Development and *in vitro* Evaluation of Sustained Release Matrix Tablets of Indapamide from Methocel® K15 MCR and K100 LVCR

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ABSTRACT: Indapamide, a low-dose thiazide-type diuretic, is used for the treatment of essential hypertension. In this study, we developed an indapamide sustained release formulation using Methocel K15 MCR (a modified hydroxypropyl methylcellulose), Methocel K100 LVCR (a modified hydroxypropyl methylcellulose), magnesium stearate, talc and starch 1500 by direct compression**.** 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. The *in vitro* dissolution study was carried out in the gastric medium (pH 1.3) for first two hours and then in the intestinal medium (pH 6.8) for 22 hours using United States Pharmacopoeia (USP) 22 paddle-type dissolution apparatus. The granules showed satisfactory flow properties, compressibility index etc. All the tablets complied with pharmacopoeial specifications. The results of dissolution studies indicated that the formulation F-5 and F-7 (up to 75.36 % drug release in 12 hours) could extend the drug release up to 12 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 was 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: Indapamide, Hypertension, Sustained Release, Methocel® K15M CR, Methocel® K100 LVCR

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. It is important especially in the case of antihypertensive agents to maintain constant blood levels, as otherwise dose dumping may cause hypertension.

Indapamide, a thiazide-type diuretic, is a widely used antihypertensive agent. Numerous randomized controlled studies have shown its antihypertensive efficacy in the immediate-release (IR) formulation at the dosage of 2.5 mg/day. In accordance with the current recommendations, a sustained-release (SR), low-dose formulation (Indapamide SR 2.5 mg) was developed with the objective of achieving an optimal efficacy/ acceptability ratio.[2-5] Indapamide free base is practically insoluble in water (0. 75 mg/l) and thus poorly absorbed from the gastro-intestinal tract. It exhibits poor absolute bioavailability of 30-40%.[3] Half life of Indapamide is 14-18 hrs.[2] Its very poor aqueous solubility indicates that its absorption is dissolution rate-limited which might result in irregular and delayed absorption.

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The primary benefit of an SR preparation of indapamide 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. Indapamide SR 2.5 mg/day was well tolerated and demonstrated reduced blood pressure as effectively as therapeutic dosages of amlodipine, candesartan, enalapril, hydrochloro-thiazide or Indapamide.

In the present investigation an attempt has been made to formulate Indapamide as sustained release tablet matrix with the addition of release retarding polymers and to evaluate the effect to sustain the release of Indapamide 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.[6] These polymers are hydrophilic in nature and can hold active ingredients firmly that depend on the concentration or ratio of polymers used.[7] Methocel K15M CR and K100 LVCR are two typically used methocel polymers for the formulation of hydrophilic matrix systems, providing a robust mechanism for the slow 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.[8] The permeability of drug through Methocel K15M CR and/or K100 LVCR 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 K15 MCR, Methocel K100 LVCR and starch 1500 was purchased from Colorcon Ltd, India. Magnesium stearate and Talc was obtained from Wilfrid Smith Ltd. UK. Indapamide was obtained from Incepta Pharmaceuticals 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 K15 MCR, Methocel K100 LVCR , 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.

Table 1. Proposed formulations of Indapamide SR matrix tablets containing Methocel K15MCR and Methocel K100 LVCR

Name	F1	F2	F3	F4	F5	F6	F7	F8	F9
Indapamide	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Methocel K15M*	25	25	25	20	20	20	15	15	15
Methocel K100 LVCR*	20	15	10	20	15	10	20	15	10
Talc (1.5%)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mg Stearate (1.5%)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Starch 1500	49.5	54.5	59.5	54.5	59.5	64.5	59.5	64.5	69.5
TOTAL (in mg)	100	100	100	100	100	100	100	100	100

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 Indapamide 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 100 rpm. The dissolution medium was 900ml of 0.1N HCl for first 2 hours and 900 ml of 0.05M pH 6.8 phosphate buffer for next 22 hours at 37.0 ± 0.5ºC. The amount of drug present was determined according to the USP monograph for Indapamide tablets using UV spectrophotometer testing at 275nm. Samples were taken over a 24 hour time period at the 2^{nd}, 4^{th}, 6^{th}, $8^{th,}$ and 12^{th} 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.

$LogC_0 - LogC = kt / 2.303$ …… (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, Qt 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).

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:

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

Where, M_t / M_∞ is 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 for cylindrical shaped matrices:

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

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 indapamide by direct compression method using Methocel K15MCR and K100 LVCR as rate retarding polymer (Table 1). Methocel K15M and K100M 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 24 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 0.35 ± 0.02 to 0.48 ± 0.02 and 0.49 ± 0.03 to 0.55 ± 0.03 respectively. The results of compressibility index (%) ranged from 7.69 to30.00. The results of angle of repose ranged from 26.78 ± 0.01 to 29.25 ± 0.03°. The percentage porosity values of the granules ranged from12.4 to 16.4 % indicating that the packing of the Granules may range from close to

Table 2. Properties of granules of Indapamide and excipients containing Methocel K15M CR and Methocel K100LV CR

Formulation	Loose bulk density (LBD) gm/ml	Tapped bulk density(TB) gm/ml	Carr's index (%)	Hausner ratio	Total porosity (%)	Moisture content (%)
F-1	0.35±0.02	0.50±0.03	30.00	1.43	14.3	2.22
F-2	0.42±0.03	0.54±0.02	22.22	1.29	16.4	2.54
F-3	0.44±0.02	0.49±0.03	10.20	1.11	13.4	1.48
F-4	0.46±0.01	0.55±0.03	16.36	1.20	12.4	1.96
F-5	0.48±0.02	0.52±0.01	7.69	1.08	16.3	1.86
F-6	0.46±0.02	0.51±0.02	9.80	1.11	15.3	3.24
F-7	0.41±0.04	0.51±0.06	19.61	1.24	14.3	2.96
F-8	0.38±0.03	0.54±0.02	29.63	1.42	13.6	1.93
F-9	0.44±0.03	0.51±0.03	13.73	1.16	13.9	2.38

Table 3. Percentage release of nine formulations (F-1 to F-9) of indapamide matrix tablets against time

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	16.42	11.30	22.72	20.62	22.26	16.68	18.38	20.12	11.24
4	31.63	22.38	31.65	43.08	38.50	26.24	31.82	32.62	18.32
6	33.50	40.66	34.94	46.65	46.48	42.10	48.36	41.35	32.65
8	39.62	47.48	43.52	52.30	52.68	49.43	55.76	48.55	48.58
12	48.26	57.65	54.75	75.36	58.60	55.50	70.66	56.28	56.53

loose packing and also further confirming that the particles are not of greatly different sizes. 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 2.28 to 2.60 mm.The hardness and percentage friability of the tablets was ±0.5%. 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. Except the proposed formulation F-7 (using 15% Methocel K15M and 20% Methocel K100M) all formulations fails to exhibit official drug release according to United States Pharmacopeia (USP) for any sustained release formulation (Table 3). 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, Higuchi (Figure 3), First order (Figure 2), 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 Higuchi's 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 >0.6, 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.

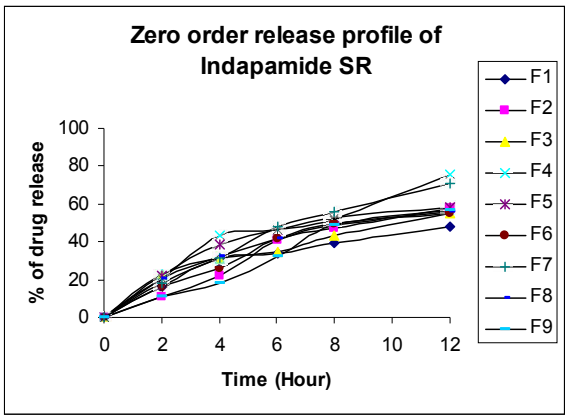

Figure 1. Zero order release kinetics of Indapamide SR tablets

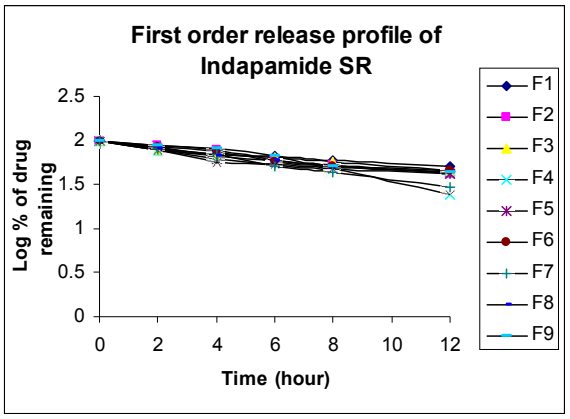

Figure 2. First order release kinetics of Indapamide SR tablets

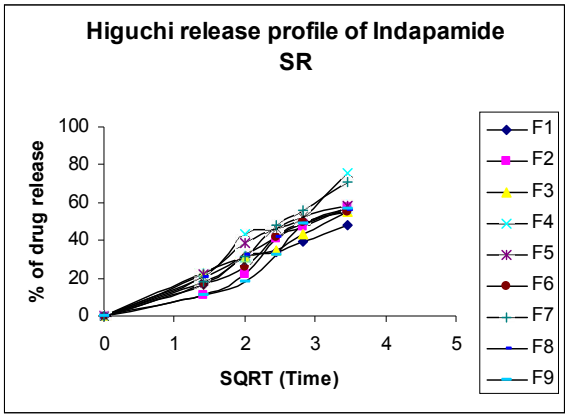

Figure 3. Higuchi release kinetics of Indapamide SR tablets

CONCLUSION

The experiment revealed that Methocel K15M CR and Methocel K100 LVCR in varying proportions control the Indapamide release effectively for 12 hours; hence the formulations can be considered as a once daily sustained release tablet of Indapamide which was comparable to theoretical release profile. In most cases the release kinetics of Indapamide from the matrix tablets appeared to follow Higuchi and Korsmeyer Pappas equation which indicated that the drug was released from the matrix tablets predominantly by diffusion. Further study on the Indapamide sustained release is required to obtain *in vivo* data of these formulations. The optimized formulations (F-5 and F-7) may be used for the development of Indapamide sustained release tablet for commercial production in order to combat against essential hypertension and mild-to-severe chronic heart failure.

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