: AUTOMATIC
- RUN METHOD: EQUILIBRATED
- EQUILIBRATION TIME: 10 seconds

**Intrusion Data Summary**

- TOTAL INTRUSION VOLUME = 0.5925 mL/g
- TOTAL PORE AREA = 20.711 sq-μm/g
- MEDIAN PORE DIAMETER (VOLUME) = 16.744 μm
- MEDIAN PORE DIAMETER (AREA) = 0.0979 μm
- AVERAGE PORE DIAMETER (A/V) = 0.1144 μm
- BULK DENSITY = 0.6928 g/mL
- APPARENT (SKELETAL) DENSITY = 1.1752 g/mL
- POROSITY = 41.05 %
- STEM VOLUME USED = 11 % ****
Appendix 4

Determination of nifedipine in plasma after oral administration of nifedipine erosion matrix pellet capsule and Adalat® soft gelatin capsule in fasted dogs.
HPLC METHOD VALIDATION:

DETERMINATION OF NIFEDIPINE IN PLASMA AFTER ORAL ADMINISTRATION OF NIFEDIPINE EROSION MATRIX PELLETS AND ADALAT® SOFT GELATIN CAPSULES IN FASTED DOGS.

1. TEST ARTICLES:

Nifedipine erosion matrix pellets (30 mg capsules, Lot # KM 280/2).

Adalat® soft gelatin capsules (10 mg and 20 mg, Lot # 6 EAB and 5 HAX respectively manufactured by Bayer Corporation, West Haven, CT, USA).

2. HPLC METHOD:

System:

Pump: Waters 600 E Multi Solvent Delivery System (Waters Corporation, Milford, MA, USA).

Injector: Waters 717 Plus Auto Sampler (Waters Corporation, Milford, MA, USA).

Column: Zorbax ODS, 4-6 microns reverse phase, 25 cm X 4.6 mm (I. D., Dupont Inc., Wilmington, DE).

Heater: Column Heator Model Code 600 (Waters Corporation, Milford, MA, USA).

Detector: Variable wavelength detector, Model Spectra Physics 100, UV/VIS (Spectra Physics, USA).
Parameters:

Flow Rate: 0.8 mL/min
Injection Vol: 20 µL
Col Temp: 55°C
Col Pressure: 1200 Psi
Detector: $\lambda_{\text{max}}$, 237 nm, 0.001 AUFS
Run Time: 30 minutes

Solutions:

Mobile Phase:
0.01 M disodium hydrogen phosphate buffer: methanol (45:55) was mixed for 30 minutes. Before mixing, the buffer was brought to pH 6.1 with 50% v/v phosphoric acid. This solution was then sonicated for 10 minutes and was filtered through a 0.5µ filter.

Extraction Solvent:
Chloroform : acetone were mixed in ratio of 1:1 for 30 minutes and was used as the extraction solvent for nifedipine from the plasma.

3. LINEARITY:
Linearity of nifedipine in methanol and plasma samples spiked with standard methanolic solution of nifedipine was determined by simple linear regression method. Figure 1
depicts the standard curve and linear regression of nifedipine in methanol and plasma. The following concentrations were used for linearity determinations.

| Solution # | Concentration in methanol and plasma (µg/mL) |
|------------|---------------------------------------------|
| 1.         | 0.05014                                     |
| 2.         | 0.10028                                     |
| 3.         | 0.20050                                     |
| 4.         | 0.40010                                     |
| 5.         | 0.60480                                     |
| 6.         | 0.80220                                     |
| 7.         | 1.00280                                     |
| 8.         | 10.02800                                    |

Correlation coefficient for linearity determinations in methanol was 0.9998 and in plasma was 0.9940. Extraction ratio of drug from plasma to organic phase at all concentrations was not less than 95%.

4. PRECISION:

Assay precision was determined by plotting the peak height ratios of triplicate injections of nifedipine samples of known concentrations against the standard curves generated in the previous section. The mean % difference between the actual concentration of the samples and that determined by the standard curve were always below 5% during the entire analysis period.
5. REPRESENTATIVE CHROMATOGRAMS:

Figures 2 through 41 are the chromatograms of plasma samples after injection, obtained from four dogs each administered with nifedipine erosion matrix pellet capsule (30 mg/dog/day) at 0, 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours. Figures 42 through 73 are the chromatograms of plasma samples after injection, obtained from four dogs each administered with Adalat® soft gelatin capsule (10 + 20 mg/dog/day) at 0, 0.5, 1, 2, 4, 6, 8 and 12 hours.
Figure 1
Calibration graph of nifedipine in methanol and plasma.

methanol, $Y = 2.7097X - 0.0127$, $r^2 = 0.9998$

plasma, $Y = 2.28744X + 0.0731$, $r^2 = 0.9940$
Figure 2

Chromatogram of plasma sample obtained from dog #1 administered with nifedipine erosion matrix pellet capsule at 0.0 hours.
Figure 3

Chromatogram of plasma sample obtained from dog #1 administered with nifedipine erosion matrix pellet capsule at 1.0 hours.
Figure 4

Chromatogram of plasma sample obtained from dog #1 administered with nifedipine erosion matrix pellet capsule at 2.0 hours.
Figure 5

Chromatogram of plasma sample obtained from dog #1 administered with nifedipine erosion matrix pellet capsule at 4.0 hours.
Figure 6

Chromatogram of plasma sample obtained from dog #1 administered with nifedipine erosion matrix pellet capsule at 6.0 hours.
Figure 7

Chromatogram of plasma sample obtained from dog #1 administered with nifedipine erosion matrix pellet capsule at 8.0 hours.
Figure 8

Chromatogram of plasma sample obtained from dog #1 administered with nifedipine erosion matrix pellet capsule at 12.0 hours.
Figure 9

Chromatogram of plasma sample obtained from dog #1 administered with nifedipine erosion matrix pellet capsule at 16.0 hours.
Figure 10

Chromatogram of plasma sample obtained from dog #1 administered with nifedipine erosion matrix pellet capsule at 20.0 hours.
Figure 11

Chromatogram of plasma sample obtained from dog #1 administered with nifedipine erosion matrix pellet capsule at 24.0 hours.
Chromatogram of plasma sample obtained from dog #2 administered with nifedipine erosion matrix pellet capsule at 0.0 hours.
Figure 13

Chromatogram of plasma sample obtained from dog #2 administered with nifedipine erosion matrix pellet capsule at 1.0 hours.
Figure 14

Chromatogram of plasma sample obtained from dog #2 administered with nifedipine erosion matrix pellet capsule at 2.0 hours.
Figure 15

Chromatogram of plasma sample obtained from dog #2 administered with nifedipine erosion matrix pellet capsule at 4.0 hours.
Figure 16

Chromatogram of plasma sample obtained from dog #2 administered with nifedipine erosion matrix pellet capsule at 6.0 hours.
Chromatogram of plasma sample obtained from dog #2 administered with nifedipine erosion matrix pellet capsule at 8.0 hours.
Figure 18

Chromatogram of plasma sample obtained from dog #2 administered with nifedipine erosion matrix pellet capsule at 12.0 hours.
Chromatogram of plasma sample obtained from dog #2 administered with nifedipine erosion matrix pellet capsule at 16.0 hours.
Figure 20

Chromatogram of plasma sample obtained from dog # 2 administered with nifedipine erosion matrix pellet capsule at 20.0 hours.
Figure 21

Chromatogram of plasma sample obtained from dog #2 administered with nifedipine erosion matrix pellet capsule at 24.0 hours.
Figure 22
Chromatogram of plasma sample obtained from dog #3 administered with nifedipine erosion matrix pellet capsule at 0.0 hours.
Figure 23

Chromatogram of plasma sample obtained from dog #3 administered with nifedipine erosion matrix pellet capsule at 1.0 hours.
Figure 24

Chromatogram of plasma sample obtained from dog # 3 administered with nifedipine erosion matrix pellet capsule at 2.0 hours.
Figure 25

Chromatogram of plasma sample obtained from dog #3 administered with nifedipine erosion matrix pellet capsule at 4.0 hours.
Figure 26

Chromatogram of plasma sample obtained from dog #3 administered with nifedipine erosion matrix pellet capsule at 6.0 hours.
Figure 27

Chromatogram of plasma sample obtained from dog #3 administered with nifedipine erosion matrix pellet capsule at 8.0 hours.
Figure 28

Chromatogram of plasma sample obtained from dog # 3 administered with nifedipine erosion matrix pellet capsule at 12.0 hours.
Figure 29

Chromatogram of plasma sample obtained from dog #3 administered with nifedipine erosion matrix pellet capsule at 16.0 hours.
Figure 30

Chromatogram of plasma sample obtained from dog #3 administered with nifedipine erosion matrix pellet capsule at 20.0 hours.
Figure 31

Chromatogram of plasma sample obtained from dog #3 administered with nifedipine erosion matrix pellet capsule at 24.0 hours.
Figure 32

Chromatogram of plasma sample obtained from dog #4 administered with nifedipine erosion matrix pellet capsule at 0.0 hours.
Figure 33

Chromatogram of plasma sample obtained from dog #4 administered with nifedipine erosion matrix pellet capsule at 1.0 hours.
Figure 34

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 2.0 hours.
Figure 35

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 4.0 hours.
Figure 36

Chromatogram of plasma sample obtained from dog #4 administered with nifedipine erosion matrix pellet capsule at 6.0 hours.
Figure 37

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 8.0 hours.
Chromatogram of plasma sample obtained from dog #4 administered with nifedipine erosion matrix pellet capsule at 12.0 hours.
Chromatogram of plasma sample obtained from dog #4 administered with nifedipine erosion matrix pellet capsule at 16.0 hours.
Figure 40

Chromatogram of plasma sample obtained from dog # 4 administered with nifedipine erosion matrix pellet capsule at 20.0 hours.
Figure 41

Chromatogram of plasma sample obtained from dog #4 administered with nifedipine erosion matrix pellet capsule at 24.0 hours.
Figure 42

Chromatogram of plasma sample obtained from dog #1 administered with Adalat soft gelatin capsules at 0.0 hours.
Figure 43

Chromatogram of plasma sample obtained from dog #1 administered with Adalat soft gelatin capsules at 0.5 hours.
Figure 44

Chromatogram of plasma sample obtained from dog # 1 administered with Adalat soft gelatin capsules at 1.0 hours.
Figure 45

Chromatogram of plasma sample obtained from dog # 1 administered with Adalat soft gelatin capsules at 2.0 hours.
Figure 46
Chromatogram of plasma sample obtained from dog #1 administered with Adalat soft gelatin capsules at 4.0 hours.
Figure 47

Chromatogram of plasma sample obtained from dog #1 administered with Adalat soft gelatin capsules at 6.0 hours.
Figure 48

Chromatogram of plasma sample obtained from dog #1 administered with Adalat soft gelatin capsules at 8.0 hours.
Figure 49

Chromatogram of plasma sample obtained from dog # 1 administered with Adalat soft gelatin capsules at 12.0 hours.
Figure 50

Chromatogram of plasma sample obtained from dog # 2 administered with Adalat soft gelatin capsules at 0.0 hours.
Figure 51

Chromatogram of plasma sample obtained from dog #2 administered with Adalat soft gelatin capsules at 0.5 hours.
Figure 52
Chromatogram of plasma sample obtained from dog #2 administered with Adalat soft gelatin capsules at 1.0 hours.
Figure 5.3

Chromatogram of plasma sample obtained from dog #2 administered with Adalat soft gelatin capsules at 2.0 hours.
Figure 54

Chromatogram of plasma sample obtained from dog # 2 administered with Adalat soft gelatin capsules at 4.0 hours.
Figure 55

Chromatogram of plasma sample obtained from dog # 2 administered with Adalat soft gelatin capsules at 6.0 hours.
Figure 56

Chromatogram of plasma sample obtained from dog #2 administered with Adalat soft gelatin capsules at 8.0 hours.
Figure 57

Chromatogram of plasma sample obtained from dog #2 administered with Adalat soft gelatin capsules at 12.0 hours.
Figure 58

Chromatogram of plasma sample obtained from dog # 3 administered with Adalat soft gelatin capsules at 0.0 hours.
Figure 59

Chromatogram of plasma sample obtained from dog # 3 administered with Adalat soft gelatin capsules at 0.5 hours.
Figure 60

Chromatogram of plasma sample obtained from dog #3 administered with Adalat soft gelatin capsules at 1.0 hours.
Figure 61

Chromatogram of plasma sample obtained from dog # 3 administered with Adalat soft gelatin capsules at 2.0 hours.
Figure 62

Chromatogram of plasma sample obtained from dog #3 administered with Adalat soft gelatin capsules at 4.0 hours.
Figure 64

Chromatogram of plasma sample obtained from dog #3 administered with Adalat soft gelatin capsules at 8.0 hours.
Figure 65

Chromatogram of plasma sample obtained from dog #3 administered with Adalat soft gelatin capsules at 12.0 hours.
Figure 66

Chromatogram of plasma sample obtained from dog #4 administered with Adalat soft gelatin capsules at 0.0 hours.
Figure 67

Chromatogram of plasma sample obtained from dog # 4 administered with Adalat soft gelatin capsules at 0.5 hours.
Figure 68

Chromatogram of plasma sample obtained from dog #4 administered with Adalat soft gelatin capsules at 1.0 hours.
Figure 69

Chromatogram of plasma sample obtained from dog #4 administered with Adalat soft gelatin capsules at 2.0 hours.
Figure 70

Chromatogram of plasma sample obtained from dog # 4 administered with Adalat soft

gelatin capsules at 4.0 hours.
Figure 71

Chromatogram of plasma sample obtained from dog #4 administered with Adalat soft gelatin capsules at 6.0 hours.
Figure 72

Chromatogram of plasma sample obtained from dog # 4 administered with Adalat soft gelatin capsules at 8.0 hours.
Figure 73

Chromatogram of plasma sample obtained from dog #4 administered with Adalat soft gelatin capsules at 12.0 hours.
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