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FORMULATION AND *IN-VITRO* EVALUATION OF THEOPHYLLINE SR MATRIX TABLETS AND COMPARISON OF RELEASE RATE WITH MARKETED PRODUCTS DISPENSED IN BANGLADESH

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ABSTRACT

Sustained release Theophylline matrix tablets constituting METHOCEL K4MCR, were developed in this study for the purposeof designing a dosage form that manifests desirable release profile. Five matrix tablet formulations were prepared by direct compressionof METHOCEL K4MCR in varying proportion with fixed percentage of Theophylline. Formulation,containing 10% METHOCEL K4MCR, shows highest percentage of release and on the other hand formulation, containing 50% METHOCEL K4MCR, shows lowest percentage of release. This is also apparent by the MDT and t_{50} value of the drug formulations that with the decreasing amount of METHOCELK4MCR, the release rate is increased.The release rates of Theophylline from prepared tablets were compared with those of commercial SR tablets of Theophylline. Formulation,containing 30% METHOCEL K4MCR, was found to be the optimum formulation in providing controlled drug delivery with similar release profile of the market product. The release of the studied drug shows first order kinetics and by the Higuchi model and the Korsmeyer-Peppas plot it is evident that, drugs were released by diffusion method and the release of the drugs follow non-fickian release respectively.

Key Words:- Theophylline, Sustained Release (SR), Matrix Tablet,Methocel, METHOCEL, Drug release kinetics.

INTRODUCTION

Sustained drug delivery involves the application of physical and polymer chemistry to produce well characterized and reproducible dosage forms, which control drug entry into the body within the specifications of the required drug delivery profile (Alderman, 1984).A sustained release dosage forms allows a twofold or greater reduction in frequency of administration of the drug in comparison with frequency required by a conventional dosage forms (Brahmankar, *et al.*, 1995).Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect (Lachman*et al*., 1986). Typically, sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period. In this type of dosage forms, the rate of drug release mainly controlled by the delivery system itself, though it may be influenced by external conditions, like pH, enzymes, ions, motility and physiological conditions(Alderman, 1984).A wide array of

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polymers has been employed as retarding agents each of which presents a different approach to the matrix concept. Polymers that primarily forming insoluble of skeleton matrices are considered as the first category of retarding materials are classified as plastic matrix systems. The second class represents hydrophobic and water-insoluble materials, which are potentially erodible and the third group behaves hydrophilic properties. Plastic matrix systems, due to their chemical inertness and drug embedding ability, have been widely used for sustaining the release of drug. Liquid penetration into the matrix is the rate limiting step in such systems unless channeling agents are used. The hydrophobic and waxy materials, on the other hand, are potentially erodible and control the release of drug through pore diffusing and erosion (Lordi, 1990).Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, does not disintegrate, but immediately hydrated with aqueous fluid and form viscous gelatinous surface barrier that control release of drugs and allowed liquid penetration into the center of the matrix system (Taluckder*et al*., 1996). The drug release from matrix tablet depends on other factors such as pore permeability, shape and size of matrix, drug solubility, polymer molecular weight, drug loading, compression force, and hydrodynamic conditions (Veiga*et al*., 1988; Kim *et al*., 1997). Previous studies developed by Williams, 2002led to the conclusion that the type and level of excipients influence the rate and extension of drug release. Various formulation factors influence the drug release form HPMC matrices, viz., polymer viscosity, polymer particle size, drug/polymer ratio, drug solubility, drug particle size, drug loading, compression force, tablet shape, formulation excipients, coatings, processing techniques, as well as the testing medium (Ranga-Rao*et al*., 1988). Theophylline, a bronchodilator, relaxes and opens the air passages to the lungs, making it easier to breathe. This drug is used mainly in solid oral dosage forms, particularly slow release forms, and has a narrow therapeutic index, requiring regular monitoring of serum Theophylline concentrations to avoid adverse effects (Turner-Warwick, 1988).

MATERIALS AND METHODS

Materials

The ingredients and the equipmentsused in the formulations are mentioned in Table 1 and Table 2 respectively.

Methods

Preparation of matrix tablets

The tablets were prepared by direct compression(Figure 1). In all the formulations the weight of the active is 400 mg and the total weight of the tablet is 1000 mg. At first all the ingredients along with the active were measured appropriately and carefully. The initial stage of the preparation was mixing. The active ingredient, matrix forming polymer Methocel and the filler or diluents lactose were mixed well. The next step is milling of the mixed ingredients. At the last stage of the method, talc, magnesium stearate and aerosilwas added to the formulation.The tablets were prepared by compressing the mixture in using 5 punch compression machine with a 21.00×8.00 mm cylindrical punch and die set. The compression force was 10 ton. Before the compression, the face of the die and punch was lubricated with purified talc. Different formulations of Theophylline SR tablets (T4F-1, T4F-2,T4F-3, T4F-4,T4F-5) containing different amounts formulation materials are mentioned in Table 3.

Physical Characterization of Theophylline

Length, Width, Size and Shape

The length and width of tablets depends on the die and punches selected for making the tablets. The tablets of various sizes and shapes are prepared but generally they are circular with either flat or biconvex faces. Here we prepared round cylindrical shape tablets.

Thickness

The thickness of a tablet can vary without any change in its weight. This is generally due to the difference of density of granules, pressure applied for compression and the speed of compression. The thickness of the tablets was determined by using a Digital Caliper (range 0-150 mm).

Uniformity of Weight

It is desirable that every individual tablet in a batch should be in uniform weight and weight variation within permissible limits. If any weight variation is there, that should fall within the prescribed limits (generally ±10% for tablets weighing 130 mg or less, ±7.5% for tablets weighing 130 to 324 mg and ±5% for tablets weighing more than 324 mg) (British Pharmacopoeia, 2000)**.**The weights of 10 tablets of each batch were taken at individually and calculate the average weight of 10 tablets. The weights were determined by using an electronic balance (Adventurer TM electronic balance, AR2140, Capacity (Max) - 210 gm, Readability 0.0001 gm). Then we determined the percentage of weight variation of each tablet by using following formula.

Percentage of weight variation=[(Average weight – Individual weight)/ Average wt.] ×100

Friability

Friability test was performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The instrument used for this test is known as 'Friability Test Apparatus' or 'Friabilator'. Friability of the tablets was determined by using Electrolab, EF-2 friability test apparatus. It consists of a plastic chamber which is divided into two parts and revolves at a speed of 25 rpm. A number of tablets were weighed (W1) and placed in the tumbling chamber which was rotated for four minutes or for 100 revolutions. During each revolution the tablets fall from a distance of six inches to undergo shock. After 100 revolutions the tablets were again weighed (W2) and the loss in weight indicates the friability. The acceptable limits of weights loss should not be more than 1 percent (Gupta, 1994).

Friability= $\{(W_1 - W_2)/W_1\} \times 100$

Hardness

The hardness of tablet depends on the weight of the material used, space between the upper and lower punches at the time of compression and pressure applied during compression. The hardness also depends on the nature and quantity of excipients used during compression.The hardness of the tablets was determined by using a hand operated hardness tester apparatus (Electrolab, EH-01P). A tablet hardness of about 6-8 kg-ft was considered for mechanical stability (British Pharmacopoeia, 2000).If the finished tablet is too hard, it may not disintegrate in the required period of time and if the tablet is too soft it may not withstand the handling during packing and transporting. Therefore it is very necessary to check the hardness of tablets when they are being compressed and pressure adjusted accordingly on the tablet machine.

Assay of Theophylline

Preparation Sample Solution

At first,10 tablets of Theophylline SR tablets from each formulation were weighed accurately and were grinded to a fine powder. Then 50 mg of powder (equivalent to 20 mg) was taken in a 100 ml volumetric flask and diluted with distilled water up to the mark. Then 1ml solution was taken into another 100ml volumetric flask and diluted with water upto the mark. Then their absorbance was measured at 271 nm using a UV spectrophotometer (UV- 1800, UV-VIS spectrophotometer,Shimadzu, Japan).

Then the percentage of potency was calculated by the following equation:

$$\% \text{ of Potency} = \frac{Aspl \times Wstd \times Pstd \times \text{Average weight}}{Astd \times Wspl \times \text{Label claimed value}}$$

Where,
Aspl=Absorbance of Sample
Wstd=Weight of Standard
Pstd=Potency of standard
Astd= Absorbance of standard
Wspl=Weight of sample

Dissolution procedure

Dissolution studies were conducted byUSP type II test apparatus (Electrolab, TDL-80L Plus,India) at a speed of 50 rpm and the temperature was maintained at $37^0 \pm 0.5^0$C.

This operation was continued for 8 hours. At every 1-hour interval samples of 6ml were withdrawn from the dissolution medium and replaced with fresh dissolution medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 271 nm for theophylline by UV spectrophotometer. The amounts of the drug present in the sample were calculated with the help of straight line equation obtained from the standard curve for the drugs. The dissolution study was continued for 8 hours to get a simulated picture of the drug release in the in-vivo condition and drug dissolved at specified time periods was plotted as percent release versus time (hours) curves. This drug release profile was fitted into several mathematical models to get an idea of the release mechanism of the drug from the dosage form.

Analysis of Release Data

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of drug release versus square root of time), Korsmeyer-Peppas (log cumulative percentage of drug release versus log time) and Hixson-Crowell (cubic root of percentage drug release versus time) equation models.

Dissolution data were also fitted according to the well-known exponential equation, which is often used to describe the drug release behavior from polymeric systems introduced by Korsmeyer-Peppas*etal*., 1983.

$M_t / M_\infty = k\, t^n$

Where, M_t is the amount of drug release at time t, M_∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet and n is the

diffusion exponent indicative of the mechanism of drug release. A value of n = 0.45 indicates Fickian (case I) release, > 0.45 but < 0.89 for non-Fickian (anomalous) release and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release (Shato*et al.*, 1997). Mean dissolution time (MDT) was calculated from dissolution data using the following equation (Mockel*et al.*, 1993).

$MDT = (n/n+1)\ k^{-1/n}$

Where, n= release exponent and k= release rate constant

RESULT AND DISCUSSION

Physical Characterization of Theophylline tablets

After preparing the tablets, they were undergone some physical test (hardness, thickness, friability, weight variation, drug content etc.). The thickness of the tablets was ranged from 7.5-8.0 mm for the MethocelK4MCR containing formulations. The hardness of the tablets was 11.86-12.75 Kg-ft for the Methocel K4MCR containing formulations. Physical parameters of formulated Theophylline tablets containing Methocel K4MCR are shown in table 4.

Comparison of the formulated tablets with the market products

The formulated Theophylline tablets and three market products were put through dissolution test. Among the formulated five batches T4F-1, T4F-2, T4F-3, T4F-4 and T4F-5 containing 50%, 40%, 30%, 20% and 10% Methocel K4M CR polymer respectively, the T4F-3 tablets' results remain consistent and parallel with the results shown by the market products (Table 5).

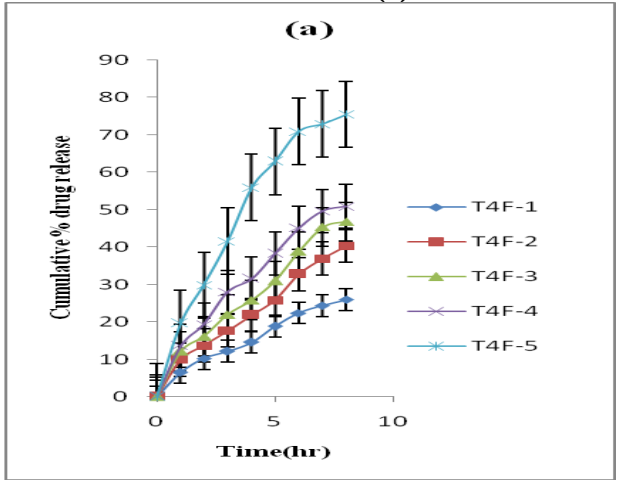
Polymeric effect on formulated Theophylline tablets

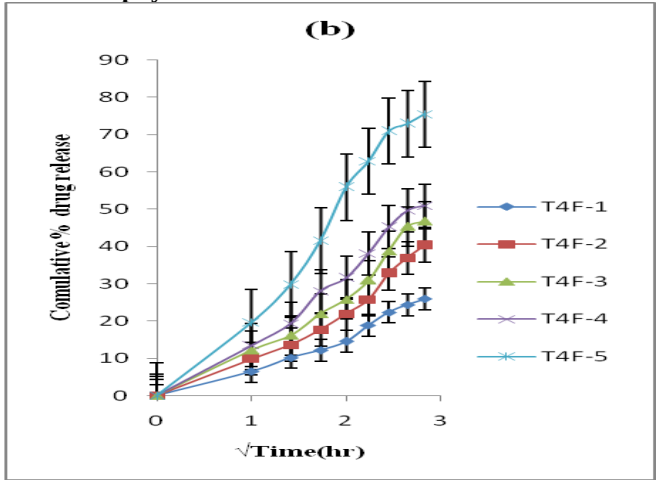
From Figure 2, we can see the zero order, first order, Higuchi and Korsmeyer-Peppas release kinetics of the formulated drugs.The formulation T4F-5 shows highest drug releasepercentage, and T4F-1 shows the lowest percentage of drug release(Table 5). From release kinetics data in table 6, we can see all formulations best fits in first order release paterns, and n value from Korsmeyer-Peppas equation we can see, all formulations follow anomalous transport (non-Fickian).The MDT and t_{50} value of the drugs (Figure 3) also show that the highest amount of METHOCEL K4MCR containing formulation T4F-1 shows the highest MDT and t_{50} value, which indicates the rate retarding effect of METHOCEL K4MCR.

Figure 1.Flow diagram of method of preparing Theophylline sustained release tablets

Mixing of active theophylline, filler lactose and matrix forming polymer methocel.	⇨	Milling of the mixed ingredients and addition of talc, magnesium stearate, aerosil	⇨	Compression of the mixed drug materials.

Figure 2.(a) Zero order release kinetics of Theophylline from METHOCEL K4MCR matrices (b) HiguchiRelease kinetics of Theophylline from METHOCEL K4MCR matrices. (c) : Korsmeyer Release profile of Theophylline from METHOCEL K4MCR matrices.(d) First order Release kinetics of Theophylline from METHOCEL K4MCR matrices.





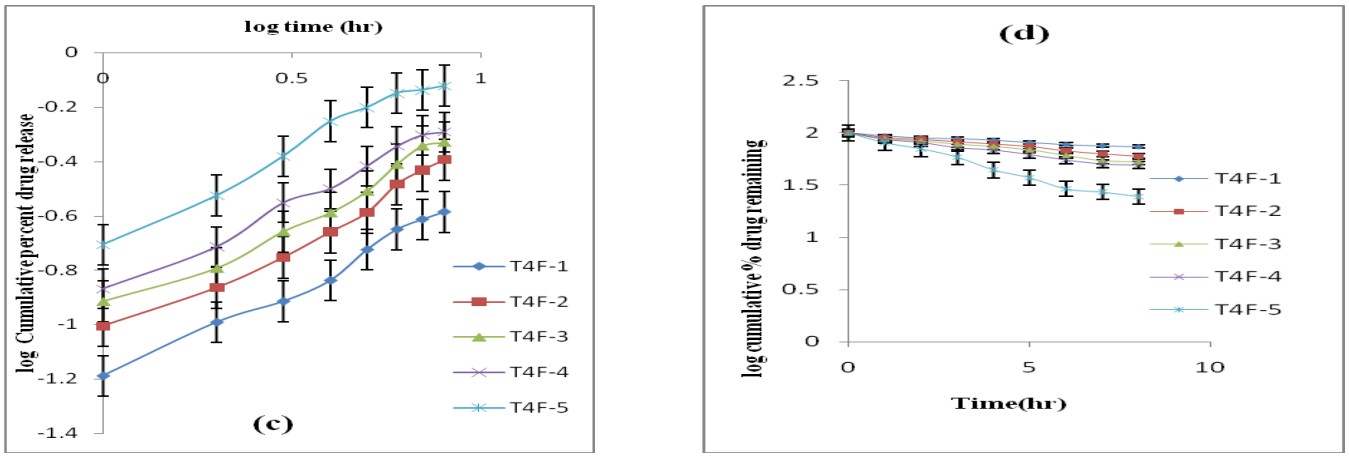


Figure 3.MDT and t_{50} value compared with the Market product (Formulation T4F-1 to T4F-5 & market products B-1 to B-3)

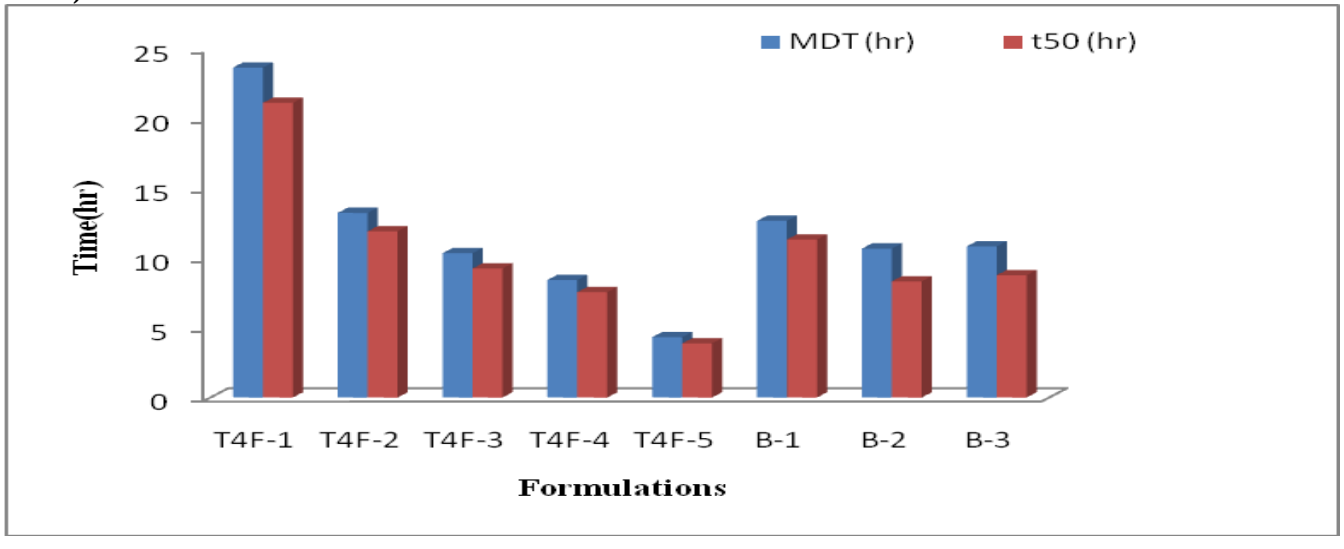


Table 1.List of active ingredient and other excipients used in the preparation of matrix tablets

Name	Category	Source
Theophylline	Active Ingredient	Merck, Germany
METHOCEL K4M CR	Matrix forming agent	Colorcon, USA
Lactose	Diluent	Colorcon, USA
Talc	Lubricant	Colorcon, USA
Magnesium stearate	Antiadherent	Colorcon, USA
Aerosil	Flow promotor	Colorcon, USA

Table 2.List of equipments used in the method of Theophylline SR tablets

Name	Source	Country of origin
Electric balance	Sartorious	Germany
Sieve	Endecotts test sieve	UK
Blender	Drum blender	India
Compression machine	tablet compression machine (5 Punch)	India

Table 3.Formulation of Theophylline sustained release drug containing Methocel K4MCR

Ingredient	Formulations (mg)				
	T4F-1	T4F-2	T4F-3	T4F-4	T4F-5
Theophylline	400	400	400	400	400
METHOCEL K4M CR	500	400	300	200	100
Lactose	90	190	290	390	490
Talc	5	5	5	5	5
Magnessium stearate	4	4	4	4	4
Aerosil	1	1	1	1	1
Total weight	1000	1000	1000	1000	1000

Table 4.Physical parameters of Theophylline tablets containing Methocel K4MCR

Code	Hardness (Kgf)**±SEM	Friability (%)**	Weight variation*(%) ±SEM	Drug content**(%) ±SEM	Diameter (mm)	Thickness (mm)**
T4F-1	12.75±0.73	0.81	999.60±0.52	98.08%±0.11	21	7.5
T4F-2	12.53±0.85	0.4008	999.60±0.70	102%±0.12	21	8
T4F-3	12.2 ±0.89	0.835	999.50±0.71	99%±0.12	21	7.8
T4F-4	12.04±0.73	0.7	999.70±0.45	102%±0.10	21	8
T4F-5	11.86±0.92	0.661	990.72±0.50	104%±0.14	21	8

Table 5.% of drug release of formulated tablets and market products (Formulations T4F-1 to T4F-5 & market products B-1 to B-3)

Time(hr)	% Drug release							
	T4F-1	T4F-2	T4F-3	T4F-4	T4F-5	B-1	B-2	B-3
1	6.479297	9.87655	12.175	13.55273	19.6554	10.54688	14.45313	13.47656
2	10.20078	13.6543	16.1112	19.31923	29.7866	14.51641	25.47734	22.73711
3	12.17031	17.6433	21.96523	28.02109	41.5464	18.64141	32.18359	29.62813
4	14.52578	21.8754	25.7685	31.5622	55.87031	22.37695	36.12969	35.3332
5	18.83672	25.7544	30.9123	38.18594	62.83398	26.89141	38.8875	37.51563
6	22.37813	32.7554	38.7854	45.11992	70.88281	34.14492	41.05234	40.26289
7	24.35234	36.8786	45.32813	49.6432	72.88398	38.28984	43.6043	41.45117
8	25.92656	40.26523	46.75508	50.8707	75.43477	42.02539	45.57266	44.19258

Table 6.formulations Release kinetics of the Theophylline from METHOCEL K4MCR matrices

Formulation code	Zero order		Higuchi		First order		Korsmeyer-Peppas	
	R^2	K_0	R^2	K_H	R^2	K_1	R^2	n
T4F-1	0.977	3.139	0.964	9.505	0.985	0.016	0.986	0.683
T4F-2	0.987	4.806	0.949	14.36	0.990	0.027	0.977	0.698
T4F-3	0.981	5.679	0.950	17.03	0.984	0.034	0.973	0.684
T4F-4	0.967	6.225	0.976	19.06	0.988	0.039	0.991	0.669
T4F-5	0.940	9.414	0.975	29.23	0.986	0.080	0.984	0.688

CONCLUSION

The study reveals that it is possible to design sustained release drug delivery systems with METHOCEL K4MCR polymer. It has been observed that with the decreased amount of the polymer and increased amount of lactose, the release of Theophylline has been increased. The polymers which were used in the formulations seem to be satisfactory for sustained release properties. The polymeric effects on the formulated tablets are evident. The MDT and t_{50} value of the formulated tablets were also satisfactory. However, further investigation is required to establish in-vivo-in-vitro correlation to reveal the accurate pattern of drug release in-vivo environment from this polymeric system.

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REFERENCES

Alderman DA.A review of cellulose ethers in hydrophilic matrices for oralcontrolled release dosage form.*Int J. Pharm. Tech. Prod. mfr*.,5, 1984, 1-9.

BrahmankarDM and JaiswalSB. Biopharmaceutics and Pharmacokinetics. 1st ed. VallabhPrakashan, Delhi, 1995,336-341.

British Pharmacopoeia.Her Majesty's stationary office, London, England.2, 2000, 266-268.

Gupta AK.Introduction to Pharmaceutics volume I. 3rd ed.CBS publishers, Delhi,1994, 267-268.

Kim H and Fassihi R. Application of binary polymer system in drug release ratemodulation. 2. Influence of formulation variables and hydrodynamic conditions on release kinetics. *J. Pharm. Sci*.,86, 1997, 323-328.

Korsmeyer RW, Gurny R, Peppas N A, et al. Mechanism of solute release from porous hydrophilic polymers. *Int. J. Pharm*.,15, 1983, 25-35.

Lachman L, Liberman HA,Kanig JL.The Theory and Practice of Industrial Pharmacy.3rd ed. Lea &Febiger, Philadelphia, 1986, 430-456.

Lordi NG. 1990, Sustain Release Dosage Froms.In Leon Lachman, Herbert A. Lieberman, and Joseph L. Kanig,1986, Theory and Practice of Industrial Pharmacy, Philadelphia: Lea &Febiger, 430-456.

MockelJE, Lippold BC.Zero-order release from hydrocolloid matrics.*Pharm.Res*., 10, 1993, 1066-70.

Ranga-RaoKV, Padmalatha-DeviK, Buri P. Cellulose matrices for zero-order release of soluble drugs. *Drug Dev. Ind. Pharm*., 14, 1988,2299-2320.

Shato H, Miyagawa Y, Okabe T, et al. Dissolution mechanism of diclofenac sodium from wax matrix granules. *J. Pharm. Sci*., 86, 1997, 929- 934.

TaluckderMM, Michoel A, Rombaut P,Kinget R. Comparative Study on Xanthun Gum and Hydroxypropylmethy cellulose as Matrices for Controlled-Release Drug Delivery.*Int J pharm*.,129, 1996, 231-241.

Turner-Warwick, M. Asthma. A Nocturnal Disease: Epidemiology of nocturnal asthma. London, United Kingdom. *Am. J. Med*.,85, 1988, 6-8.2.

Veiga F, Salsa T,Pina ME. Oral Controlled Release Dosage Forms IIglassy polymers in hydrophilic matrices.*Drug Dev. Ind. Pharm*.,24, 1988, 1-9.

Williams IIIRO, ReynoldsTD,CabelkaTD, SykoraMA, MahagunaV. Investigation of excipient type and level on drug release from controlled release tablets containing HPMC.*Pharm. Dev. Tech*., 7(2), 2002, 181-193.