Design and In Vivo Evaluation of Solid Dispersions Using Manidipine

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ABSTRACT

The study was aimed to formulate solid dispersions of Manidipine by using different novel carriers like Labrafac PG, Kolliwax RH 40, Soluplus, Kolliwax GMS II, Kolliphor EL and SLS in drug carrier ratio by using solvent evaporation method. The formulations were characterized for physical appearance, solubility and in vitro dissolution studies. The optimized formulation was characterized by, Formulation SD13 was found to be optimized one based on the solubility, dissolution and other parameters using Kolliwax GMS II and SLS. The drug release of the optimized formulation was found to be 99.41±5.38% within 90min. Powder X-ray diffraction studies performed on solid dispersion showed that Manidipine existed in the amorphous form within the solid dispersion formulation fabricated using the solvent evaporation process. Additionally, scanning electron microscopy studies suggested the conversion of crystalline Manidipine to an amorphous form. Furthermore, the pharmacokinetic parameters of the optimized Manidipine solid dispersions showed increased AUC0–t, AUC0–∞ and Cmax by 2-folds. These results suggest that the preparation of Manidipine solid dispersions using the solvent evaporation technique without might be a promising approach for improving the oral bioavailability of Manidipine. Therefore, the solid dispersions using Kolliwax GMS II as hydrophilic carrier in the combination of SLS can be successfully used for improvement of solubility and bioavailability of Manidipine.

Keywords: Manidipine, Solvent Evaporation method, Kolliwax GMS II, Hypertension, Bioavailability studies.

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INTRODUCTION

Poorly water-soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity\(^1\). There are various techniques available to improve the solubility of poorly soluble drugs, such as micronization, nanosuspension, modification of the crystal habits, eutectic mixtures, solid dispersions, micro emulsions, self-micro emulsifying drug delivery systems, cyclodextrin inclusion and lipid-based delivery systems etc.\(^2\). Solid dispersions (SDs) are defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix in a solid state, and are prepared by the fusion, solvent or solvent fusion method\(^3\). This technique enables reducing particle size to a nearly molecular level, offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems of poor water-soluble drugs that are cost-effective and significantly reduced in dosage\(^4\). Sekiguchi and Obi were the first to propose the SD method using water-soluble carriers to improve the dissolution characteristics of poorly water-soluble drugs\(^5\). In this method, the drug is thoroughly dispersed in a water-soluble carrier by melting, solvent, or solvent-melting methods\(^6\).

Manidipine dihydrochloride (MAN) is a third-generation dihydropyridine calcium channel antagonist. It is lipophilic and vaso selective and has strong membrane binding ability which is responsible for the gradual onset and long duration of pharmacologic action\(^7\).

In the present study an attempt has been made to improve solubility and bioavailability of Manidipine through solid dispersion technique using water soluble carriers. Solid dispersions of Manidipine were prepared using Labrafac PG, Kolliwax RH 40, Soluplus, Kolliwax GMS II, Kolliphor RH 40, Kolliphor EL in the drug carrier and SLS ratio of 1:5:2, 1:2.5:1.5 and 1:1:1 by using solvent evaporation method.

MATERIALS AND METHOD

Materials:

Manidipine pure drug was generous gift from MSN Laboratories Pvt. Ltd, Hyderabad, India. Kolliphor RH 40 and Kolliphor EL were obtained from BASF, Mumbai. Labrafac PG, Kolliwax GMS II obtained from Signet Chemical Corp. Pvt. Ltd, Mumbai. Soluplus were gifted from BASF, Germany. PEG 4000 and PVP K-30 and were gifted from Dow Chemicals, USA. PEG 600, Span 80, Tween 80 was obtained from BASF, Mumbai. All other chemicals used were of analytical grade.

Preliminary solubility studies of Manidipine:
Solubility measurements of Manidipine were performed according to a published method (Higuchi and Connors, 1965). An excess amount of Manidipine was added to 25ml of aqueous solution of water soluble carriers like Labrafac PG, Kolliwax RH 40, Soluplus, Kolliwax GMS II, Kolliphor EL, PEG 600, Span 80, Tween 80 and PVPK-30 in screw capped bottles. Samples were shaken for the 24 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solution diluted properly with methanol. The diluted solution analyzed for the Manidipine in UV 246 nm.

**Preparation of Manidipine solid dispersion by the solvent evaporation method:**

The calculated amount of Manidipine and the employed polymers (Labrafac PG, Kolliwax RH 40, Soluplus, Kolliwax GMS II, Kolliphor EL) in different drug-polymer-surfactant (SLS) ratios (1:5:2, 1:2.5:1.5 and 1:5:2) (Table 1) are weighed and mixed together in a porcelain dish. Fifteen different formulae were prepared by the solvent evaporation method. The mixture was dissolved in the least amount of methanol as a common solvent. Then the solvent was evaporated in oven at temperature 50ºC till complete evaporation. The solid dispersions prepared were pulverized in a mortar and sieved and the fraction of the powder that passed through 45 μm stored in a desiccator and used for further investigations.

**Solubility studies of Manidipine solid dispersion by solvent evaporation method:**

Solubility measurements of Manidipine were performed according to a published method. Samples were shaken for the 48 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solutions were analysed for the Manidipine in UV 246 nm.

**Evaluation of Manidipine solid dispersions:**

Solid dispersions obtained from the above method were tested for their % Practical yield, Drug content and in-vitro release studies.

**In vitro Dissolution study of Manidipine solid dispersion**

The USP dissolution test type II apparatus was used. Amount of samples equivalent to 10 mg of drug were dispersed into the dissolution vessel containing 900 mL of pH 6.8 phosphate buffer at 37°C and stirred at 50 rpm. Samples were withdrawn periodically, filtered and replaced with a fresh dissolution medium. After filtration through 0.45 μm microfilter, concentration of Manidipine was determined spectrophotometrically at λ max 246 nm.

**Stability studies:**

Prepared solid dispersions were placed inside sealed 40cc HDPE container with child resistant cap under controlled temperature environment inside stability chamber (Thermo Lab, India) with
relative humidity of 75%±5%RH and temperature of 40°C±2°C for stability studies. Samples were removed after 1, 2 and 3 months and evaluated for % drug content and in vitro dissolution studies.

**In vivo bioavailability studies**

**Animal preparation**

Healthy male Wistar rats were (weighing approximately 250 ± 25 g) selected for this study, all the animals were healthy during the period of the experiment. All efforts were made to maintain the animals under controlled environmental conditions (Temperature 25°C±2°C, Relative Humidity 45%±5%RH and 12 h alternate light and dark cycle) with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply. Rats were fed with standard diet and watered libitum.

**Pharmacokinetic study**

The pharmacokinetic characteristics for Manidipine pure drug suspension 20 mg, optimized preparation of solid dispersion 20 mg were evaluated using twelve healthy Male Wister rats weighing 250±25g. Rats were divided in to two groups at random, each group containing six animals. First group was administered Manidipine (as such) suspension was prepared in 0.5% w/w of HPMC 2.5cPs, second group was administered optimized preparation of solid dispersion suspension was prepared in 0.5% w/w of HPMC 2.5cPs by oral route at an equivalent dose of 20 mg/kg body weight.

About 500 µl of blood was withdrawn from retro orbital plexus at different time intervals such as 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00, 20.00 and 24.00h. Blood samples were transferred into eppendorf tubes containing heparin in order to prevent blood clotting. The samples were centrifuged immediately at 4000 rpm and the plasma was stored in light-protected container at -20 °C till analysis.

**Determination of Manidipine in Rat plasma by HPLC method:**

Manidipine and the internal standard (IS) (Felodipine) were extracted with n-hexane and separated on a Hypersil ODS2 column with a mobile phase of methanol–5 mM ammonium acetate solution containing 0.1% acetic acid (85:15, v/v). At a flow rate 1 ml /min and the wavelength detection was 304 nm. The retention times about 5.8 min for manidipine and 5.6min for IS.

**Pharmacokinetic data analysis for optimized preparation of solid dispersions and pure drug suspension:**

The area under the drug concentration-time curve from zero to 24h (AUC) was calculated using the trapezoidal rule. The maximum plasma concentration of the drug (C_{max} and the time to reach C_{max} (T_{max}) was obtained directly from the plasma profiles.
The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean±SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with p<0.05 was considered statistically significant.

The bioavailability of the optimized preparation of solid dispersion was evaluated using rats.

RESULTS AND DISCUSSION

Preliminary solubility studies of Manidipine:
In case of solid dispersions initially preliminary solubility analysis was carried out to select the appropriate water soluble carriers for the preparation of solid dispersion in which pure drug solubility was found to be 0.000995±0.0001 mg/ml (Table 2). From this study, drug and Kolliwax GMS-II shown highest drug solubility i.e. 0.0248mg/ml, almost 25-fold increase compared to that of pure drug. For all the water-soluble carriers used in preliminary solubility studies, PEG 4000, PVP K30, PEG 600, Span 80 and Tween 80 shown low solubility when compared with other carriers and did not included in the preparation of Manidipine solid dispersions.

Table 2: Preliminary solubility studies of Manidipine in different polymers

| Physical Mixture       | Solubility(mg/ml) * |
|------------------------|---------------------|
| Pure Drug Manidipine   | 0.000995±0.0001     |
| Drug + Soluplus        | 0.0218±0.010        |
| Drug + Labrafac PG     | 0.0199±0.009        |
| Drug + Kolliphor EL    | 0.0228±0.011        |
| Drug + PEG 600         | 0.0189±0.009        |
| Drug + Kolliwax GMS II | 0.0248±0.012        |
| Drug + PVP K-30        | 0.0133±0.007        |
| Drug + Kolliphor RH 40 | 0.0208±0.010        |
| Drug + Span 80         | 0.0155±0.007        |
| Drug + Tween 80        | 0.0171±0.006        |
| Drug + PEG 4000        | 0.0159±0.007        |

*n=SD±3

Preparation of Manidipine solid dispersions
Fifteen different formulations of Manidipine solid dispersions were prepared by solvent evaporation method using Labrafac PG, Kolliwax RH 40, Soluplus, Kolliwax GMS II, Kolliphor EL in the drug carrier and SLS ratio of 1:5:2, 1:2.5:1.5 and 1:1:1. The composition of all the formulations was shown in Table 1.
Table 1: Composition of Manidipine solid dispersions

| Ingredients & formulation ratios | Manidine (mg) | Soluplus (mg) | Kolliphor RH 40 (mg) | Kolliphor EL (mg) | Labrafac PG (mg) | Kolliwax GMS II (mg) | SLS (mg) | Methanol (mL) |
|--------------------------------|---------------|---------------|---------------------|------------------|-----------------|---------------------|----------|---------------|
| SD1 1:5:2                       | 20            | 100           | -                   | -                | -               | -                   | 40       | Qs            |
| SD2 1:2.5:1.5                   | 20            | 50            | -                   | -                | -               | -                   | 30       | Qs            |
| SD3 1:1:1                       | 20            | 20            | -                   | -                | -               | -                   | 20       | Qs            |
| SD4 1:5:2                       | 20            | -             | 100                 | -                | -               | -                   | 40       | Qs            |
| SD5 1:2.5:1.5                   | 20            | -             | 50                  | -                | -               | -                   | 30       | Qs            |
| SD6 1:1:1                       | 20            | -             | 20                  | -                | -               | -                   | 20       | Qs            |
| SD7 1:5:2                       | 20            | -             | -                   | 100              | -               | -                   | 40       | Qs            |
| SD8 1:2.5:1.5                   | 20            | -             | -                   | 50               | -               | -                   | 30       | Qs            |
| SD9 1:1:1                       | 20            | -             | -                   | 20               | -               | -                   | 20       | Qs            |
| SD10 1:5:2                      | 20            | -             | -                   | -                | 100             | -                   | 40       | Qs            |
| SD11 1:2.5:1.5                  | 20            | -             | -                   | -                | 50              | -                   | 30       | Qs            |
| SD12 1:1:1                      | 20            | -             | -                   | -                | 20              | -                   | 20       | Qs            |
| SD13 1:5:2                      | 20            | -             | -                   | -                | -               | 100                 | 40       | Qs            |
| SD14 1:2.5:1.5                  | 20            | -             | -                   | -                | -               | 50                  | 30       | Qs            |
| SD15 1:1:1                      | 20            | -             | -                   | -                | -               | 20                  | 20       | Qs            |

All the solid dispersions prepared were found to be fine and free flowing powders (Figure 1).

Evaluation parameters:

Solubility studies of Manidipine solid dispersions:

Different formulations of Manidipine solid dispersions were prepared by solvent evaporation method with their respective carriers. After preparation of solid dispersion solubility analysis was carried out. The formulation (SD 13) with Drug, Kolliwax GMS-II and SLS in the ratio of 1:5:2 shown highest solubility i.e.0.0467±0.005 mg/ml, almost 47-fold compared to that of the pure drug (Pure drug solubility is 0.000995±0.0001 mg/ml). The results are tabulated in Table 3.
Table 3: Solubility studies of Manidipine solid dispersions prepared by solvent evaporation method

| S. No. | Formulation code | Solubility (mg /ml) * |
|--------|------------------|-----------------------|
| 1      | Pure drug (Manidipine) | 0.000995±0.0001 |
| 2      | SD1              | 0.0356±0.002         |
| 3      | SD2              | 0.0328±0.003         |
| 4      | SD3              | 0.0314±0.003         |
| 5      | SD4              | 0.0378±0.001         |
| 6      | SD5              | 0.0334±0.002         |
| 7      | SD6              | 0.0348±0.002         |
| 8      | SD7              | 0.0391±0.004         |
| 9      | SD8              | 0.0307±0.004         |
| 10     | SD9              | 0.0317±0.005         |
| 11     | SD10             | 0.0398±0.001         |
| 12     | SD11             | 0.0301±0.004         |
| 13     | SD12             | 0.0315±0.001         |
| 14     | SD13             | 0.0467±0.001         |
| 15     | SD14             | 0.0352±0.002         |
| 16     | SD15             | 0.0364±0.005         |

% Practical yield and drug content:

The results of % practical yield for all formulations of solid dispersions found to be 90.21±0.05% - 98.36±0.25%. The results of % practical yield studies are shown in Table 4. Maximum yield was found to be 98.36±0.25% in formulation SD13. Actual drug content of all 15 formulations are shown in Table 4. The drug content of the prepared solid dispersions was found to be in the range of 90.42±0.05 – 99.63±0.50 %. Maximum % drug content i.e. 99.63±0.50 % was found in the formulation SD 13.

Table 4: % Practical yield and drug content for Manidipine solid dispersions

| S. No | Formulation | % Practical Yield | % Drug content |
|-------|-------------|-------------------|----------------|
| 1     | SD1         | 92.15±0.15        | 95.64±0.30    |
| 2     | SD2         | 95.32±0.30        | 93.12±0.20    |
| 3     | SD3         | 93.67±0.20        | 92.36±0.15    |
| 4     | SD4         | 90.21±0.05        | 90.42±0.05    |
| 5     | SD5         | 94.46±0.25        | 94.48±0.25    |
| 6     | SD6         | 95.32±0.30        | 93.67±0.20    |
| 7     | SD7         | 97.12±0.40        | 96.59±0.35    |
| 8     | SD8         | 90.36±0.05        | 98.13±0.45    |
| 9     | SD9         | 93.45±0.20        | 97.26±0.40    |
| 10    | SD10        | 91.23±0.10        | 91.33±0.10    |
| 11    | SD11        | 92.16±0.15        | 92.67±0.15    |
| 12    | SD12        | 94.32±0.25        | 94.42±0.25    |
| 13    | SD13        | 98.36±0.45        | 99.63±0.50    |
| 14    | SD14        | 96.12±0.35        | 95.66±0.30    |
**In vitro dissolution studies**

In vitro studies reveal that there is marked increase in the dissolution rate of Manidipine from all the solid dispersions when compared to pure Manidipine itself. From the in vitro drug release profile, formulation SD13 containing Dug, Kolliwax GMS-II and SLS (1:5:2 ratio of drug: Kolliwax GMS and SLS) shown higher dissolution rate i.e. 99.41±5.38 % compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. The graphical representation of all the formulations drug release profile with pure drug was depicted in Figures 2-4.

![Graph 1](image1)

**Figure 2: In vitro dissolution profile of pure drug and different formulations of Manidipine solid dispersions (SD1-SD5)**

![Graph 2](image2)

**Figure 3: In vitro dissolution profile of pure drug and different formulations of Manidipine solid dispersions (SD6-SD10)**
Figure 4: In vitro dissolution profile of pure drug and different formulations of Manidipine solid dispersions (SD11-SD15)

CHARACTERIZATION:

FTIR STUDIES:

Figure 5: FTIR Spectrum of Manidipine pure drug
The FTIR spectra of pure Manidipine, physical mixture and optimized formulation SD13 are shown in Figure 5, 6 and 7 respectively. From Figure 7 it was observed that there were no significant changes in the position of characteristic peaks of the drug when mixed with carriers which indicated no incompatibility of excipients and the drug.

X-Ray Diffraction patterns:
The Manidipine solid dispersions were carried out to find out whether the solid dispersions of various drug polymer ratios are crystalline or amorphous. The presence of numerous distinct peaks in the XRD spectrum of pure Manidipine indicates that Manidipine was present as a crystalline material. On the other hand, the spectrum of optimized formulation SD13 of solid dispersion was characterized by the complete absence of any diffraction peak, which is characteristic of an amorphous compound (Figure 8). The enhancement in the dissolution rate of the drug from the drug-Kolliwax GMS II and SLS solid dispersion is ascribed to the marked reduction in the crystallinity of the drug.

**SEM Studies:**
SEM photographs for pure drug and optimized formulation SD13 are shown in Figures 9 and 10. The drug crystals seemed to be smooth-surfaced, irregular in shape and size. In case of Solid dispersions, it was difficult to distinguish the presence of drug crystals. The drug surface in solid dispersion seems to be more porous in nature. Solid dispersions appeared as uniform and homogeneously mixed mass with wrinkled surface. Drug crystals appeared to be incorporated into the particles of the polymers. The solid dispersion looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of the polymer.

**Stability studies:**

Optimized formulation (SD13) was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for drug content and In vitro drug release studies for 3 months at accelerated stability conditions according to ICH guidelines. The optimized formulation was stable during 3 months period. From these results it was concluded that, optimized formulation (SD13) is stable and retained their original properties with minor differences. (table 5)
Table 5: Pharmacokinetic Parameters of Manidipine Optimized Solid dispersion formulation and Manidipine pure drug

| Pharmacokinetic Parameters | Manidipine Pure drug | Manidipine solid dispersion Optimized formulation |
|----------------------------|----------------------|--------------------------------------------------|
| C<sub>max</sub> (ng/ml)    | 2.28±0.32            | 3.44±0.06                                        |
| AUC<sub>0-t</sub> (ng h/ml)| 4.62±1.55            | 7.54±1.74                                        |
| AUC<sub>0-inf</sub> (ng h/ml)| 6.85±1.24            | 10.05±0.45                                       |
| T<sub>max</sub> (h)        | 2.00±0.05            | 1.00±0.04                                        |
| t<sub>1/2</sub> (h)        | 4.02±0.01            | 2.52±0.04                                        |

In vivo bioavailability studies

Figure 11: Plasma concentration–time curves for the Manidipine optimized formulation and pure drug

The Manidipine plasma concentrations in rats treated with optimized preparation of solid dispersion was significantly higher than those treated with pure drug suspension. Based on the results, it was clearly evident that Manidipine from a solid dispersion was significantly increased in comparison with that of the pure drug (Manidipine suspension). C<sub>max</sub> of the optimized preparation of solid dispersion was 3.44±0.06ng /ml, was significantly higher as compared to C<sub>max</sub> of the pure drug suspension, i.e., 2.28±0.32ng/ml. T<sub>max</sub> of optimized preparation of solid dispersion, pure drug suspension was 1.00±0.04hr, 2.00±0.05hr respectively, AUC<sub>0-inf</sub> for optimized solid dispersion formulation was slightly higher (10.05±0.45ng h/ml) than significantly higher than AUC<sub>0-inf</sub> of the pure drug suspension 6.85±1.24ng h/ml. Statistically, AUC<sub>0-t</sub> of the optimized preparation of solid dispersion was significantly higher (p<0.05) as compared to pure.
Higher amount of drug concentration in blood indicated better systemic absorption of Manidipine from optimized solid dispersion formulation as compared to the pure drug suspension.

SUMMARY AND CONCLUSION

In the present study it was demonstrated that different formulations of Manidipine solid dispersions were produced by processing via solvent evaporation method with enhanced solubility and dissolution rate. Novel polymer–surfactant combinations were optimized, and stable SD systems were developed successfully. Utilization of Kolliwax GMS II along with suitable surfactant (SLS) offers excellent possibilities to develop stable amorphous solid dispersion. The formulations were characterized for physical appearance, solubility and in vitro dissolution studies. The optimized formulation was characterized by, Formulation SD13 was found to be optimized one based on the solubility, dissolution and other parameters using Kolliwax GMS II and SLS. The drug release of the optimized formulation was found to be 99.41±5.38% within 90min. Powder X-ray diffraction studies performed on solid dispersion showed that Manidipine existed in the amorphous form within the solid dispersion formulation fabricated using the solvent evaporation process. Additionally, scanning electron microscopy studies suggested the conversion of crystalline Manidipine to an amorphous form. From bioavailability studies the pharmacokinetic parameters of the optimized Manidipine solid dispersions showed increased AUC$_{0-t}$, AUC$_{0-\infty}$ and C$_{max}$ by 2-folds. These results suggest that the preparation of Manidipine solid dispersions using the solvent evaporation technique without might be a promising approach for improving the oral bioavailability of Manidipine. Therefore, the solid dispersions using Kolliwax GMS II as hydrophilic carrier in the combination of SLS can be successfully used for improvement of solubility and bioavailability of Manidipine.

REFERENCES

1. Varalakshmi, Siva Ramesh CH, Jyothi I, Jyothi Y, Bharathi G, Chinni Babu. Formulation and evaluation of solid dispersions of valsartan for dissolution rate enhancement. Journal of Pharmacy Research 2015; 9(2): 139-144.

2. Batra V, Shirolkar VS, Mahaparale PR, Kasture PV, Deshpande AD. Solubility and Dissolution Enhancement of Glipizide by Solid Dispersion Technique. Indian J.Phrarm Edu Res 2008; 42(4): 373-378.

3. Serajuddin ATM. Solid dispersion of poor water-soluble drugs early promises subsequent problems and recent breakthroughs. J Pharm Sci 1999; 88: 1058-1066.
4. Dhirendra K, Lewis S, Udupa N. Solid Dispersions a Review. Pak. J. Pharm. Sci 2009; 22(2): 234-246.
5. Bhawandeep G, Tejvir K, Sandeep K, Gupta GD. Formulation and evaluation of glimepiride solid dispersion tablets. Asian J Pharm 2010; 4 (3): 212-217.
6. Chiou WL and Rigelman S. Pharmaceutical application of solid dispersion system. J Pharm Sci 1971; 60:1281-302.
7. Morimoto Y and Matsumura. Manidipine hydrochloride Cardio vasc. Drug Rev 1991; 9: 201-222.
8. Lakshmi K, Pranav KR, Rajesh K. Dissolution enhancement of Telmisartan by surface solid dispersion technology. International Journal of Innovative Pharmaceutical Research 2012; 3(4): 247-251.
9. Poovi G, Uma Maheswari M, Kumar S, Raja Lakshmi AN. Development of Domperidone Solid Dispersion Powders Using Sodium Alginate as Carrier. European Journal of Applied Sciences 2013; 5(2): 36-42.