Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2014, 6 (2):10-16
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Comparative evaluation of wax incorporated alginate and pectinate gel beads of Metformin

Ganesh N. S.*, G. Bharathi, Jayanthi C. and Hanumanthachar Joshi

Department of Pharmaceutics, Sarada Vilas College of Pharmacy, Mysore

---

ABSTRACT

The purpose of this study was to prepare and compare wax-incorporated pectinate and alginate-based emulsion gel beads. The method employed was a modified emulsion-gelation method. The waxes in polymer–liquid paraffin mixtures containing a model drug, Metformin, were hot-melted, homogenized and then extruded into calcium chloride solution. The beads formed were separated, washed with distilled water and dried for 12 h. The influence of various types and amounts of wax on floating and drug release behavior of emulsion gel beads were investigated. The drug-loaded gel beads were found to float on simulated gastric fluid only if oil was used. Incorporation of wax into the emulsion gel beads affected the drug release. White beeswax increased the drug release while carnauba wax significantly retarded the drug release. However, the increased amount of incorporated wax in the formulations significantly sustained the drug release while the beads remained floating. The results suggested that sodium alginate gel beads were more optimum compared to pectinate gel beads.

Keywords: Emulsion gel beads; Floating; Intragastric drug delivery; Wax; Simulated gastric fluid.

INTRODUCTION

Oral administration is the most preferable route of drug delivery to the systemic circulation. A problem frequently encountered with conventional sustained release dosage forms is the inability to increase the residence time in an absorption window, i.e. stomach and proximal portion of the small intestine [1]. Retention of drug delivery systems in the stomach prolongs the overall gastrointestinal transit time, thereby resulting in improved oral bioavailability of poorly soluble drugs [2]. These systems are also appropriate for drugs which are locally active to the gastric mucosa in the stomach [3]. The local delivery of drugs by a means of intragastric floating drug delivery may overcome the inefficiency of conventional oral administration. Methods for prolonging the gastric retention of drugs or dosage forms have been attempted based on different mechanisms such as floating, expansion/plug type, high density, or adhesion to mucosa[2,4]. The floating system in particular has been extensively researched, mainly because the floating system does not adversely affect the motility of the GI tract. Immediate floating can be achieved if the density of the device is low at the beginning, for example, being provided by the entrapment of air or by the incorporation of low density materials such as oils and foam powders [5, 6, 7].

Hydrogel polymers were employed to formulate gel beads which are one of the form of floating systems. Hydrogel polymers include alginate, pectin, chitosan, agar & agarose and K-carrageenan etc [8]. Alginate and pectin when react with calcium chloride form complexes which were found to be insoluble and resistant to acidic media. Calcium pectinate/calcium alginate gel beads have been used as a vehicle for controlled release of drugs [9, 10, 11]. The

benefits include cheap and abundant sources, excellent biocompatibility, and total degradation without hazardous by-products [12].

Metformin has elimination half-life of 6.5 h. MH suffers from certain specific problems of which the most prominent being the high dose (1.5–2.0 g/day), low bioavailability (60%), and high incidence of gastrointestinal (GI) side effects (30% cases). Therefore, there are continued efforts to improve the pharmaceutical formulation of MH in order to achieve an optimal therapy. These efforts mainly focus on controlled/ slow release of the drug including the sophisticated gastroretentive systems [13].

The present aim of the work is to develop and compare the wax incorporated alginate and pectinate gel beads of Metformin Hcl for floating delivery and controlled drug delivery. And also to investigate the influence of beeswax and carnauba wax on release profile of alginate and pectinate gel beads.

MATERIALS AND METHODS

1 Formulation

Preparation of wax incorporated emulsion gel beads of Metformin HCl

Method used – hot melt extrusion along with ionotropic gelation method

Accurate quantity of polymer was dissolved in 50ml of distilled water and stirred to form dispersion. Drug was added to the above dispersion and again stirred for uniform distribution. Later, liquid paraffin was also added to the same and stirring was continued to get homogenous emulsion. In another beaker, various amounts of waxes (viz. white bees wax, carnauba wax) were melted in water bath at 60–85°C, depending on the melting range of the waxes used. The molten wax was added to the homogenized emulsion mixture of polymer, oil and MH which was already heated to same temperature and stirred until a homogenous mixture was obtained. The hot melted mixture was extruded through a 23G syringe needle into calcium chloride solution (2% w/v). The beads were allowed to remain in the same solution for 30 min to improve their mechanical strength. The formed beads were separated, washed with water and allowed to dry at room temperature overnight. Table 1 lists the formulation variables for different formulations of MH gel beads.

Table 1. Formulation design for MH gel beads using different ratios of drug, polymers and waxes.

S. No.	Ingredients	Formulations											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Metformin HCl	1	1	1	1	1	1	1	1	1	1	1	1
2	Sodium alginate	1.5	1.5	1.5	1.5	1.5	1.5	-	-	-	-	-	-
3	Low methoxy pectin	-	-	-	-	-	-	2	2	2	2	2	2
4	White bees wax	1	2	3	-	-	-	1	2	3	-	-	-
5	Carnauba wax	-	-	-	1	2	3	-	-	-	1	2	3

2 Evaluation of Beads

2.1 Drug polymer interaction (FTIR) study

Drug polymer interactions were studied by FT-IR spectroscopy. One to 2 mg of MH alone and mixture of drug and polymer were weighed and mixed properly with potassium bromide uniformly. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR- spectrum of the pellet from 500–4000 cm-1 was recorded taking air as the reference and compared to study any interference [14].

2.2 Surface morphology (SEM)

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan). Dry MH gel beads were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of MH gel beads were taken by random scanning of the stub [15].

2.3 Frequency distribution analysis

The diameter of a sample of gel beads (300 beads) of each formulation was determined using vernier caliper. In order to be able to define a frequency distribution or compare the characteristics of particles with many different

diameters, the frequency distribution can be broken down into different size ranges, which can be presented in the form of a histogram. Histogram presents an interpretation of the frequency distribution and enables the percentage of particles having a given equivalent diameter to be determined [16].

2.4 Buoyancy behaviour

The time between the introduction of the FDDS into the medium and its buoyancy to the upper one third of the dissolution vessel (floating lag time) and the floating ability was determined using USP dissolution tester apparatus II (Paddle method). Fifty beads were put in the vessel and the paddles were rotated at 50 rpm in 900 ml 0.1 N HCl pH 1.2, maintained at 37±0.5 °C for 12 hours. The floating ability the beads was measured by visual observation. The preparation was considered to have buoyancy, only when all beads floated on the test solution immediately or within a lag time which did not exceed 2 min [17].

2.5 Drug Content

To determine the drug content and encapsulation efficiency of the beads, 200 mg beads were crushed using a porcelain mortar and a pestle, and dispersed in suitable solvent (methanol). The dispersion was sonicated for 15 minutes and left overnight for 24 hrs, then the dispersion was filtered. A 1 ml sample was taken and diluted with suitable solvent (methanol), and drug content assayed using a UV-visible spectrophotometer at λmax of 233 nm. The drug content of each formulation was recorded as mg / 200 mg of gel beads [18].

2.6 Drug Entrapment Efficiency

The drug entrapment efficiency of prepared beads was determined by using the following equation [18].

EE (%) = Actual drug content / Theoretical drug content x 100

2.7 *In-vitro* dissolution study

The release rate of MH gel beads was determined by employing USP XXIII apparatus II (paddle method). The dissolution test was performed using 900 ml 0.1N HCL, in 37 ± 0.5°C at 50 rpm. MH gel beads equivalent to 100 mg of MH was used for the study. At various time points (hourly) 5ml of the sample solution was withdrawn from the dissolution apparatus for upto 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered and the absorbance was determined at 233nm. Dissolution profiles of the formulations were analyzed by plotting cumulative percentage drug release versus time. The data obtained were also subjected to kinetic treatment to understand release mechanism [19].

2.8 Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order (Log(Q_0-Q) v/s t), Higuchi's square root of time (Q v/s $t^{1/2}$) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q_0-Q) is the cumulative percentage of drug remaining after time t [20].

In short, the results obtained from *in vitro* release studies were plotted in four kinetics models of data treatment as follows.

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time(Peppas exponential equation)

2.9 Differential Scanning Calorimetery (DSC)

The physical state of drug in the MH gel beads was analyzed by DSC (DSC-60, Shimadzu, Japan). The thermograms of MH, physical mixture of MH and polymer, MH gel beads and were obtained at a scanning rate of 10°C/min conducted over a temperature range of 25–350ºC, respectively [21].

RESULTS AND DISCUSSION

1 Drug polymer interaction (FTIR) study

FTIR Spectra were obtained for MH, physical mixture of MH and polymers. The respective spectra are presented in Fig 1 to 3. The characteristic peaks of the MH were compared with the peaks obtained for physical mixture of MH and polymer. From the obtained spectra it appeared that there were no interaction between MH and polymers.

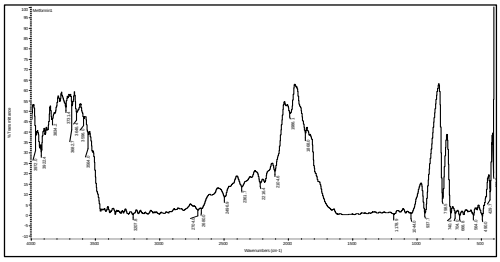

Figure 1. FTIR spectrum of pure Metformin

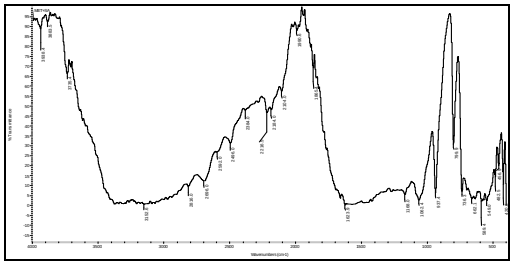

Figure 2. FTIR spectrum of physical mixture of Metformin & SA

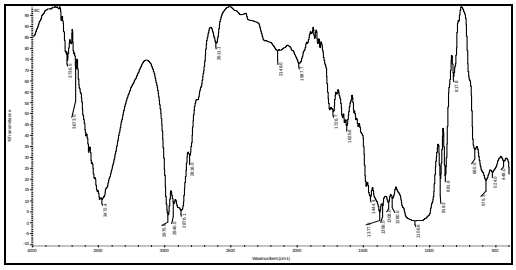

Figure 3. FTIR spectrum of physical mixture of Metformin and pectin

2 Surface morphology (SEM)

The surface morphology of the MH beads was studied by SEM. SEM photographs of the various formulations are shown in the Fig. 4 & 5. Surface smoothness was observed with beeswax incorporated MH beads when compared to carnauba wax incorporated beads which was found to have a slightly rough surface.

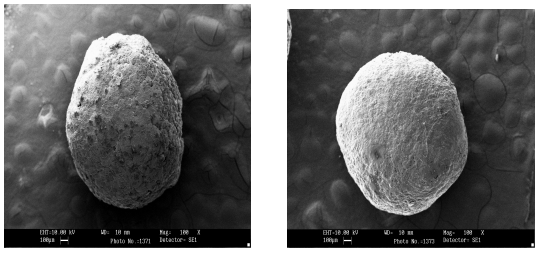

Figure 4. SEM photographs of MH gel beads using SA

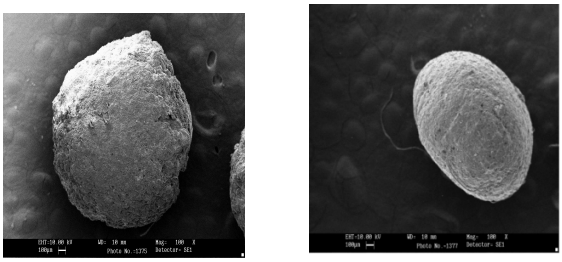

Figure 5. SEM photographs of MH gel beads using pectin

3 Frequency distribution analysis

As the ratio of wax was increased, the mean particle size of MH beads had also decreased (Fig 6). The significant decrease may be due to the increase in the viscosity of the droplets. MH beads having a size range of 1.0 to 2.1 mm (Fig 7) with normal frequency distribution was obtained. Compared to pectin gel beads, sodium alginate beads were smaller in size.

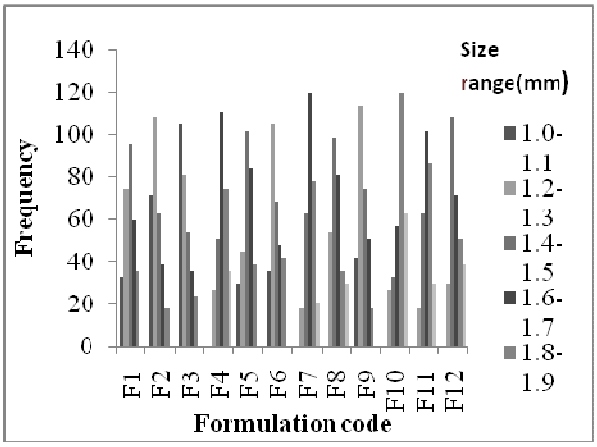

Figure 6. Frequency Distribution analysis of MH gel beads

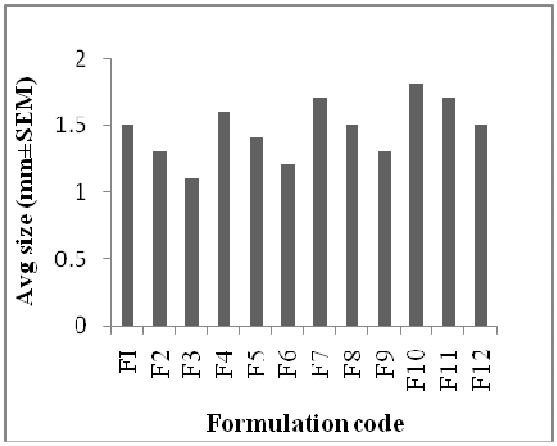

Figure 7. Determination of Average particle size

4 Buoyancy

The floating ability of prepared beads was evaluated. The beads without oil sank immediately in 0.1 N HCl (pH 1.2), while beads containing sufficient amount of liquid paraffin (F1 to F12) demonstrated instantaneous and excellent floating ability. The beads remained afloat throughout the study period (12hrs). It was observed that varying the wax concentrations in the bead formulations did not affect the floating lag time or the floating duration of the beads in the dissolution media.

5 Percentage drug entrapment efficiency

Entrapment efficiency increased with increase in the wax concentration. From the results it can be inferred that there is a proper distribution of MH in the beads and the deviation were within the acceptable limits. The percent of drug content in the formulations were found to be in the range of 25.06 to 16.67mg. The percentage entrapment efficiency was found to be 94.35% to 83.28%. The results obtained are shown in Fig 8. A maximum of 94.35% drug entrapment efficiency was obtained in MH beads which were prepared using sodium alginate and beeswax. It was further observed that the drug entrapment was proportional to the MH: wax ratio and size of the MH beads. By increasing the wax concentration, the encapsulation efficiency was increased. The entrapment efficiency of alginate gel beads was better than pectin gel beads.

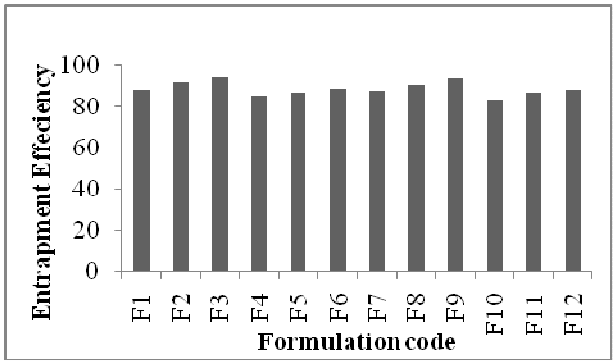

Figure 8. Percentage Drug entrapment efficiency of MH gel beads

6 ***In vitro*** **dissolution studies**

The *in vitro* performance of MH beads showed prolonged and controlled release of MH. The results of the *in vitro* dissolution studies showed controlled release in a predictable manner. As the wax concentration was increased, the drug release from the floating beads was found to decrease. Compared to beeswax, carnauba wax retarded drug release more effectively; however, the bees wax incorporated alginate gel beads had an optimum release at the end of 12th hour. The *in vitro* release profiles of all the formulations (F1 to F12) are shown in Fig. 9 & 10.

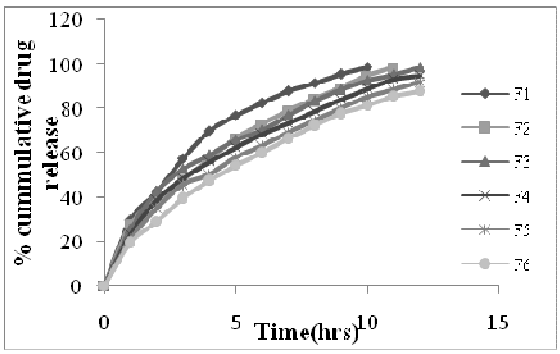

Figure 9. In-vitro release profile of MH gel beads using SA

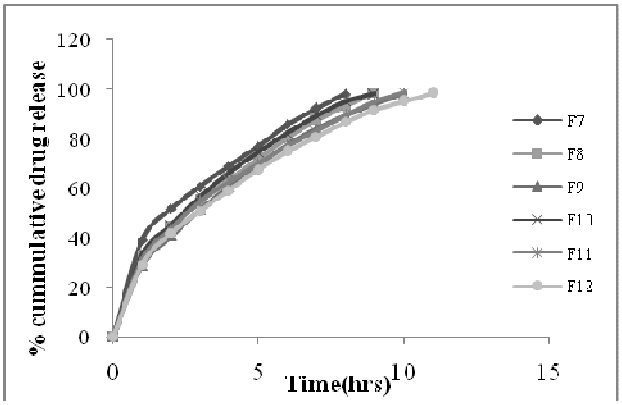

Figure 10. In-vitro release profile of MH gel beads using Pectin

7 Release kinetics of MH gel beads

The plots of cumulative percentage drug release V/s. time, cumulative percent drug retained V/s. root time, log cumulative percent drug retained V/s. time and log cumulative percent drug release V/s. log time were drawn. The slopes and the regression co-efficient of determinations (r^2) were listed in Table 2. The co-efficient of determination indicated that the release data was best fitted with zero order as-well-as first order kinetics. Higuchi equation explains the diffusion controlled release mechanism.

Table 2. Release kinetics of MH beads

Formulation	Zero order	First order	Higuchi Matrix	Peppa's model
F1	0.888	0.953	0.990	0.970
F2	0.935	0.903	0.997	0.996
F3	0.908	0.911	0.996	0.989
F4	0.920	0.971	0.997	0.991
F5	0.936	0.984	0.997	0.996
F6	0.949	0.993	0.993	0.997
F7	0.899	0.892	0.997	0.975
F8	0.930	0.879	0.998	0.985
F9	0.932	0.918	0.997	0.990
F10	0.919	0.925	0.998	0.980
F11	0.918	0.894	0.999	0.993
F12	0.920	0.922	0.998	0.996

8 Differential scanning colorimetry (DSC)

In order to confirm the physical state of MH in the beads, DSC of the MH, polymers and MH loaded floating beads were carried out and shown in Fig 11 & 12. The DSC trace of MH showed a sharp endothermic peak at 235°C, its melting point. The pure sodium alginate and pectin showed at 250^0C and 165^0C respectively. MH beads showed the thermal behavior at 180^0C with drug loaded pectinate beads and at 200^0C with drug loaded sodium alginate beads.

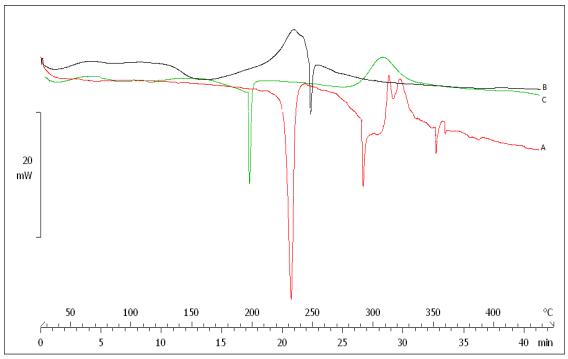

Figure 11. DSC thermograms of MH (A); SA polymer (B); sodium alginate drug loaded beads(C).

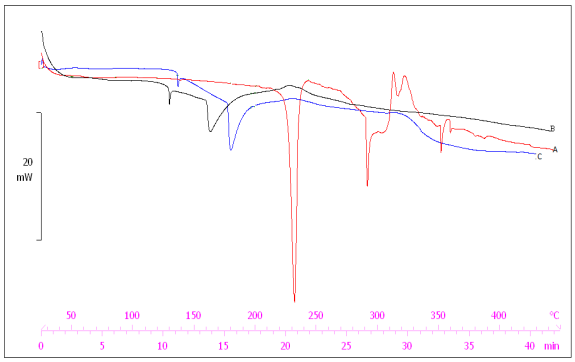

Figure 12. DSC thermograms of MH (A); Pectin polymer (B); pectin drug loaded beads(C).

CONCLUSION

It can be concluded that wax incorporated gel beads offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time. And From the study it is evident that sodium alginate beads are more promising controlled release gel beads than pectinate gel beads and in waxes, beeswax is more optimum than carnauba wax.

REFERENCES

[1] A. Streubel, J.Siepmann R., Bodmeier, *Curr Opin Pharmacol*, **2006**, 6, 501–508.
[2] AJ. Moes, *Crit Rev Ther Drug Carrier Syst*, **1993**, 10, 143–195.
[3] MP. Cooreman, P. Krausgrill, KJ. Hengels, *Antimicrob Agents Chemother*, **1993**, 37, 1506–1509.
[4] SS. Davis, *Drug Discov Today*, **2005**, 10, 249–257.
[5] I. Krogel, R. Bodmeier, *J Control Release*, **1999**, 61, 43–50.
[6] S. Desai & S. Bolton, *Pharm Res*, **1993**, 10, 1321–1325.
[7] A. Streubel, J. Siepmann, R. Bodmeier, *Int J Pharm*, **2002**, 241, 279–292.
[8] Amos Nussinovitch, Polymer macro- and micro-gel beads fundamentals and applications, physical properties of beads and their estimation. USA, springer science+business media, **2010**.
[9] P. Sriamornsak, J. Nunthanid, *Int J Pharm* , **1998**, 160, 207–212.
[10] P. Sriamornsak, J. Nunthanid, *J Microencapsul* , **1999**, 16, 303–313.
[11] Hanne Hjorth Tonnesen, Jan Karlsen, *Drug Development and Industrial Pharmacy*, **2002**, 28, 621–630.
[12] P. Sriamornsak, *Silpakorn Univ Int J*, **2003**, 3, 206–228.
[13] A. Patel, S. Ray, RS. Thakur, *Daru*, **2006**, 14, 57–69.
[14] KM. Manjann, TM. Pramod Kumar, B. Shivakumar, *Asian Journal of Pharmaceutical Sciences*, 2012, 7, 28-39.
[15] J. Kawadkar, K. Chauhan Meenakshi, A. Ram, *Daru*, **2010**, 18, 211-220.
[16] D. Nagasamy Venkatesh, N. Ramesh, S. Karthick, K. Mohammed Fakrudeen, B. Uthayakumar, RM. Valliappan, S. Vinu Deepak, Biplab Debnath, MK. Samanta & B. Suresh, *Journal of Pharmacy Research*, **2008**, 1, 139-142.
[17] Peeush Singhal, Kapil Kumar, Manisha Pandey, Shubhini A Saraf, *International Journal of ChemTech Research*, **2010**, 2, 2076-2085.
[18] MT. Lena, IK. Yehia, *Iraqi J Pharm Sci*, **2011**, 20, 70-80.
[19] J. Wang, DR. Flanagan, *J Pharm Sci* **1999**, 88, 731-738.
[20] P. Costa, JMS. Lobo, *Eur J Pharm Sci* , **2001**, 13, 123-33.
[21] Rajat Ray, Siddhartha Maity, SanchitaMandal, K, Tapan Chatterjee, Biswanath Sa, *Pharmacology & Pharmacy*, **2010**, 1, 9-17.