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FORMULATION AND EVALUATION OF GLIMEPIRIDE MICROSPHERES

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ABSTRACT

The present study is an attempt to formulate microspheres of Glimepiride, an orally administered ant-diabetic drug with a view of improving its oral bioavailability and giving a prolonged release of drug, where here the microspheres with polymers such as Ethyl cellulose and Eudrajit RS 100 and Eudrajit RL 100 were successfully prepared by emulsification solvent evaporation method and the particle size analysis revealed that the size of microspheres was increased with increase in the concentration of polymer. Formulation with combination of Ethyl cellulose, Eudrajit RS 100 and Eudrajit RL 100 gave large particles in the range of 250.6±1.34 µm, Scanning electron microscopy showed that microspheres of drug with combination of Ethyl cellulose, Eudrajit RS 100 and Eudrajit RL 100 showed smooth surface and a good spherical shape where the *in-vitro* drug release studies showed that drug release was more in case of formulations MP_{9}- MP_{12} containing both hydrophilic and hydrophobic polymers as compared to formulations MP_{1}- MP_{8} only hydrophobic polymer.

Keywords: Glimepiride, Eudrajit RS 100, Eudrajit RL 100, Oral Bioavailability.

INTRODUCTION

Glimepiride is a drug which is absorbed from the gastrointestinal tract (GIT) and has a short half-life and eliminated quickly from the blood circulation, so it required frequent dosing. To avoid this drawback, the oral sustained-controlled release formulations have been developed in an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the serum for longer period of time. Microparticulate drug delivery system is one of the processes to provide the sustained & controlled delivery of drug to long period of time and maintain an effective drug concentration in the serum for longer time. The microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs where their spherical particles ranging from 1 to 1000 micrometers. Where here the microspheres are prepared from the solvent evaporation method, microspheres are prepared by two particles core m material and coating material, where the core material is made up of drug and particulate is of polymers. Microencapsulation for oral use has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided. Microencapsulation is used to modify and retard drug release, due to its small particle size they are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa [1-4].

MATERIAL AND METHODS

Glimepiride was a gift sample from Dr. Reddy's Laboratories, Hyderabad, Ethyl Cellulose (Richer chemicals pvt.LTD., Hyderabad, India), Eudrajit RL100 and Eudrajit RS 100 (Richer chemicals pvt.LTD., Hyderabad, India), Dichloromethane (Merck specialities private limited, Mumbai), Poly vinyl alcohol (S D fine-chem limited, Mumbai), Ethanol (Merck specialities private limited).

Method

Solvent evaporation method for Glimepiride microspheres

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Emulsification (o/w) solvent evaporation method was employed in the preparation of Glimepiride microspheres using ethyl cellulose and combination of ethyl cellulose and Eudrajit RS 100 and Eudrajit RL 100 as the polymers.

Polymer was dissolved in 10ml of dichloromethane. To this 1mg of drug was added and mixed thoroughly. The above organic phase was added drop wise to 100ml of 1% PVA solution under magnetic stirrer at 800 rpm by keeping at 40˚c till the DCM evaporated. Different formulations were prepared by taking different drug to polymer ratios 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5 and 1:4 and 1:1, 1:2, 1:3 and 1:4 of Eudrajit RS 100 with Ethyl cellulose and combination of equal ratios of Eudrajit RS 100, Eudrajit RL 100 and Ethyl cellulose [5-9].

Characterization of Glimiperide Microspheres

Determination of practical yield

The obtained microspheres were dried at room temperature and weighed. The yield of microspheres was calculated using the formula [10].

$$\text{Percentage yield} = \frac{\text{Amount of microspheres obtained}}{\text{Amount of Non-volatile material taken}} \times 100$$

Encapsulation Efficiency

Glimepiride microsphere (100mg) was digested in 100ml distilled water. Then the suspension was warmed for a few minutes, filtered then the 1ml filterate was made up to 10ml with distilled water [11]. The solution was analyzed at 225nm using UV spectroscopy (Shimadzu).

$$\% \text{ Encapsulation efficiency} = \frac{\text{Amount of drug encapsulated}}{\text{Theoretical amount of drug}} \times 100$$

Determination of mean particle size of microspheres

A minute quantity of dried microspheres was suspended in glycerine and the particle size of 100 microspheres was determined in each batch by optical microscopy (Olympus, India) and the mean particle size was calculated [12].

Scanning electron microscopy (SEM)

For the external morphology studies, the samples were mounted on a metal slab with double adhesive tape and coated with platinum under vacuum and the air dried particles were visualized using scanning electron microscopy (FEI-Quanta 200F) operating at 15kv.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of the formulated microspheres and drug were recorded. Microspheres were taken in a KBr pellet [13].

Approximately 5mg samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR range from 500-3500cm^{-1}, with a resolution of 4 cm^{-1}.

RESULTS AND DISCUSSION

Release kinetics

In Vitro Release Profile

In vitro release profile for microspheres performed using USP type 1 dissolution apparatus. Sample equivalent to 45 mg of Glimepiride was added to 900ml phosphate buffer of pH 7.4 at 37±0.5ºC and stirred at 100 rpm. Aliquot of 5 mL was withdrawn at time intervals of 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10 and 12 h. The withdrawn volume was replenished with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured at λ_{max} 225 nm using phosphate buffer of pH 7.4 as blank. Results of *in vitro* drug release studies obtained from absorbance data were tabulated and shown graphically as Cumulative % drug released Vs Time.

Higuchi Release Model

To study the Higuchi release kinetics, the release rate data was fitted to the following equation

$$F = KH.t\ 1/2$$

Where, F is the amount of drug release

KH is the release rate constant

t is the release time

When the data was plotted as a cumulative percentage drug release versus square root of time, yields a straight line, indicating that the drug released by diffusion mechanism the slope is equal to k.

Y=31.02 X -9.919 R2= 0.962

Korsmeyer and Peppas Model

The release rate data were fitted to the following equation,

$$Mt/M8 = K_M.t^n$$

Where, Mt/M8 is the fraction of drug release

K_M is the release constant

t is the release time

N is the diffusional exponent for the drug release that dependent on the shape of the matrix dosage form. When the data is plotted as log percentage release versus log time, yields as straight line with a slope equal to n and the k can be obtained from y- intercept. For non-fickian release the n values falls between 0.5 and 1.0 while for fickian (case I) diffusion n= 0.5 and zero order release (case II transport) n=1.0.

Y =0.710 X 1.265

R^2=0.972

Zero order release rate kinetics

To study the zero order release kinetics the release rate data are fitted to the following equation

$$F = K_0 t$$

Here, F is the fraction of drug release

K_0 is the rate constant

T is the release time

Hen data is plotted a cumulative percentage drug release versus time, if the plot is linear then the data obey zero order release kinetic, with a slope equal to K_0.

y=8.929x10.46
R2=0.959

First order model

This model has also been used to describe absorption and /or elimination of some drug, the release of the drug which followed first order kinetic can be expressed by the equation

$LogC = logC_0-Kt/2.303$

Where, C_0 is the initial concentration of drug
K is the first order rate constant
t is the time

The data obtained are plotted as log cumulative percentage of drug m remaining Vs time. This yields a straight line with a slope of –K/2.303.

Y= -0.098+2.048
R^2= 0.972

Drug and Excipients Compatibility Studies

FTIR spectroscopy was used to ensure that no chemical interactions between the drugs and polymer occurred.

Linearity Plot of Glimipiride in pH 7.4 Phosphate Buffer

The solutions of Glimepiride were prepared and the absorbance of resulting solutions was measured in UV spectrophotometer at 269 nm. The absorbance are noted and given in table 3.

The standard graph between concentration Vs absorbance was given in figure 6.

Fig 1.Dissolution graph of MP1 to MP6

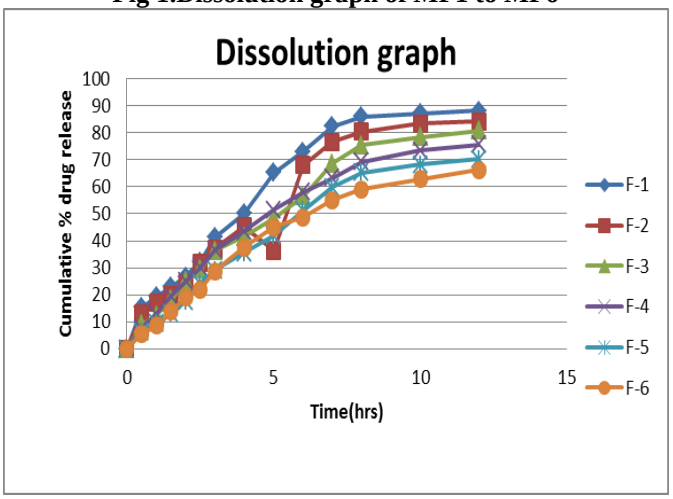

Fig 2. Dissolution graph of MP7 to MP12

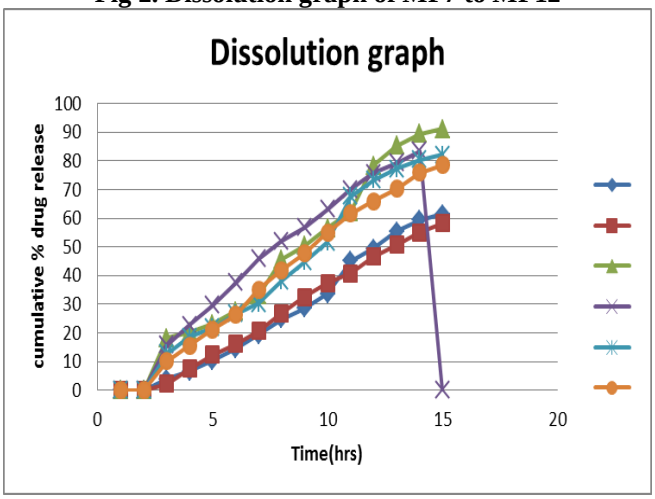

Fig 3. FTIR of Drug Glimepiride

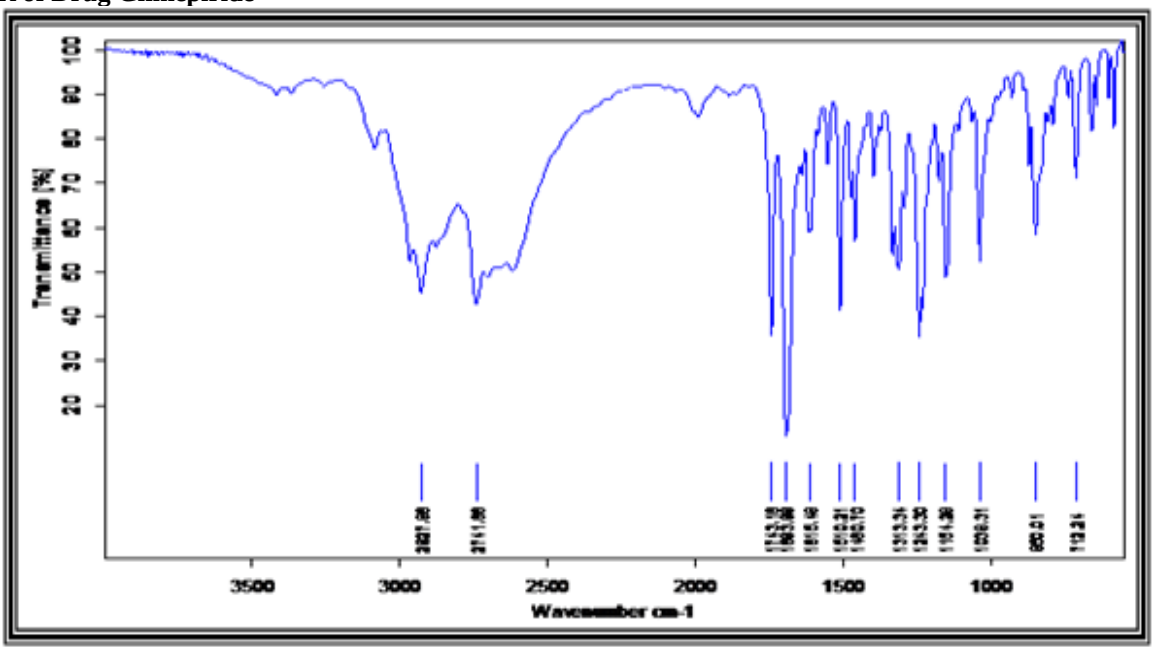

Fig 4. FTIR of Glimepiride Microspheres

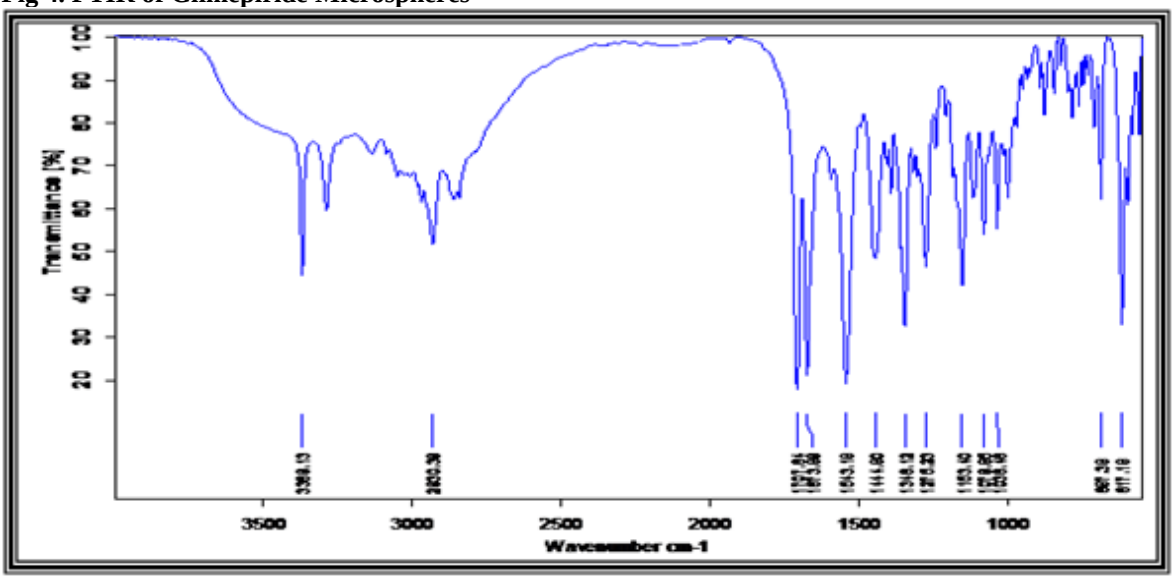

Fig 5. FTIR of Final Best Formulation

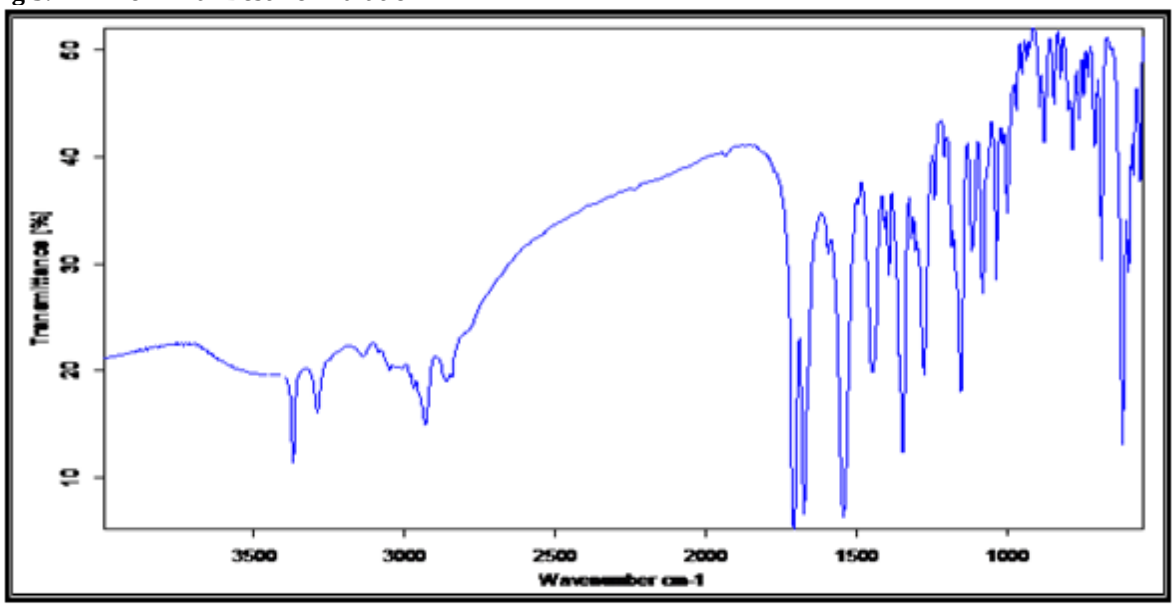

Fig 6. Linearity plot of Glimepiride

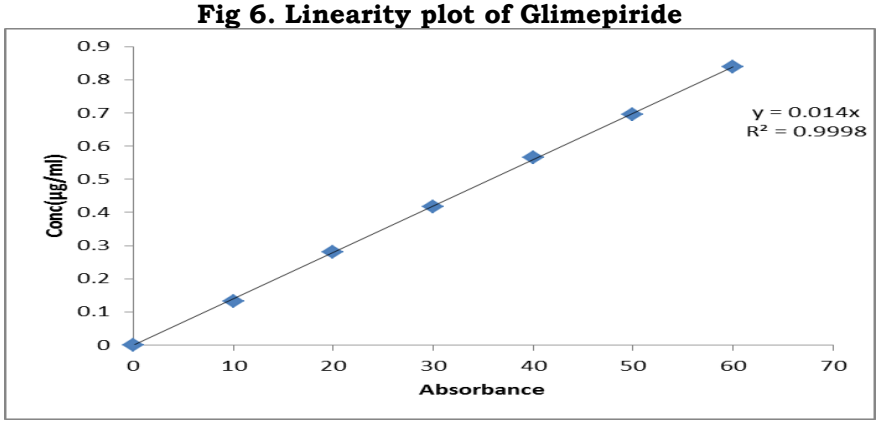

Table 1. Formulation table of Glimepiride microspheres

Formulation code	Drug(mg)	Eudrajit RS 100 (mg)	Eudrajit RL 100 (mg)	DCM (ml)	Ethanol (ml)	Ethyl Cellulose (%)	Drug : Polymer
M1	1	0.5	_	10	_	1	1:0.5
M2	1	1	_	10	_	1	1:1
M3	1	1.5	--	10	_	1	1:1.5
M4	1	2	_	10	_	1	1:2
M5	1	2.5	_	10	_	1	1:2.5
M6	1	3	_	10	_	1	1:3
M7	1	3.5	_	10	_	1	1:3.5
M8	1	4	_	10	_	1	1:4
M9	1	1	0.5	5	5	1	1:1
M10	1	2	1	5	5	1	1:2
M11	1	3	1.5	5	5	1	1:3
M12	1	4	2	5	5	1	1:4

Table 2. Particle size, %Encapsulation efficiency and percentage yield.

Formulation	Particle Size (µm)	Encapsulation efficiency (%)	Percentage yield (%)
MP_1	133.5±1.25	65.87±1.56	59.25
MP_2	157.4±1.34	67.13±1.84	63.88
MP_3	189.3±1.28	68.24±0.97	68.88
MP_4	200.5±.87	68.55±2.34	74.07
MP_5	215.6±2.34	74.44±1.39	78.73
MP_6	223.5±1.84	79.04±1.52	83.33
MP_7	234.7±1.57	86.17±1.13	91.35
MP_8	246.1±0.96	94.75±1.40	93.33
MP_9	210.1±1.23	70.15±2.15	60.55
MP_{10}	235.4±1.45	75.87±0.80	74.07
MP_{11}	243.9±1.72	88.88±1.62	86.11
MP_{12}	250.6±1.34	95.23±1.55	94.44

Table 3. Standard Graph of Glimepiride in Buffer pH 7.4

CONCENTRATION (µg/ml)	ABSORBANCE
0	0
10	0.132
20	0.280
30	0.416
40	0.565
50	0.696
60	0.838

CONCLUSION

The present study has been a satisfactory attempt to formulate microspheres of Glimepiride, an orally administered antidiabetic drug with a view of improving its oral bioavailability and giving a prolonged release of drug. FT-IR spectra of physical mixture showed no significant shifting of the peaks therefore it reveals that the drug is compatible with the polymer used. Microspheres with polymers such as Ethyl cellulose and Eudrajit RS 100 and Eudrajit RL 100 were successfully prepared by emulsification solvent evaporation method. The percentage yield obtained in all the formulations was good and in the range of 59.25-94.44%. The particle size analysis revealed that the size of microspheres was increased with increase in the concentration of polymer. Formulation with combination of Ethyl cellulose Eudrajit RS 100 and Eudrajit RL 100 gave large particles in the range of 250.6±1.34 µm. Scanning electron microscopy showed that microspheres of drug with combination Formulation with combination of Ethyl cellulose Eudrajit RS 100 and Eudrajit RL 100 showed smooth surface and a good spherical shape. The *in-vitro* drug release studies showed that drug release was more in case of formulations MP_9- MP_{12} containing both hydrophilic and hydrophobic polymers as compared to formulations MP_1- MP_8 only hydrophobic polymer.

REFERENCES

1. Abhishek Pandey, Vivek singh Bhadoria. Formulation Development & Optimization of Glimepiride Microspheres Using Ionotropic Gelation Technique. Pharmacia, 1(2), 2011, 67-72.
2. Alagusundaram M, Madhu Sudana Chetty C, Umashankari K, Attuluri Venkata Badarinath, Lavanya C and Ramkanth S. Microspheres as a Novel Drug Delivery Sysytem - A Review. *International Journal of ChemTech Research*, 1(3), 2009,526-534.
3. Salvadeo. Glimepiride-Glimepiride in the Treatment of Giuseppe Derosa and Sibilla Anna Teresa Type 2 Diabetes. *Clinical Medicine: Therapeutics*, 1, 2009, 835–845.
4. Harshad Parmar, Sunil Bakliwal, Nayan Gujarathi, Bhushan Rane, Sunil Pawar. Different Methods of Formulation And Evaluation Of Mucoadhesive Microsphere. *International Journal of Applied Biology and Pharmaceutical Technology*, 1(3), 2010, 1157-1167.
5. Kedar Prasad Meena, Dangi JS, Samal PK and Namdeo KP. Recent Advances in Microspheres Manufacturing Technology. *International Journal Pharmacy & Technology*, 3(1), 2011, 854-893.
6. *Kristi Monson, Arthur Schoenstadt. Pioglitazone Uses: An Overview*, 2007.
7. Satheesh Madhav NV, Shivani Kala. Review on Microparticulate Drug Delivery System. *Int.J. PharmTech Res*, 2011, 3(3), 1255-1259.
8. Prasanth VV, Akash Chakraborthy Moy, Sam T Mathew, Rinku Mathapan. Microspheres - An Overview. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 2 (2), 2011, 1242-1254.
9. Ram Chand Dhakar, Sheo Datta Maurya, Bhanu PS Sagar, Anish K Gupta, Ghanshyam Maurya. Development and evaluation of mucoadhesive microspheres of pioglitazone maleate. *Journal of Pharmacy Research*, 4(2), 2011, 456-458.
10. Satish V. Shirolkar, Mukund G. Tawar, Nishant S. Gandhi, Nilesh B. Deore. Development and evaluation of floating microspheres of Glimepiride using ethyl cellulose. *Der Pharmacia Lettre*, 2(5), 2010, 261-11.
11. SSipai Altaf Bhai M, Vandana Yadav, Mamatha Y, Prasanth VV. Mucoadhesive Microspheres An Overview. *American Journal of PharmTech Research*, 2(1), 2012, 2249-338.
12. Jain NK. Controlled and novel drug delivery, 4th Edition, 236-237, 21.
13. Lin WJ and Wu TL. Modification of the initial release of a highly water-soluble drug from ethylcellulose microspheres. *J Microencapsulation*, 16(5), 1999, 639- 646.