Formulation and Characterization of Cefaclor Microspheres

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Abstract: The purpose of this research work was to increase the residence time of drug Cefaclor by formulating as floating microspheres and to study the effect of formulation variables on microsphere characteristics. Microspheres were prepared by solvent evaporation method in which ethyl cellulose was used as a release retardant polymer. Nine different formulations were prepared by changing drug to polymer ratio, volume of internal phase, volume of external phase and stirring time. The prepared microspheres were characterized for drug - polymer compatibility by IR, percentage yield, particle size analysis, drug entrapment efficiency, surface morphology by SEM, bulk density, percentage buoyancy, in-vitro release and release kinetic studies. Results of these evaluations showed that particle size in the range of 100.8±1.6 μm to 106.2±1.3μm, entrapment efficiency was found to be 75.72±1.94 to 92.02±1.07%, drug content was found to be in the range 96.89±2.1 to 99.92 ± 2.67. Fourier-Transform Infra Red (FT-IR) studies ensured that no drug - polymer interaction in the formulated microspheres and the surface topography revealed a spherical surface for all the formulations and a round cavity enclosed by an outer shell composed of the drug and polymer. In- vitro release profile of microspheres for F14 formulation was found to be 98.45±0.47 at the end of 12hrs. In release kinetic studies, the F14 formulation followed zero order drug release with non-Fickian diffusion mechanism.

Keywords: Cefaclor, FT-IR, SEM, Microspheres

1. Introduction

Microspheres are defined as solid spherical particles containing dispersed drug in either solution or microcrystalline form. They are ranging in size from 1 to 1000 micrometer. Microspheres are in strict sense, spherical solid particles. Microcapsules are small particles that contains an active agent as a core material and coating agent as shell, at present there is no universally accepted size range that particle must have in order to be classified as microcapsules. However, many workers classify capsules smaller than 1 micrometer as nanocapsules and capsules layer more than 1000 micrometer as macro particles. Commercial microcapsules typically have a diameter between 3-80 micrometer and contain 10-90 weight % cores.

Cefaclor is a second generation cephalosporin antibiotic with a spectrum resembling first-generation cephalosporins. The bioavailability of above mention drugs are well absorbed with a half-life of 0.6-0.9 hour. To increase the bioavailability of the Cefaclor with reducing dosing frequency microspheres were selected as a suitable approach.

2. Material and Methods

Materials: Cefaclor was obtained as a gift sample from Hetero drugs, Hyderabad (India), SMC, HPMCK4M, EUDRAGIT was obtained from Colorcon india pvt.ltd. Ethanol, DCM, Tween80, Liquid paraffin were purchased from Colorcon India pvt.ltd. All other chemicals and reagents used were of analytical grade.

a) Preparation of Cefaclor Microspheres by non-aqueous solvent evaporation technique:

Microspheres containing Cephalosporin drugs as a core material were prepared by a non-aqueous solvent evaporation method. Drug and different polymer ratio were mixed in the mixture of dichloromethane and ethanol at a 1:1 ratio. The slurry was slowly introduced into 30 ml of liquid paraffin containing 0.01% Tween 80, while stirring at 1200 rpm using a mechanical stirrer equipped with three bladed propellers at room temperature. The solution was stirred for 2 h and the solvent evaporated completely, and filtered by using filter paper. The microspheres obtained were washed repeatedly with petroleum ether (40-60 °C) until free it was from oil. The collected microspheres were dried at room temperature and subsequently stored in desiccators.

b) Physical characterization of microspheres: [8, 9]

Solubility study:
Excess drug was added carefully using a spatula to 10 ml of the media in a conical flask, while stirring until a heterogeneous system (solid sample and liquid) was obtained. The solution containing excess solid was then capped, and stirred at 150 rpm at room temperature for 24 hours. The solution containing excess solid was then filtered using 0.45μm PVDF filter, appropriate dilutions were then made and analyzed using UV spectrophotometer at required nanometer range of drug. The same procedure was followed for all selected drugs. (Saturation solubility was carried out at 25°C using required different buffers).

Determination of absorption maximum (λmax):
The wavelength at which maximum absorption of radiation takes place is called as λmax. This λmax is characteristic or
unique for every substance and useful in identifying the substance. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Most drugs absorb radiation in ultraviolet region (190-390nm), as they are aromatic or contain double bonds.

Accurately weighed 100mg of drug was dissolved in pH 6.8 buffer taken in a clean 100 ml volumetric flask. The volume was made up to 100ml with the same which will give stock solution-I with concentration 1000μg/ml. From the stock solution-I, 5ml was pipette out in 50ml volumetric flask. The volume was made up to 50ml using pH 6.8 buffer to obtain stock solution-II with a concentration 100μg/ml. From stock solution-II, 1ml was pipette out in 10ml volumetric flask. The volume was made up to 10ml using pH 6.8 buffer to get a concentration of 10μg/ml. This solution was then scanned at 200-400nm in UV-Visible double beam spectrophotometer to attain the absorption maximum (λ_max).

c) Preparation of Calibration Curve

**Procedure for standard curve in pH 6.8:**
10 mg of drug was dissolved in 10 ml of pH 6.8 by slight shaking (1000 mcg/ml). 1 ml of this solution was taken and made up to 20 ml with pH 6.8, which gives 20 mcg/ml concentration (stock solution). From the stock solution, concentrations of 5, 10, 15, 20 and 25 μg/ml in pH 6.8 were prepared. The absorbance of diluted solutions was measured at particular nanometer and a standard plot was drawn using the data obtained. The correlation coefficient was calculated.

**FTIR analysis:**
The drug-polymer interactions were studied by FTIR spectrometer, Shimadzu 8400 S. 2% (w/w) of the sample, with respect to a potassium bromide (KBr; SD Fine Chem. Ltd., Mumbai, India) was mixed with dry KBr. The mixture was ground into a fine powder using mortar and then compressed into a KBr disc in a hydraulic press at a pressure of 10000 PSI. Each KBr disc was scanned 10 times at a resolution of 2 cm–1 using Happ-Genzel apodization. The characteristic peaks were recorded.

**Micromeretic Parameters**

**Bulk Density:** Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. It is determined by pouring pre-sieved blend into a graduated cylinder via a large funnel and measure the volume and weight as is given by

\[
\text{Bulk density} = \frac{\text{weight of blend}}{\text{Bulk volume}}
\]

**Tapped density:** Tapped density is determined by placing a graduated cylinder containing known mass of blends on a mechanical tapped apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

\[
\text{Tapped density} = \frac{\text{weight of blend}}{\text{tapped volume of blends}}
\]

**Compressibility Index:** The compressibility index of the granules was determined by Carr’s compressibility index.

\[
\text{Carr’s index} (%) = \left\{ \left( \frac{\text{Tapped Density}}{\text{Bulk Density}} \right) \times 100 \right\}
\]

Hausner’s ratio: Hausner’s ratio was determined as the ratio between the tapped density to that of the bulk density.

\[
\text{H.R} = \frac{\text{Tapped Density}}{\text{Bulk Density}}
\]

**Angle of repose:** The manner in which stresses are transmitted through a bed and beds response to applied stress is reflected in the various angles of friction and response. The most commonly used of these is angle of repose, which may be determined experimentally by a number of methods. The method used to find the angle of repose is to pour the powder in a conical heap on a level flat surface and measure the inclined angled with the horizontal pile.

\[
\theta = \tan^{-1}(h/r)
\]

**Particle Size**
It is possible to use ordinary microscope for particle size determination in the range of 0.2 to above 100 μm to measure particle size of individual microsphere. All the microspheres were evaluated with respect to their size and shape using optical microscope fitted with an ocular micrometer and a stage micrometer. Ocular micrometer was calibrated with the stage micrometer. Slides of dilute suspensions of microspheres in liquid paraffin were prepared and slides were placed on mechanical stage of microscope. The diameter of 100 microspheres was measured randomly by optical microscope and average particle size was determined.

**Scanning electron microscopy (SEM)**
In the pharmaceutical industry, SEM may be used as a qualitative tool for the analysis of drug substance and drug product in order to obtain information on the shape and surface structure of the material. SEM plays an important role in the characterization of nanoscale and sub-micron particles. It has been used to determine surface topography, texture and to examine the morphology of fractured or sectioned surfaces. The examination of the surface of polymeric drug delivery systems can provide important information about the porosity and microstructure of device.

**Actual drug content and entrapment efficiency**
10 mg of microspheres were accurately weighted and transferred in a 50 ml volumetric flask. Volume was adjusted with 1% SLS and microspheres were dissolved by ultra-sonication for 3 h at25 °C. The samples were filtered through 0.2 μm membrane filter. 5 ml from the sample solution was transferred to 50 ml volumetric flask and volume was adjusted to 50 ml with same medium and absorbance of samples was measured at 288 nm using UV-spectrophotometer. Actual drug content (AC) and encapsulation efficiency (EE) were calculated using following equations. All analyses were carried out in triplicate.

\[
\text{AC(%) = } \left( \frac{C_{\text{meas}}}{C_{\text{the}}} \right) \times 100
\]

\[
\text{EE(%) = } \left( \frac{C_{\text{the}}}{C_{\text{the}}} \right) \times 100
\]
concentration range of 5 

A linear relationship was observed between concentrations of drug solution obeys Beer’s Lambert law in the concentration range of 5-25μg/mL. Hence it was concluded that dissolution samples can be analyzed in 0.1N HCl by measuring absorbance at 268nm using UV-Visible Spectrophotometer.

**Invitro Dissolution Studies:**
The dissolution test measures the amount of time required for certain percentage of the drug substance in a tablet to go into solution under a specified set of conditions. It describes a step towards physiological availability of the drug substance, but it is not designed to measure the safety or efficacy of the formulation being tested.

**Release Kinetic Models**
To analyse the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted in to Zero order, First order, Higuchi matrix, Krosmeyers-Peppas and Hixson Crowell model. In this by comparing the R-values obtained, the best-fit model was selected.

**Stability studies**
Stability studies were conducted for the optimized formulation confirmed from the in vitro dissolution data, for Particle size, % Yield, Entrapment efficiency, &% Drug content at at 40°C /75%RH for a period of 3 months.

**3. Results and Discussion**

**Preparation of microspheres:** Microspheres were prepared by solvent evaporation method. Many of the researchers employed with solvent evaporation method due to its simplicity and reproducibility. The solubility of Cefaclor is very poor in water (0.52 mg/ml) and in 0.1N HCl (0.072mg/ml). The solubility of Cefaclor increased with increase in pH 6.8 of the buffer from 0.39 to 1.88 mg/ml.

**Solvent combination:**
Selection of solvent is very important for microspheres preparation. A mixture of ethanol and dichloromethane used for this microspheres preparation as solvent. Because when non-polar solvent dichloromethane used alone the polymer get precipitated rapidly at the time of mixing with water. So to reduce the non-polarity of the dichloromethane, ethanol was added to that solvent. During microspheres formation ethanol gets diffused in to the water and dichloromethane was evaporated.

**Determination of absorption maxima (\(\lambda_{max}\)) of CEFACLOR:**
The maximum absorbance of the Cefaclor in pH 6.8 was found to be 268nm as shown in Fig. Hence, the wavelength of 268nm was selected for analysis of drug in dissolution media.

**Standard curve of Cefaclor:**
A linear relationship was observed between concentrations of drug solution in pH 6.8and absorbance, over the concentration range of 5-25μg/mL. The coefficient of correlation (R²) was found to be 0.9990, indicating that the drug solution obeys Beer’s Lambert law in the concentration range of 5-25μg/ml. Hence it was concluded that dissolution samples can be analyzed in 0.1N HCl by measuring absorbance at 268nm using UV-Visible Spectrophotometer.

**FTIR Studies**
The Cefaclor and Excipients interaction was studied by comparing the FTIR spectrum of the optimized blend with that of Cefaclor pure drug as shown in Table and Fig. The comparison study demonstrates that there was no interaction between the drug and other ingredients of the formulation including Excipients such as HPMC, Eudragit and SCMC as shown in Table and Fig, thus revealing compatibility of the selected drug with the excipients.

**Micromeretic Parameters**
The flow properties like bulk density, tapped density, angle of repose, compressibility index and Hausner’s ratio was found to be 0.306 g/cc, 0.348 g/cc, 25.30°, 12.06 and 1.13 respectively, which indicates that flow of API is poor as per I.P limits.

**Particle Size**
The particle size of the formulations F-10 to F-18 was found to be in the ranges from 100.8±1.6μm to 106.2±1.3μm.

**Scanning electron microscopy analysis (SEM)**
The optimized formulation was evaluated for its surface morphology by using Scanning electron microscopy. The outer surface of the microspheres was found to be smooth. The surface topography revealed a spherical surface for all the formulations and a round cavity enclosed by an outer shell composed of the drug and polymer. The particle size was found to be 100μm.

**Actual drug content and entrapment efficiency**
The particle size of the formulations F-10 to F-18 were found to be in the ranges from 75.72±1.94 to 92.02±1.07% and 95.55±1.4 to 99.92±2.67 respectively.

**Invitro dissolution studies of CEFACLOR:**
The formulations F10- F12 prepared with (ratios range 1:1, 1:1.5, 1:2) concentration of polymer like SCMS and drug release as shown in Table. As the polymer concentration was decreases the drug release was increases. This might be due to insufficient entrapment of the drug formulations contain low concentration of hydrophilic polymer (SCMC).

The formulations F10 showed burst effect and released 100.23±0.74% at the end of 6hrs. The formulations F11 and F12 drug release was 99.46±0.30%, 97.73±0.70 at the end of 8 and 10 hrs respectively, due to increase the polymer concentration, further increases the concentration of polymer (F12) drug release was decreased.

The formulations F13 releases 99.23±0.64% at the end of 8 hrs, F14 and F15 releases 98.45±0.47% & 80.45±0.87 at the end of 12hrs. The HPMC (high viscosity and high molecular weight) upon contact with dissolution medium swelling occur due to the disruption of hydrogen bonding among the polymeric chains and form a thick gel layer on the surface, which gets eroded over period of time. Thus, this parameter was responsible for sustained/controlled drug release rate.
The formulations (F16, F17 and F18) were tried with Eudragit (ratios range 1:1, 1:1.5, 1:2), as retardant being insoluble in gastric pH. The formulations F16 was found to be 82.45±0.65 at the end of 12hrs due to low polymer concentration effect. F17 and F18 showed better control on drug release than other formulations and also exhibited incomplete drug release which might be due to hydrophobic polymer (Table and Fig).

The formulation F14 was made with the HPMC in the drug polymer ratio of 1:1.5 and drug release was found to be 98.45±0.47% at the end of 12hrs with better drug release pattern. The reason might be to this fact is formation of thick gel layer by matrices around the surface that delays diffusion and release of drug, thus F14 was considered as optimized formulation.

Release Kinetic Models

The optimized formulation F14 has coefficient of determination (R²) values of Zero order, First order, Higuchi and Korsmeyer Peppas of 0.954, 0.764, 0.977 and 0.959 respectively. A good linearity was observed with the zero order. The slope of the regression line from the Higuchi plot indicates the rate of drug release through mode of diffusion, and further confirms the diffusion mechanism. The data fitted into the Korsmeyer Peppas equation which showed linearity with slope n value of 0.493 for optimized formulation F14. This n value indicates the coupling of (swelling, polymer relaxation) diffusion and erosion mechanism. This type of drug release is called as anomalous diffusion. Thus, it indicates the drug release from the tablet follows non-Fickian diffusion mechanism. The presence of swelling and crosslinked polymers within the matrix structure might be responsible for the drug release controlled by more than one process. Thus, with regarded to release kinetics, the optimized batch F14 follows best fitted into peppas model and showed zero order drug release with non-Fickian diffusion mechanism.

Stability studies of optimized formulation (F14):
Stability studies were conducted for Particle size,% Yield, Entrapment efficiency, &% Drug content and confirmed that there was no significant change in the parameters of optimized formulation at storage condition of 40°C ± 2°C / 75 ± 5 %RH after 6 months.

4. Conclusion

In this research work attempt was made to increase the bioavailability of the Cefoclor with reducing dosing frequency microspheres. Formulation was successfully made and in vitro evaluation of shows encouraging results. By these evaluations following statement can be concluded (i) No interaction between the drug and polymer was confirmed. (ii) The desired yield and entrapment efficiency was obtained. (iii) It provides sustained release of drug over more than 12 hours. (iv) Drug release from microspheres follows zero order drug release with non-Fickian diffusion mechanism. (v) The drug: polymer ratio has significant effect on the all characteristics of microspheres but other variables have effect on only few characteristics of the microspheres.

| Sr.no | Ingredients                  | F10   | F11   | F12   | F13   | F14   | F15   | F16   | F17   | F18   |
|-------|------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 1     | CEFACLOR                     | 0.5   | 0.5   | 0.5   | 0.5   | 0.5   | 0.5   | 0.5   | 0.5   | 0.5   |
| 2     | SCMC(gm)                     | 1     | 1.5   | 2     | ------| ------| ------| ------| ------| ------|
| 3     | HPMCK4M                      | ------| ------| ------| 1     | 1.5   | 2     | ------| ------| ------|
| 4     | EUDRAGIT(gm)                 | ------| ------| ------| ------| ------| ------| 1     | 1.5   | 2     |
| 5     | Ethanol (ml)                 | 6     | 10    | 12    | 15    | 20    | 23    | 10    | 15    | 20    |
| 6     | DCM (ml)                     | 6     | 10    | 12    | 25    | 20    | 23    | 10    | 15    | 20    |
| 7     | Tween (ml)                   | 0.18  | 0.18  | 0.18  | 0.18  | 0.18  | 0.18  | 0.18  | 0.18  | 0.18  |
| 8     | Liquid paraffin (ml)         | 90    | 90    | 90    | 90    | 90    | 90    | 90    | 90    | 90    |

Figure 1: Saturation solubility of CEFACLOR

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Figure 2: UV-Spectra of CEFACLOR in pH 6.8

Figure 3: Standard curve of CEFACLOR in pH 6.8 (λ_{max} 268)

Figure 4: FTIR of CEFACLOR
Table 2: Characterization of CEFACLOR microspheres

| Parameter          | Bulk density (gm/cc) | Tapped density (gm/cc) | Hausner’s ratio | Compressibility index |
|--------------------|----------------------|------------------------|-----------------|-----------------------|
| F10                | 0.516±0.55           | 0.587±0.23             | 1.13±0.16       | 12.09±0.47            |
| F11                | 0.520±0.14           | 0.570±0.66             | 1.09±0.30       | 98.77±0.85            |
| F12                | 0.487±0.58           | 0.546±0.50             | 1.12±0.07       | 10.80±0.21            |
| F13                | 0.455±0.25           | 0.501±0.44             | 1.10±0.60       | 9.18±0.14             |
| F14                | 0.448±0.78           | 0.516±0.36             | 1.15±0.89       | 13.17±0.25            |
| F15                | 0.510±0.07           | 0.568±0.14             | 1.11±0.55       | 10.21±0.61            |
| F16                | 0.476±0.15           | 0.526±0.22             | 1.10±0.23       | 9.50±0.55             |
| F17                | 0.515±0.66           | 0.570±0.01             | 1.10±0.08       | 9.64±0.14             |
| F18                | 0.432±0.14           | 0.478±0.88             | 1.10±0.12       | 9.62±0.05             |

Table 3: Particle size, Drug Entrapment Efficiency of CEFACLOR microspheres

| Formulation Code | Particle Size (µm) | % Yield | Entrapment Efficiency | Drug Content |
|-----------------|--------------------|---------|-----------------------|--------------|
| F10             | 102.1±1.3          | 87.82±2.01 | 78.68±2.1             | 97.65±1.6    |
| F11             | 102.9±1.4          | 85.95±1.98 | 76.87±1.91            | 96.89±2.1    |
| F12             | 101.9±1.7          | 94.82±2.16 | 88.35±2.67            | 98.28±1.7    |
| F13             | 104.2±1.2          | 86.90±2.45 | 75.72±1.94            | 98.73±1.9    |
| F14             | 105.1±1.5          | 93.55±1.37 | 86.68±2.08            | 97.89±1.92   |
| F15             | 106.2±1.3          | 85.35±1.98 | 76.84±1.98            | 98.48±2.08   |
| F16             | 101.8±1.1          | 86.27±2.05 | 76.68±2.12            | 99.24±1.91   |
| F17             | 100.8±1.6          | 98.70±1.87 | 92.02±1.07            | 99.92±2.67   |
| F18             | 101.1±1.1          | 85.82±2.01 | 88.68±1.1             | 95.55±1.4    |

Table 4: Dissolution profile of CEFACLOR formulations (Mean±SD; n=6)

| Time (hr) | F10 | F11 | F12 | F13 | F14 | F15 | F16 | F17 | F18 |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 0         | 38.82±0.71 | 30.23±0.40 | 28.89±0.14 | 35.69±0.12 | 28.23±0.34 | 15.23±0.10 | 20.12±0.49 | 13.35±0.10 | 12.21±0.82 |
| 1         | 63.45±0.45 | 54.23±0.36 | 38.23±0.53 | 50.23±0.05 | 26.53±0.54 | 32.43±0.22 | 19.54±0.92 | 18.15±0.09 | 24.23±0.09 |
| 2         | 84.46±0.41 | 70.63±0.12 | 49.99±0.52 | 67.74±0.47 | 43.45±0.10 | 39.42±0.12 | 44.52±0.30 | 27.84±0.36 | 24.23±0.79 |
| 6         | 100.23±0.74 | 81.23±0.55 | 68.89±0.74 | 82.12±0.59 | 59.53±0.06 | 48.86±0.74 | 51.23±0.78 | 45.57±0.56 | 29.47±0.56 |
| 8         | --- | 99.46±0.30 | 83.45±0.02 | 99.23±0.64 | 71.25±0.40 | 60.99±0.65 | 63.33±0.04 | 53.84±0.05 | 38.89±0.34 |
| 10        | --- | 97.73±0.70 | --- | 83.45±0.20 | 73.45±0.02 | 75.23±0.25 | 59.99±0.02 | 49.98±0.05 | 65.54±0.10 |
| 12        | --- | 98.45±0.47 | 80.45±0.87 | 82.45±0.65 | 65.54±0.70 | 59.98±0.54 | 65.54±0.70 | 59.98±0.54 | 65.54±0.70 |

Figure 6: In vitro dissolution profile of CEFACLOR formulations
Table 5: Stability data of optimized formulation (F14) physico-chemical parameters

| Parameter                  | Initial     | After 3 months at 40°C/75%RH | After 6 months at 40°C/75%RH |
|----------------------------|-------------|------------------------------|------------------------------|
| Particle size              | 105.1±1.5   | 105.20±0.87                  | 105.12±1.8                   |
| % Yield                    | 93.55±1.37  | 93.47±1.08                   | 93.45±1.20                   |
| Entrapment efficiency      | 86.68±2.08  | 86.50±2.41                   | 86.79±1.56                   |
| % Drug content             | 97.89±1.92  | 97.74±1.08                   | 97.92±1.54                   |

Figure 7: Optimized formulation of CEFACLOR (F14) *invitro* dissolution at 40°C/75%RH

References

[1] Chein W.Yie, “Novel Drug delivery System”, 2nd Edition, Revised and expanded, 50, Mercel Dekker Inc., 139 -140.
[2] Ansel H.C., Loyd.A, Popovich.N.G. “Pharmaceutical Dosage form and drug delivery system” 7th Edition ; 229,535.
[3] Lachman L., Libermann H. A., Kanig J. L., “The theory and practice of industrial pharmacy”, 3rd edition, Lea and Febiger Philadelphia, 1986; 430–431.
[4] Jain, N.K.; Advances in controlled and novel drug delivery; First edition, 2001; 1-7.
[5] Brahmankar D.M. and Jaiswal S.B., “Biopharmaceutics and Pharmacokinetics: A treatise”; 1st edition, 1995, Vallabh Prakashan; 67.
[6] Chawla G., Gupta P., KoradiaV. and Bansal A. K. Gastroretention: A Means to Address Regional Variability in Intestinal Drug Absorption. Pharmaceutical Technology. 2003;50.
[7] Nayak AK , Maji R, Das B. Gastroretentive drug delivery systems: a Review. Asian Journal of Pharmaceutical and Clinical Research. 2010;3(1).
[8] Garg R , Gupta GD. Progress in Controlled Gastroretentive Delivery Systems. Tropical Journal of Pharmaceutical Research. 2008; 7 (3): 1055-1066.
[9] Arora S. Ali J, Ahuja A, Khar RK, and Baboota S. Floating Drug Delivery Systems: A Review. AAPS PharmSciTech. 2005; 6 (3) 47.
[10] Das MK, Rao KR. 2006 “Evaluation of zidovudine encapsulated ethylcellulose microspheres prepared by water-in-oil-in-oil (w/o/o) double emulsion solvent diffusion technique”. Acta Poloniae Pharmaceutica-Drug Res. 63; 141-148.