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RESEARCH ARTICLE

In Vitro Release Kinetics Study of Indomethacin 12Hr Matrix Tablet From Methocel K4M CR and Methocel K15M CR.

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ABSTRACT

The objective of the present study was to design and evaluate controlled release tablets of Indomethacin, employing release retarding materials semi synthetic polymers Methocel K4M CR and Methocel K15M CR. There were nine formulations (F1-F9), were prepared in different ratios of Methocel K4M CR and Methocel K15M CR used as release retarding agents and Starch 1500 & Lactose Monohydrate were used as diluents. Tablets were prepared by direct compression method. The powders for tableting were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, total porosity etc. The tablets were subjected to thickness, weight variation test, hardness, friability and in vitro release studies. Release profile of Indomethacin from this sustained release matrix tablet was investigated at dissolution media (Phosphate buffer PH 6.8) using USP Apparatus-2 for twelve hours. The drug release patterns were simulated in different kinetic orders such as Zero Order release kinetics, First Order release kinetics, Higuchi release kinetics, Korsmeyer-Peppas release kinetics and Hixson-Crowell release kinetics to assess the release mechanism. From the study we observed that Higuchi release kinetics, Korsmeyer-Peppas release kinetics and Hixson-Crowell release kinetics were the predominant release mechanism than Zero Order and First Order kinetics. The drug release mechanism from the matrix tablets was found to be non Fickian mechanism.

KEY WORDS: Indomethacin, Sustained Release, Methocel K4M CR, Methocel K15M CR

INTRODUCTION:

During the past 30 years, as expenses and complications involved in marketing new drug molecules have increased with concomitant recognition of therapeutic advantages of controlled drug delivery, greater attention has been focused on the development of controlled release drug delivery systems (CRDDS). The goal in designing CRDDS is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action reducing the dose required or providing uniform drug delivery.[1] The use of controlled release (CR) formulations offers many potential advantages, such as sustained blood levels, attenuation of adverse effects and improved patient compliance. Indomethacin is a more potent inhibitor of COX than is aspirin, but patient intolerance generally limits its use to short-term dosing. Indomethacin has analgesic properties distinct from its anti-inflammatory effects, and there is evidence for central and peripheral actions.[2] Indomethacin is 90% bound to plasma proteins and tissues. The $t_{1/2}$ in plasma is variable, perhaps because of enterohepatic cycling, but averages 2.5 hours. In accordance with the current recommendations, a sustained-release (SR), low-dose formulation (Indomethacin SR 75 mg) was developed with the objective of achieving an optimal efficacy/ acceptability ratio. Indomethacin is insoluble in water, sparingly soluble in alcohol, in chloroform, in ether. It's very poor aqueous solubility indicates that its absorption is dissolution rate-limited which might result in irregular and delayed absorption. The primary benefit of an SR preparation of Indomethacin is that a lower dose is needed to maintain a uniform blood plasma concentration and therefore uniform clinical effect. This drug is challenging to formulate due to its low dose and the fact that this is practically insoluble in water. Indomethacin SR 75 mg/day was well tolerated and mediated through inhibition of the enzyme cyclooxygenase (COX), the enzyme responsible for catalyzes the rate-limiting step in prostaglandin synthesis via the arachidonic acid pathway. In the present investigation an attempt has been made to formulate Indomethacin as sustained release tablet matrix with the addition of release retarding polymers and to evaluate the effect to sustain the release of Indomethacin from tablet matrix. Methocel derivatives have been widely used in the design of complex controlled release systems because of their low toxicity and pH-independent swelling and drug embedding ability.[3] These polymers are hydrophilic in nature and can hold active ingredients firmly that depend on the concentration or ratio of polymers used.[4] Methocel K4M CR and K15 CR are two typically used methocel polymers for the formulation of hydrophilic matrix systems, providing a robust mechanism for the slow

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release of drugs from oral solid dosage forms. They are suitable for preparing formulations with soluble or insoluble drugs and at high or low dosage levels. Hydration of polymers results in the formation of a gel layer that controls the release rate of drug from the core of matrix tablets.[5] The permeability of drug through Methocel K4M CR and/or K15 CR is independent of the pH of the digestive tract. Soluble drugs are released by the combination of diffusion and erosion mechanisms whereas erosion is the predominant mechanism for insoluble drugs. As Methocel derivatives are highly hydrophilic in nature, the involvement of water or moist granulation can make the process highly problematic, therefore, a dry process that produces acceptable powder characteristics and does not intervene with drug release characteristics would be desirable.

MATERIALS AND METHODS:

Methocel K4M CR, Methocel K15M CR, Lactose Monohydrate and starch 1500 was purchased from Colorcon Ltd, USA. Magnesium Stearate and Talc was obtained from Wilfrid Smith Ltd. UK. Indomethacin was obtained from Aristopharma Ltd, Bangladesh and its potency was 99.91%. The solvents and reagents were of analytical grade.

PREPARATION OF MATRIX TABLETS:

The tablet was prepared by simple blending of active ingredient with polymers, filler, lubricant and flow promoter followed by direct compression method (Table 1). 50 tablets were prepared for each proposed formulation. Properly weighed Methocel K4M CR, Methocel K15M CR , Magnesium Stearate, Talc, Starch 1500 and the active ingredient were then taken in a photo film container and blended in a laboratory designed small drum blender machine for 30 minutes to ensure thorough mixing and phase homogenization.

Name	Justification	F1	F2	F3	F4	F5	F6	F7	F8	F9
Indomethacin	Active Ingredient	75	75	75	75	75	75	75	75	75
Methocel K4M	Polymer	20	10	15	10	5	6	6	12	0
Methocel K15M	polymer	15	20	10	10	10	6	6	0	12
Lactose Monohydrate	Diluent	87	92	97	0	107	110	0	55	55
Starch 1500	Diluent	0	0	0	102	0	0	110	55	55
Mg Stearate	Glidant	1	1	1	1	1	1	1	1	1
Talc	Lubricant	2	2	2	2	2	2	2	2	2
Total(in mg)		200	200	200	200	200	200	200	200	200

Table No. 1. Proposed formulations of Indomethacin SR matrix tablets containing Methocel K4M CR and Methocel K15M CR

PHYSICAL EVALUATION OF POWDERS:

The powders were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, total porosity, and drug content etc.

BULK DENSITY:

LBD (Loose Bulk Density) and TBD (Tapped Bulk Density) were determined by 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was placed into a 10-ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The reading of tapping was continued until no further change in volume was noted. Using the following equation LBD and TBD was calculated:

LBD = Weight of the powder / volume of the packing.

TBD = Weight of the powder / Tapping volume of the packing.

COMPRESSIBILITY INDEX:

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

Carr's index (%) = {(TBD – LBD) X 100}/TBD

TOTAL POROSITY:

Total porosity was determined by measuring the volume occupied by a selected weight of 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 (%) = $V_{bulk} - V/V_{bulk} \times 100$

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 in such a way 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 surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Angle of Repose $\theta = \tan^{-1} h/r$

Where, h = Height of the powder cone.

r = Radius of the powder cone

Physical evaluation of Indomethacin matrix tablet:

The prepared tablets were subjected to thickness, weight variation test, hardness, friability, moisture content, and drug content determination.

IN VITRO DISSOLUTION STUDIES:

Dissolution testing was performed in an ''Erweka Dissolution Tester, Germany'' using Apparatus 2 (paddle method) at 75 rpm. The dissolution medium was 750ml pH 6.8 phosphate buffer at 37.0 ± 0.5ºC. The amount of drug present was determined according to the USP monograph for Indomethacin tablets using UV spectrophotometer testing at 318nm. Samples were taken over a 12 hour time period at the 2nd, 4th, 6th, 8th, 10th and 12th hours from starting.

DATA ANALYSIS:

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$C = k_o t$ ..... (1)

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$\text{Log}C_0 - \text{Log}C = kt / 2.303$ ..... (2)

Where, C_0 is the initial concentration of drug and K is first order constant.

$Q = Kt_{1/2}$ ..... (3)

Where, K is the constant reflecting the design variables of the system.

$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t$ ..... (4)

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation. The following plots were made: cumulative % drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model) log cumulative % drug release vs. log time (korsmeyer model) and cube root of drug % remaining in matrix vs. time (hixsoncrowell cube root law).

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

MECHANISM OF DRUG RELEASE:

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

$M_t / M_\infty = Kt^n$ ..... (5)

Where, M_t / M_∞ are the fraction of drug released at time t, K is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in the following table for cylindrical shaped matrices:

Diffusion exponent and solute release mechanism for cylindrical shape

STATISTICAL ANALYSIS:

Data from the experiments were analyzed using the Statistical Package for Social Science (SPSS) software for windows version 17 (SPSS Inc., Chicago, Illinois, USA). Statistical analysis of the results was performed by using one-way analysis of variance (ANOVA) followed by Dennett's t-test for comparisons. The limit of significance was set at $p<0.05$.

RESULTS AND DISCUSSION:

In the present study, an attempt has been taken to develop sustained release tablets of Indomethacin by direct compression method using Methocel K4M CR and

K15M CR as rate retarding polymer (Table 1). Methocel K4M CR and K15M CR was utilized in the proposed formulations F-1 to F-9 in order to evaluate the amount of polymer required to provide desired release rate for 12 hour period. The powders of proposed formulations (F-1 to F-9) were evaluated for LBD, TBD, compressibility index, total porosity, angle of repose and drug content (Table 2). The results of LBD and TBD ranged from 0.423±0.06 to 0.449±0.02 and 0.516±0.02 to 0.544±0.04 respectively. The results of compressibility index (%) ranged from 14.203±0.03 to 20.857±0.04. The results of angle of repose ranged from 26.74±0.03 to 29.25±0.03°.

Formulation	Loose Bulk Density (LBD) (gm/ml)	Tapped Bulk Density (TBD) (gm/ml)	Carr's Index (%)	Hausner ratio	Angle of Repose (°)	Moisture content (%)
F1	0.434±0.01	0.519±0.04	16.378±0.02	1.196±0.03	29.25±0.03	3.2412
F2	0.423±0.06	0.526±0.01	16.730±0.02	1.219±0.02	28.17±0.04	2.9524
F3	0.445±0.04	0.526±0.01	18.609±0.04	1.201±0.03	27.98±0.02	3.3211
F4	0.431±0.04	0.539±0.02	14.203±0.03	1.189±0.03	26.54±0.03	2.9008
F5	0.447±0.01	0.527±0.03	20.857±0.04	1.229±0.05	27.11±0.02	2.8993
F6	0.439±0.03	0.521± 0.03	15.879±0.02	1.166±0.01	26.54±0.03	3.2412
F7	0.425±0.02	0.519±0.03	14.836±0.03	1.189±0.03	28.44±0.03	3.4502
F8	0.433±0.02	0.506±0.03	14.229±0.02	1.174±0.03	27.69±0.02	2.8524
F9	0.449±0.02	0.532± 0.06	18.023±0.02	1.166±0.04	28.36±0.02	2.9879

Table No. 2. Properties of granules of Indomethacin and excipients containing Methocel K4M CR and Methocel K15M CR

TIME (hr)	Cumulative % of Drug Released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	20	21.11	21.33	21.67	22.56	23	25.67	25.33	24.22
4	29.02	30.81	32.7	32.82	34.15	36.93	38.96	38.39	37.72
6	34.21	35.57	43.14	42.92	44.82	47.84	53.11	49.2	47.41
8	43.11	44.47	55.64	53.09	57.12	61.71	66.8	62.97	61.73
10	48.4	50.88	60.9	66.33	67.16	72.01	74.9	73.27	72.02
12	52.82	62.32	72.41	79.88	82.38	86.04	88.73	87.64	86.82

Table No. 3. Percentage release of nine formulations (F-1 to F-9) of Indomethacin matrix tablets against time

All these results indicate that the granules possess satisfactory flow properties, compressibility and drug content. The tablets of the proposed formulations (F-1 - F-9) were subjected to various evaluation tests like thickness, hardness, weight variation test and friability. The thickness of the tablets ranged from 2.85 to 3.15 mm. The hardness and percentage friability of the tablets was 8.9 to 10.9 Kg/cm^2 and ±0.15%. In this study, the percentage friability for all the formulations was below 1%, indicating that the friability was within the official limits. All the tablet formulations Showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness and friability. A polymer's ability to retard the drug release rate is related to its viscosity. However, processing factors including particle size, hardness, porosity and compressibility index etc. also affect the release rate of drug from tablets. The hydration rate of HPMC depends on the nature of the substituent like hydroxypropyl group content. Hence, methocel was used because it forms a strong viscous gel in

contact with aqueous media, which may be useful in controlled delivery of drugs. The drug release data obtained were extrapolated by Zero order (Figure 1) First order (Figure 2), Higuchi (Figure 3) Korsmeyer-Peppas and Hixson-Crowell equations to know the mechanism of drug release from these formulations. In this experiment, the in vitro release profiles of drug from all these formulations could be best expressed by Korsmeyer-Peppas and Hixson-Crowell equation, as the plots showed highest linearity (R^2 0.97 to 0.99). To confirm the diffusion mechanism, the data were fitted into comparatively high slope (n) values of >0.5, which appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion. Hence, diffusion coupled with erosion might be the mechanism for the drug release from Methocel based matrix tablet.

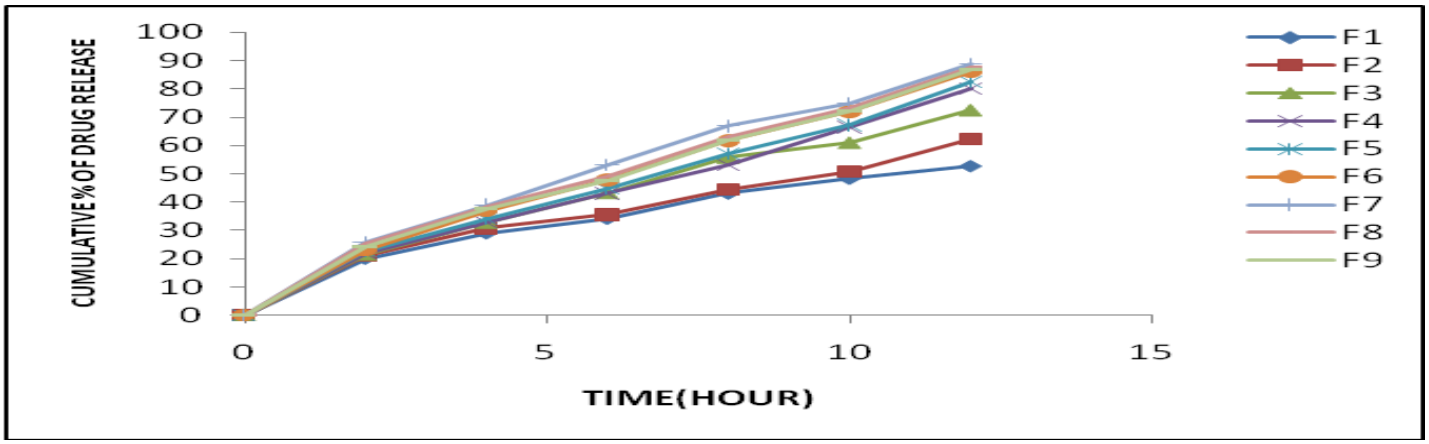

Figure No. 1. Zero order release kinetics of Indomethacin SR tablets

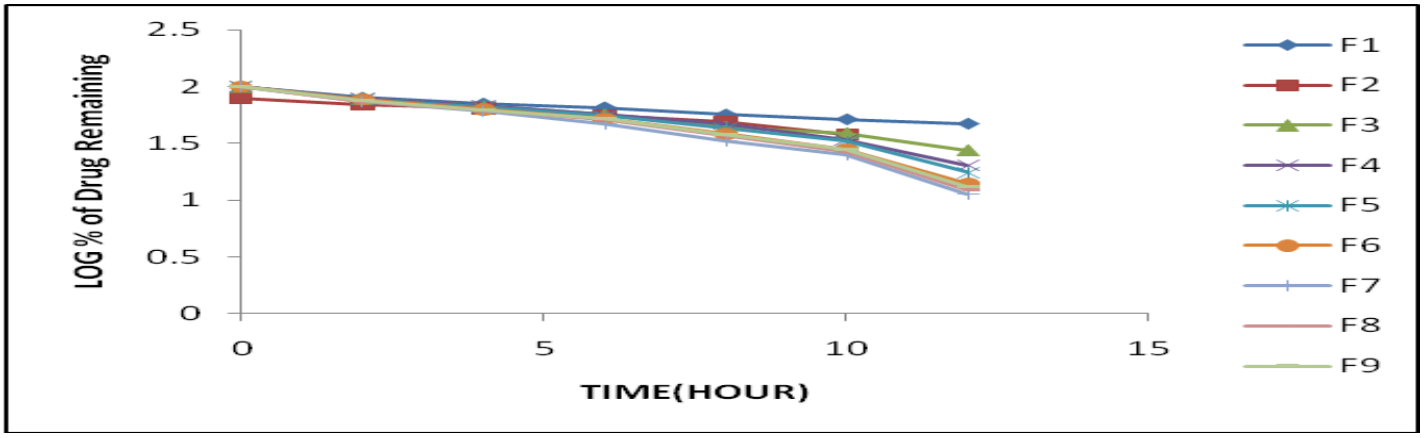

Figure No. 2. First order release kinetics of Indomethacin SR tablets

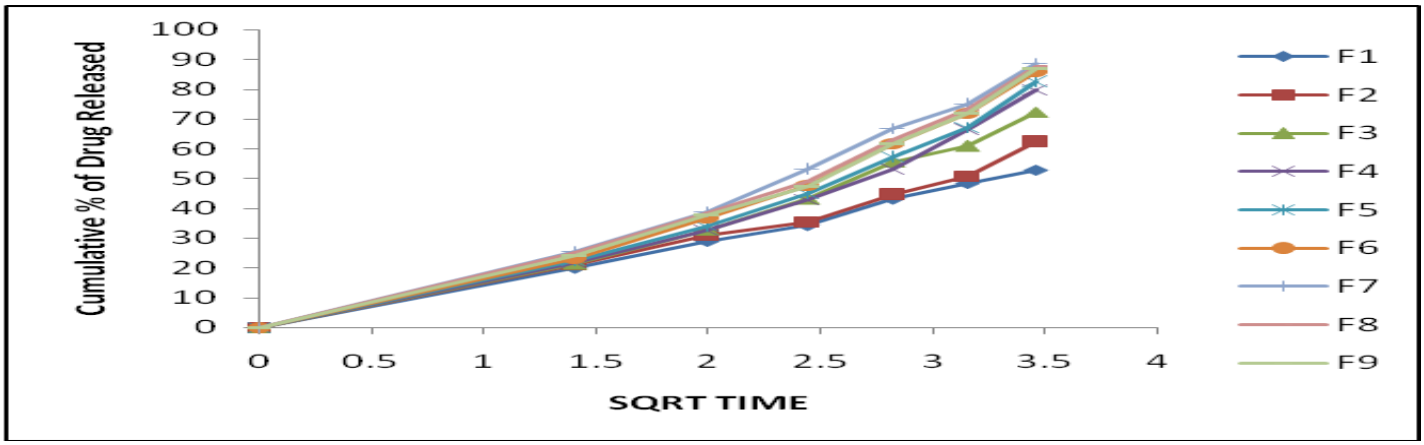

Figure No. 3. Higuchi release kinetics of Indomethacin SR tablets

CONCLUSION:

The experiment revealed that Methocel K4M CR and Methocel K15M CR in varying proportions control the Indomethacin release effectively for 12 hours; hence the formulations can be considered as a once daily sustained release tablet of Indomethacin which was comparable to theoretical release profile. Drug release kinetics indicated that the drug release was best explained by Higuchi, Korsmeyer-Peppas and Hixson-Crowell equations as these plots showed the highest value of linearity. Kinetic modeling of in vitro dissolution profiles revealed the drug release mechanism from all proposed formulations (F-1 to F-9) followed anomalous type or non-Fickian transport ($n>0.43$ and $n<0.85$). This study reveals that the release of Indomethacin critically depends on the rate retarding polymer level in the matrices. Proper adjustment of polymer with drugs will enable a desirable release characteristic of active ingredient.

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