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Research Article

PREPARATION AND *IN-VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF PHENYTOIN SODIUM USING NATURAL POLYMERS

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ABSTRACT

The aim of the present study was to develop sustained release matrix tablets of phenytoin sodium an antiepileptic drug. Advantages of sustained-release tablets are that they can often be taken less frequently than instant release formulations of the same drug, and that they keep steady levels of the drug in the blood stream. The tablets were fabricated by the wet granulation method using water as granulating agent along with matrix materials like guar gum, sodium alginate, tragacanth and xanthan gum with varying percentage. The granules were evaluated for angle of repose, bulk density, compressibility index, total porosity, and drug content. The tablets were subjected to weight variation test, drug content, hardness, friability, and in vitro release studies. The swelling behavior of matrix was also investigated. The granules showed satisfactory flow properties, compressibility, and drug content. The I.R spectral analysis studies confirmed no interaction between phenytoin with used natural gums. All the tablet formulations showed acceptable pharmacotechnical properties and complied with in-house specifications for tested parameters. In the further formulation development process, F8 (55% guar gum with 10% acacia), the most successful formulation of the study, exhibited satisfactory drug release and could extend the release up to 12 hours. The mechanism of drug release from all the formulations was diffusion coupled with erosion

Keywords: Matrix tablet, Sustain release, Guar gum, Phenytoin sodium.

INTRODUCTION

Phenytoin, an antiepileptic drug, has been the drug of choice for treatment of most types of epileptic seizures. The effective therapeutic plasma level is 10-20 µg/ml[1]. It is poorly soluble in water. Dissolution characteristics were improved by preparing solid dispersion system such as co-precipitation[2] or mechanochemical pulverization[3].

However the plasma level following administration of these systems decreases rapidly therefore it might become necessary for the patient to take the drug several times a day to maintain the effective therapeutic plasma level.

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years[4]. Regular research is going on in field of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration[5-7]. Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of dosage form[8]. Guar gum a polysaccharide derivative with glycoside linkage has been used as matrix former for controlled release of isoniazide[9] and diltiazem[10].

Xanthan gum is a high molecular weight extracellular polysaccharide, produced on commercial scale by the viscous fermentation of gram negative bacterium *Xanthomonas campesteris*. The molecule consists of a backbone identical to that of cellulose, with side chains attached to alternate glucose residues. It is a hydrophilic polymer, which until recently had been limited for use in thickening, suspending and emulsifying water based systems[11].

The present study is aimed to prepare sustained release tablet of phenytoin sodium with natural gums as matrix materials like guar gum, sodium alginate, tragacanth and xanthan gum with varying percentage. The effect of type and amount of polymer, their swellibility, erosion on drug release profile are studied.

MATERIALS AND METHODS

Materials

Phenytoin sodium, guar gum (GM), and xanthan gum (XG) was procured from Himedia, Mumbai. Gum acacia, tragacanth, lactose, talc and magnesium stearate were procured from Merck. Other materials used were of analytical grade and procured from commercial sources.

Methods

Preparation of sustained release matrix tablets

Drug was mixed with the polymer guar gum alone or in combination of auxiliary substances in different proportion in a turbula mixer for 30 minutes. The powder mixture was moistened by adding water drop by drop in a mortar and passed through sieve. The granules obtained were dried in a hot air oven at 45°C for about 2 hours or till constant weight was obtained. The dried granules were then mixed with magnesium stearate and talc, further subjected to compression on single punch tabletting machine with flat punches (9 mm diameter).

Evaluation of granules

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted such that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the graph paper placed on the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\tan \theta = h/r \quad \ldots\ldots (1)$$

Where h and r are the height and radius of the powder cone respectively

Bulk density

A quantity of 2 g of powder from each individual formula, shaken lightly to break any agglomerates formed and was introduced into a 10 mL measuring cylinder, Initial volume was observed, further cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted. Loose

bulk density (LBD) and tapped bulk density (TBD) were calculated using the following formulae

LBD = weight of the powder/volume of the packing …….. (2)

TBD = weight of the powder/tapped volume of the packing …..(3)

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index

Carr's index (%) = [(TBD – LBD) × 100] / TBD …… (4)

Total porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V bulk) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space, V).

Porosity (%) = (V bulk – V) / V bulk × 100 …… (5)

Drug content

An accurately weighed amount of powdered phenytoin sodium granules (100 mg) was extracted with water and the solution was filtered. The absorbance was measured spectophotometrically at 222 nm after suitable dilution.

Evaluation of tablets

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver), and the test was performed according to the official method.

Swelling behavior of matrix tablets

The extent of swelling was measured in terms of percentage weight gain by the tablets. The swelling behavior of all the formulations was studied. One tablet from each formulation was kept in petridish containing phosphate buffer pH 6.8. At the end of 2, 4, 6, 8, 10 and 12 hours tablets were withdrawn, soaked on tissue paper and weighed, and then percentage weight gain by the tablet was calculated using formula[6].

$$SI = M_t\text{-}M_0/M_0 X\ 100 \quad \ldots\ldots (6)$$

Where, SI = Swelling index, M_t = Weight of tablet at time't' and M_0 = Weight of tablet at zero time

Drug content

Five tablets were weighed individually, and the drug was extracted by vortexing in water. The drug content was determined spectrophotometrically.

Hardness and friability

The hardness and friability of 6 tablets of each batch, were determined using the Monsanto Hardness tester and the Fraibility test apparatus (Lab india, Mumbai, India), respectively.

***In vitro* release studies**

The in vitro dissolution studies were carried out using USP apparatus type II (Lab India, Mumbai, India) at 50 rpm. The dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and the phosphate buffer pH 7.4 from 3 to 12 hours (900 mL), maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by UV-visible spectrophotometer (Shimadzu 1701).

Study of release kinetics

In order to investigate the mode of release from tablets, the release data was analyzed with the following mathematical models[12]:

Zero order equation $Q_t = K_0 t$ …….. (7)

First order equation $\ln Q_t = \ln Q_0 + K_1 t$ …… (8)

Higuchi equation $Q_t = k t^{1/2}$ …… (9)

Korsmeyer and peppas equation $Q_t = k_p t^n$ ……..(10)

Hixson-Crowell equation $Q_0^{1/3} - Q_t^{1/3} = k_s t$ …… (11)

Where Q_t is the percent of the drug release at time t and K_0 and K_t are the coefficients of equation, K_p is constant incorporating structural and geometric characteristics of the release device, K_s is a constant incorporating the surface-volume relation and n is the release exponent indicate the release mechanism.

Stability study

The stability study of the tablet was carried out according to ICH guidelines at 40±2 °C/ 75±5% RH for 90 days by storing the samples in stability chamber.

Table 1: Formulation of sodium phenytoin matrix tablets (100mg)

S .no.	Ingredients	Formulations							
		F1	F2	F3	F4	F5	F6	F7	F8
1		25	25	25	25	25	25	25	25
2	Guar Gum(%)	25	50	55	55	55	55	55	55
3	Gum acacia(%)	–	–	–	–	–	–	5	10
4	Gum tragacanth(%)	–	–	–	—	5	10	—	—
5	Xanthum gum(%)	–	–	5	10	–	–	–	–
6	Lactose(%)	49	24	14	9	14	9	14	9
7	Talc(%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
8	Mag.stearate(%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
9	Disttilad water	qs	qs	qs	qs	qs	qs	qs	qs

Table 2: Release mechanism with variation of n* values

n value	Mechanism	dM_t/d_t dependence
n<0.5	Quasi-Fickian diffusion	$t^{0.5}$
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous (non-Fickian) diffusion	t^{n-1}
1	Non-Fickian case II	Zero order
n>1.0	Non-Fickian super case II	t^{n-1}

*The diffusional exponent is based on Korsmeyer-Peppas equation, $M_t/M_\infty = Kt^n$

RESULTS AND DISCUSSION

Since the guar gum was found to have poor flow properties, wet granulation method was used to improve the flow properties of guar gum[13]. A granule is an aggregation of component particles that is held together by the presence of bonds of finite strength. Physical properties of granules such as specific surface area, shape, hardness, surface characteristics, and size can significantly affect the rate of dissolution of drugs contained in a heterogeneous formulation[14].

The granules of different formulations were evaluated for angle of repose, LBD, TBD, compressibility index, total porosity, and drug content. The results of angle of repose and compressibility index (%) ranged from 21.84 ± 0.03 to 24.68 ± 0.02, and 11.01 ± 0.03 to 16.08 ± 0.02, respectively. The results of LBD and TBD ranged from 0.219 ± 0.04 to 0.421 ± 0.03 and 0.248 ± 0.03 to 0.485 ± 0.05, respectively. The results of percentage porosity of the granules ranged from 26.92 ± 0.06 to 34.25 ± 0.03. The drug content in a weighed amount of granules of all formulations ranged from 95.53 ± 0.02 to 98.14 ± 0.05%.

The results of angle of repose (<30) indicate good flow properties of the granules[15, 16]. This was further supported by lower compressibility index values. Generally, compressibility index values up to 15% result in good to excellent flow properties. The percentage porosity values of the granules ranged from 26.92% to 34.25%, indicating that the packing of the granules may range from close to lose packing and also further confirming that the particles are not of greatly different in sizes. Generally, a percentage porosity value below 26% shows that the particles in the powders are of greatly different in sizes and a value greater than 48% shows that particles in the powder are in the form of aggregates or flocculates. The drug content in the weighed amount of granules of all formulations was found to be uniform. All these results indicate that the granules possessed satisfactory flow properties, compressibility, and drug content.

Table 3: Properties of granules

Formulations	Angle of repose (°) ±SD, n=3	Loose bulk density (g/ml) ±SD, n=3	Tapped bulk density (g/ml) ±SD, n=3	Compressibility index (%)	Total porosity (%) ±SD, n=3	Drug content (%) ±SD, n=3
F1	24.68±0.02	0.396±0.03	0.445±0.06	11.01	34.25±0.03	97.68±0.06
F2	23.97±0.08	0.267±0.02	0.301±0.03	11.29	33.09±0.07	96.41±0.01
F3	22.73±0.04	0.407±0.05	0.485±0.05	16.08	27.21±0.02	95.62±0.03
F4	21.84±0.03	0.312±0.02	0.364±0.01	14.28	31.42±0.01	95.64±0.04
F5	23.91±0.01	0.338±0.07	0.385±0.02	12.20	28.43±0.03	98.14±0.05
F6	24.11±0.07	0.421±0.03	0.481±0.07	12.47	26.92±0.06	95.53±0.02
F7	23.95±0.02	0.219±0.04	0.248±0.03	11.69	31.74±0.04	97.77±0.01
F8	22.01±0.06	0.298±0.08	0.342±0.02	12.86	32.03±0.02	98.01±0.04

The tablets of different formulations were subjected to various evaluation tests, such as uniformity of weight, drug content, hardness, friability, swelling index and in vitro dissolution. In a weight variation test, the average percentage deviation of all tablet formulations was found to be within the limit of IP, and hence all formulations passed the test for uniformity of weight as per official requirements.

The swelling index was calculated with respect to time (Fig. 1). As time increases, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration up to 4 hours. Later on, it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium except formulation F8. The swelling effect was still continuing even after 12 hours, which indicating the drug released from the above formulation was more sustained as compared to other formulations. It has been observed that the cumulative percent drug release decreases with increasing concentration of gum and swelling index. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of gums.

Good uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was more than 95%. The formulation F8 showed a comparatively high hardness value of 4.9 kg/cm^2. Tablet hardness is not an absolute indicator of strength. Another measure of tablet strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable.

The *in-vitro* drug release characteristics were studied in simulated gastric and intestinal fluids for a period of 12 hours using USP XXIII dissolution apparatus 2 (paddle type at 50 rpm). The results of dissolution studies indicated that F1, F2, released 84%, and 61.6%, of drug at the end of 2 hours; whereas F1 give 99.6% drug release in 3 hours and F2 give 97.6% drug release in 6 hours which indicate that on increasing the % of guar gum drug release was sustained but the results were not satisfactory.

In further formulation development process different polymer were used in combination with guar gum and release study was carried out. However problem in wet granulation was found when the polymer such as xanthan gum, gum tragacanth and gum acacia were used in more than 10%. Among the formulations, F3 (55% guar gum and 5% xanthan gum) F4 (55% guar gum and 10% xanthan gum) formulations, the drug release was found for about 8 hours, but the better release was found with F4. F5 (55% guar gum and 5% tragacanth gum) and F6 (55% guar gum and 10% gum tragacanth) were evaluated for release characteristic, and found 94% and 91% drug release occurred in the time span of 6 hours respectively. More over F6 formulation was found to be release the drug upto 8 hours, which indicate the release rate of F6 is more sustained than F5.

On further study, formulation F7 (55% guar gum and 5% gum acacia) and F8 (55% guar gum and 10% gum acacia) showed further slower the release of drug i.e 97% and 92% for 10 hours respectively. Further more the F8 formulation was found to be release 99% of the drug upto 12 hours. From the fig. 2, result shows that initially 45% and 32% drug was release from matrix within 2 hours may be due to bursting effect i.e. presence of drug in the external surface of the tablet followed by slow and constant release of drug upto 97.2% and 99.6% of drug in 10 hours and 12 hours respectively might be due to entanglement of the drug into the networking structure of the matrix.

To know the mechanism of drug release kinetics from these formulations, the data were treated according to Higuchi[17] (cumulative percentage of drug released vs. square root of time), Korsmeyer-Peppas model[18] (log cumulative percentage of drug released vs. log time) equations and Hixson-Crowell model (cube root % drug remaining vs time) along with zero order (cumulative amount of drug released vs. time) pattern. As clearly indicated in Table 5, the formulations did not follow a zero-order release pattern. By using Higuchi's kinetics or square-root kinetics this would explain why drug diffuses at a comparatively slower rate as the distance of diffusion increases. To evaluate the drug release with changes in the surface area and the diameter of the tablets due to swelling effect which is well explained by Hixson-Crowell cube root law.

Table 4: Properties of compressed matrix tablets

Formulations	Weight variation (%) ±SD, n=20	Hardness (kg/cm²) ±SD, n=5	Friability (%) ±SD, n=3	Drug content (%) ±SD, n=3
F1	3.24±0.06	4.0±0.12	0.69±0.02	96.45±0.04
F2	2.45±0.02	4.2±0.81	0.78±0.04	95.89±0.56
F3	2.09±0.08	4.7±0.04	0.76±0.01	97.25±0.23
F4	3.00±0.05	4.5±0.23	0.71±0.06	96.93±0.45
F5	2.54±0.01	4.6±0.63	0.68±0.05	97.12±0.67
F6	2.16±0.04	4.0±0.21	0.85±0.03	96.81±0.78
F7	2.98±0.01	4.5±0.18	0.76±0.02	98.12±0.34
F8	2.68±0.02	4.9±0.23	0.88±0.01	98.68±0.34

Table 5: Release kinetics of matrix tablets

	Kinetic models					
Formulations	**First order**	**Zero order**	**Higuchi**	**Korsmeyer-Peppas**		**Hixon-Crowell**
	R²	**R²**	**R²**	**R²**	**n**	**R²**
F1	0.949	0.870	0.979	0.977	0.710	0.947
F2	0.995	0.765	0.962	0.992	0.509	0.899
F3	0.993	0.911	0.981	0.968	0.547	0.941
F4	0.998	0.937	0.990	0.998	0.607	0.949
F5	0.990	0.923	0.960	0.994	0.514	0.979
F6	0.991	0.945	0.942	0.987	0.584	0.981
F7	0.997	0.916	0.985	0.986	0.519	0.982
F8	0.989	0.930	0.996	0.998	0.589	0.989

In our experiments, the in-vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity (R2= 0.974 to 0.993). To confirm the diffusion mechanism, the data were fit into Korsmeyer-Peppas model.

All formulations F1 to F8 showed high linearity (R^2 = 0.981 to 0.998), with slope (n) values ranging from 0.51 to 0.87), this (n) value indicating that coupling of diffusion and erosion mechanism so called anomalous diffusion and may indicate that the drug release is controlled by more than one mechanism, which indicate that formulation F8 release the drug by diffusion coupled with erosion mechanism. Hixson-Crowell plots showed linearity (R^2 = 0.941 to 0.989) indicated a change in surface area and diameter of the tablet with the progressive dissolution of the matrix as a function of time.

CONCLUSION

Guar gum alone could not control the phenytoin release effectively for 12 hours. It was clear and evident from the results that matrix tablet prepared from the acacia gum 10% (F8) with water as granulating agent is a better formulation for the sustained released matrix tablets of phenytoin.

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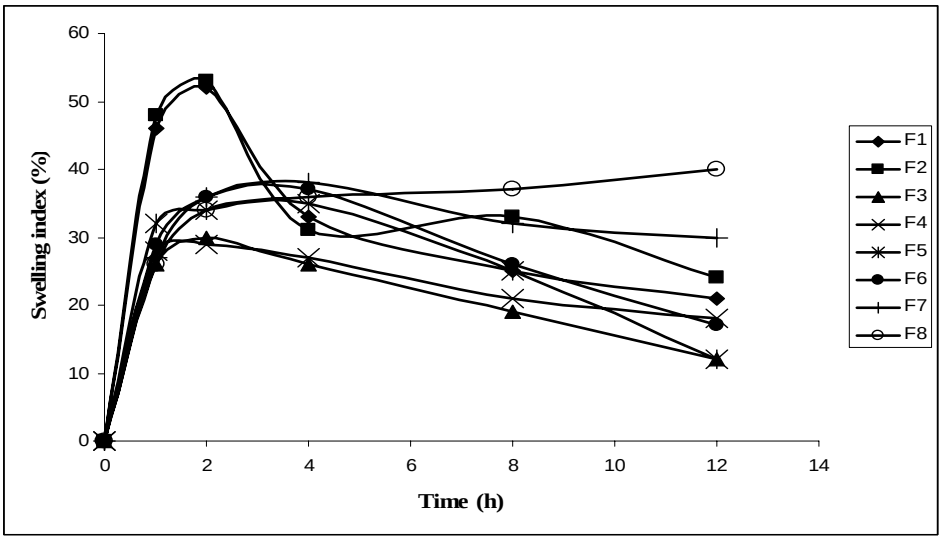

Fig. 1: Relationship between swelling index and time

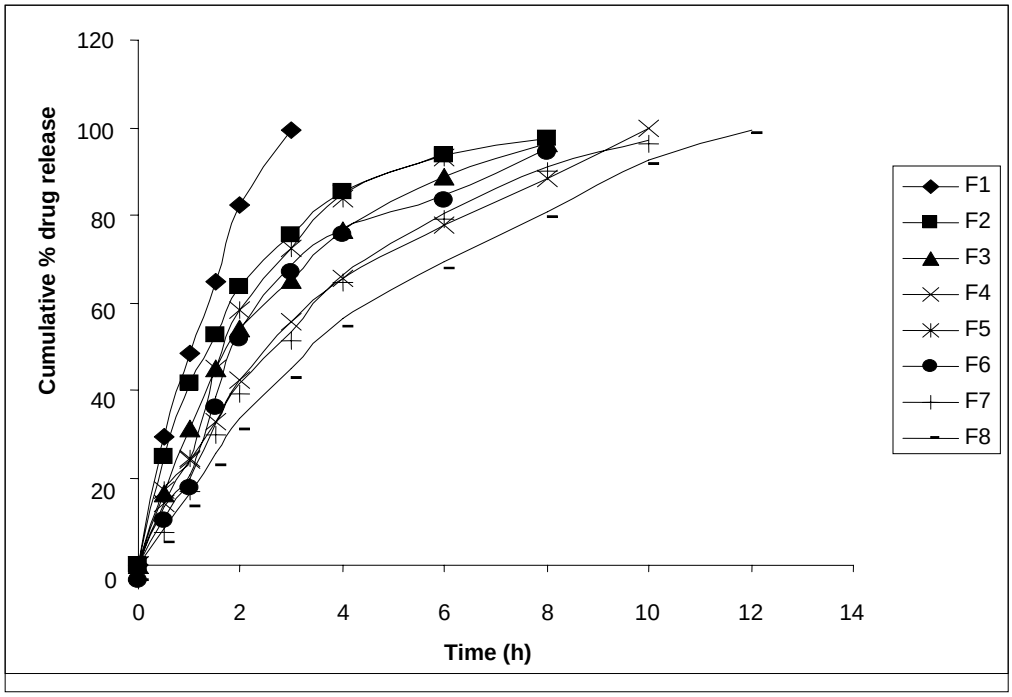

Fig. 2: *In-vitro* dissolution profile of different formulations containing phenytoin sodium

REFERENCES

1. Woodury DM, Penry JK, Schmit RP. Antiepileptic drugs. New York: Raven Press; 1972. P. 193.
2. Sekikawa H, Fujiwara J, Naganuma T, Nakano M, Arita T. Dissolution behaviors and gastrointestinal absorption of phenytoin in human. Chem. Pharm. Bull. 1978; 26: 3033-3039.
3. Yamamoto K, Nakano M, Arita T, Takayama Y, Nakai Y. Dissolution behavior and bioavailability of phenytoin from a ground mixture with microcrystalline cellulose. J. Pharm. Sci. 1976; 65: 1484-1488.
4. Ansel HC, Loyyd VA. Pharmaceutical dosage forms and drug delivery system. Hong Kong :Lippincott's Williams and Wilking; 1999. p. 275-280.
5. Jain S, Yadav SK, Patil UK. Preparation and evaluation of sustained release matrix tablet of furosemide using natural polymers. Research J. Pharm. and Tech. 2008; 1(4): 374-376.
6. Sujja AJ, Munday DL, and Khan KA. Development and evaluation of a multiple-unit oral sustained release dosage form for S (+)-ibuprofen: preparation and release kinetics. Int. J. Pharm. 1999; 193(1): 73-84.
7. Khullar P, Khar RK, Agarwal SP. Guar gum as a hydrophilic matrix for preparation of theophylline controlled release dosage form. Ind. J. Pharm. Sc. 1999; 61(6): 342-345.
8. Nokano M, Ogata A. *In-vitro* release characteristics of matrix tablets: Study of karaya gum and guar gum as release modulators. Ind. J. Pharm. Sc. 2006; 68(6): 824-826.
9. Jain NK, Kulkarni K, Talwar N. Controlled-release tablet formulation of isoniazid. Pharmazie. 1992; 47: 277.
10. Altaf S, Jones DB. Controlled release matrix tablets of isoniazide, diltiazem and nafronyl oxalate. Pharm. Res. 1998; 15: 1196.
11. Gwen MJ, Joseph RR, Rhodes CT. Modern Pharmaceutics. New York: Marcel Dekker; 1996. 72(3): p. 581.
12. Costa P, Lobo JMS. Modeling and comparison of dissolution profile. Eur. J. pharm. Sci. 2001; 13: 123-133.
13. Krishnaiah YSR, Rama Rao T, Ushasree M, Satyanarayana S. A study on the *in-vitro* evaluation of guar gum as a carrier for oral controlled drug delivery. Saudi Pharm. J. 2001; 9: 91-98.
14. Banker GS, Anderson LR. Tablets. In: Lachman L, Liberman HA, Kanig JL, editors. The theory and practice of industrial pharmacy. Mumbai, India: Varghese Publishing House; 1987. p. 293-345.
15. Aulton ME, Wells TI. Pharmaceutics: The Science of dosage form design. 2nd ed. London, England: Churchill Livingstone; 1988.
16. Martin A. Micromeritics. In: Martin A, ed. Physical Pharmacy. Baltimore, MD: Lippincott Williams & Wilkins; 2001; 423-454.
17. Higuchi T. Mechanism of sustained action medication: Theoretical analysis of rate release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 1963; 52: 1145-1149.
18. Korsmeyer RW, Gurny R, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 1983; 15:.25-35