Development of Indapamide Sustained Release Tablet using Methocel K15 MCR and a Comparative Study with a Reference Product

B.M. Rahman[1], M.I.I. Wahed[1], M.S. Amran[2], P. Khondkar[1], M.M. Rahman[2], M.R. Islam[1] and M. Ahmed[1]

[1]Department of Pharmacy, University of Rajshahi, Rajshahi-6205, Bangladesh
[2]Department of Pharmaceutical Chemistry, University of Dhaka, Dhaka-1000, Bangladesh

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), lactose and magnesium stearate considering technical feasibility and performed a comparative study with the release pattern of the reference product, Natrilix SR® tablet**.** The tablets showed sustained release curves at pH 6.8 phosphate buffer for up to 12 h. The data obtained from the dissolution profiles were compared in the light of different kinetics models and the regression coefficients were also compared. The kinetics of dissolution fit the Higuchi kinetics model. The release rate decreased exponentially with the addition of Methocel K15 MCR. Indapamide release rate was observed to be the highest with the lowest concentration of Methocel K15 MCR used in the present study. On the other hand, Indapamide release rate was the lowest when Methocel K15 MCR concentration was 25%. Stability tests of the drug pellets showed no notable changes in the rate of drug release, related substances and drug content.

Key words: Indapamide, Hypertension, Sustained Release, Methocel K15 MCR.

INTRODUCTION

Indapamide, a thiazide-type diuretic, is a widely used antihypertensive agent. Numerous rando-mized controlled studies have shown its antihyper-tensive efficacy in the immediate-release (IR) formulation at the dosage of 2.5 mg/day.[1–6] In accordance with the current recommendations, a sustained-release (SR), low-dose formulation (Indapamide SR 1.5 mg) was developed with the objective of achieving an optimal efficacy/ acceptability ratio. The sustained-release formulation has demonstrated its effectiveness at reducing blood pressure and acceptability in studies carried out in middle-aged hypertensive patients,[7,8] in patients with target organ damages such as left ventricular hypertrophy in the LIVE (Left ventricular hypertrophy Indapamide SR Versus Enalapril) study,[9] and in type 2 diabetic patients with micro-albuminuria in the NESTOR (Natrilix SR vs Enalapril Study in Type 2 diabetic hypertensives with microalbuminuria) study.[10] London assessed the antihypertensive efficacy of indapamide 1.5 mg SR tablets on Systolic blood pressure (SBP) and found it to be very effective as compared to the treatment with a standard dose of a true thiazide diuretic (hydrochlorothiazide), a calcium channel blocker (amlodipine), and an angiotensin-converting enzyme inhibitor (enalapril).[11] The good acceptability profile

Correspondence to: Md. Bytul Mokaddesur Rahman
Telephone: +88(0721) 750041/4110, Fax: (+880721) 750064
E-mail: bmokaddes3@yahoo.com,

of indapamide SR has been demonstrated in terms of renal function and glucidic and lipidic metabolism.[12] However, the efficacy of indapamide SR in the treatment of older hypertensive patients, including those with isolated systolic hypertension (ISH) remained to be documented.

The primary benefit of an SR preparation of indapamide is that a lower dosage 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.[13] Indapamide SR 1.5 mg/day was well tolerated and demonstrated reduced blood pressure as effectively as therapeutic dosages of amlodipine, candesartan, enalapril, hydrochlorothiazide or indapamide IR.[14]

The SR formulation contains a hydrophilic matrix, which delivers a smoother pharmacokinetic profile. This avoids unnecessary plasma peak concentrations, which may be associated with side effects.[15] Indapamide SR preparation has now been extensively used in hypertensive patients, including those at increased risk, for example elderly or diabetic patients. In the present study, the preparation of a sustained release indapamide tablet formulation using a modified HPMC, Methocel K15 MCR has been investigated and the results were compared with those of a reference product, Natrilix SR®.

MATERIALS AND METHODS

Methocel K15 MCR, the modified HPMC, was purchased from Colorcon Ltd, India. Lactose was procured from Fonterra Ltd. Magnesium stearate was obtained from Peter Greven, Netherlands. Indapamide was purchased from Calao Srl, Italy. The solvents and reagents were of analytical grade.

Preparation of Indapamide matrix tablets. The formulations evaluated in this study have been listed (Table 1). Indapamide tablets were prepared by wet granulation method. Indapamide and lactose for each batch was pre-blended for 5 minutes. The Methocel K15 MCR mass was then added and blended for an additional 5 minutes. Finally, purified water was added and the formulation was mixed for further 35 minutes to achieve an agglomerated mass. The wet mass was passed through the Multi-Mill equipped with 0.5 inch sieve with Gear No. 1. The granules were dried with incoming air temperature 60 - 85°C, till the outgoing temperature reaches 40 - 65°C and the drying time around 120 minutes and moisture content 2.0 - 3.0%. The dried granules were pulverized through Ganscomminutor equipped with 2.0 mm sieve. Dried granules were lubricated with magnesium stearate and mixed for 5 minutes. Tablet (200mg) were manufactured using a tablet compression machine (instrumented 35 station BB4, Manesty, England), fitted with 8mm deep concave tooling at 18 rpm.

Table 1. Formulation of Indapamide sustained release tablet

Formulation	Indapa-mide	Methocel K15 MCR		Mg-Stearate	Lactose
	mg	%	mg	mg	mg
1	1.5	0	0	2	196.5
2	1.5	18	36	2	160.5
3	1.5	20	40	2	156.5
4	1.5	23	46	2	150.5
5	1.5	25	50	2	146.5

A single tablet weighs 200 mg

Evaluation of tablets. The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a hardness tester (Erweka GmbH, Germany). Friability of the tablets was determined by a friabilator (Pharmatest, Germany). The thickness of the tablets was measured with a Vernier Calliper (Mitutoyo, Japan). Weight variation test was performed according to an official method. Drug content for indapamide was carried out by measuring the peak area of standard and samples at 242nm using HPLC method.

***In vitro* dissolution studies.** Dissolution testing was performed in an "Erweka Dissolution Tester, Germany" using Apparatus 2 (paddle method) at 100rpm. The dissolution medium was 500ml of 0.05M pH 6.8 phosphate buffer at 37.0 ± 0.5ºC. The amount of drug present was determined according to the USP monograph for Indapamide tablets using

HPLC testing at 242nm. Samples were taken over a 12 hour time period at the 2nd, 4th, 6th, 8th and 12th hours from starting.

Stability studies. One selected prepared matrix tablet batch was alu-alu blister packaged and kept at 40°C with 75% RH. Samples were withdrawn at 0, 90 and 180 days for evaluation of appearance, drug content and *in vitro* drug release.

RESULTS AND DISCUSSION

Hydroxypropyl methylcellulose (HPMC)-based pharmaceutical devices have major advantages which are: (i) the elucidation of the underlying mass transport mechanisms; and (ii) the possibility to predict the effect of the device design parameters (e.g., shape, size and composition of HPMC-based matrix tablets) on the resulting drug release rate, thus facilitating the development of new pharmaceutical products.[15] Physical properties of the finished good are shown in Table 2. Indapamide (1.5mg) SR tablets were based on similar thickness, weight and mechanical strength to the reference product. The content uniformity results (98.0±0.9%) were well within the USP limits.

Table 2. Properties of sustained release Indapamide tablets

Formulation	Weight (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
Batch 1	200.45 ± 0.98	7.54 ± 0.21	4.2 ± 0.05	0.03	99.0 ± 1.2
Batch 2	200.51 ± 1.1	7.56 ± 0.35	4.3 ± 0.04	0.04	101.12 ± 0.97
Batch 3	200.43 ± 1.23	7.9 ± 0.65	4.5 ± 0.04	0.02	99.23 ± 0.27
Batch 4	201.3± 0.95	8.1 ± 0.24	4.4 ± 0.03	0.03	100.52 ± 0.86
Batch 5	201.7 ± 1.12	8.0 ± 0.37	4.2 ± 0.04	0.02	98.33 ± 0.96

Results are the mean ± S.E.M. of three independent experiments.

Indapamide release kinetics from tablets was studied in a phosphate buffer, (pH 6.8) at 37°C and 100 rpm paddle speed using a USP dissolution test apparatus (Erweka, Germany). When percent release was plotted against time (Figure 1), no straight lines were obtained indicating that indapamide release did not follow the zero order kinetics. First order plot (log % remaining vs. time) showed a linear release pattern (Figure 2). In contrast, when percent release was plotted against square root of time (Figure 3), release profile showed linear relationship. This confirms that matrix tablets were released in a Higuchian diffusion fashion. The slopes (Higuchi

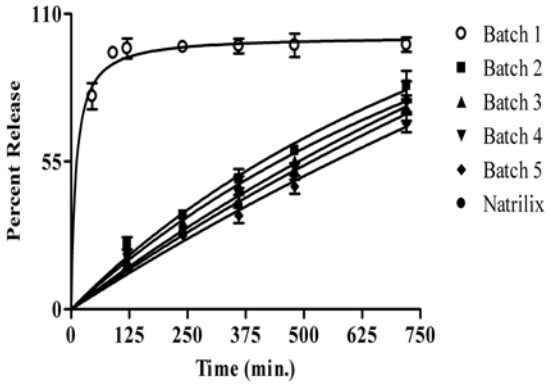

Figure 1. Zero order release profile of Indapamide from polymeric tablets and Natrilix®, a reference product.

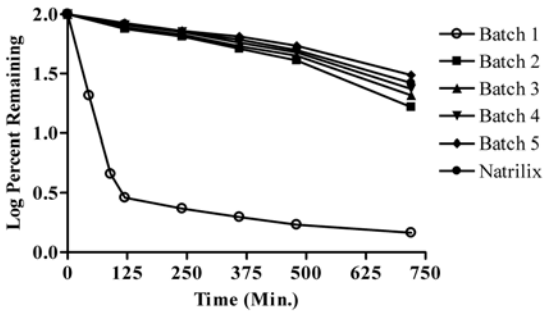

Figure 2. First order release profile of Indapamide from polymeric tablets.

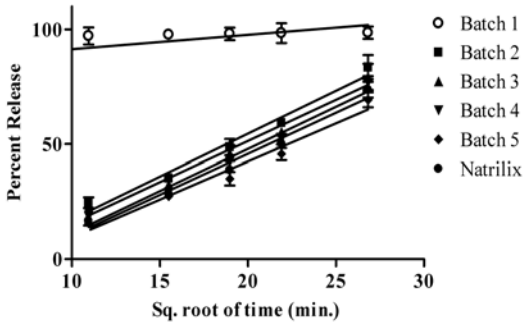

Figure 3. Higuchi release profile of Indapamide from polymeric tablets.

release rate constants, Kh) obtained from the straight line portions of the Figure 3 were 3.015, 2.858, 2.763, 2.465 in percent release versus square root of time plots for the formulation of Batches 2, 3, 4, and 5 respectively. These values were plotted against the percent of Methocel K15 MCR content in the matrix tablets and Figure 4 was obtained. This figure indicated that the release rate decreased with the increase of percent of Methocel K15 MCR. The reason for gradually decreasing release rate may be due to the plasticization of the Methocel K15 MCR polymer thereby forming films around the core indapamide crystal. The decrease in "Higuchian" release rate constant with the increase of Methocel K15 MCR percentage was due to lower rate of permeability of Methocel K15 MCR in the dissolution medium of pH 6.8.

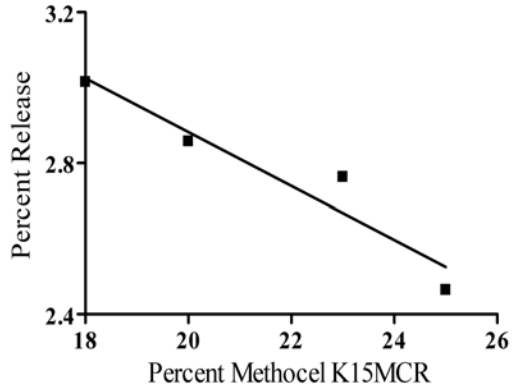

Figure 4. Release rate of Indapamide from different proportion of Methocel K15 MCR in tablets.

The calculated correlation coefficient (r^2) of the percent drug release versus square root of time was within 0.9788 to 0.9932 whereas those of the percent drug release versus time and log percent drug remained versus time were within 0.9302 to 0.9748 and 0.8807 to 0.9564, respectively. This implied that the release of drug from the prepared tablets followed Higuchi model. The percent release versus time plot suggests that Batch 5 with the Methocel K15 MCR of 25% is preferred proportion in the preparation of indapamide tablets for the therapy. The data for stability studies carried out for batch 5 at 40°C with 75% RH for 180d revealed no considerable differences in drug content and dissolution rate (Table 3).

Table 3. Stability studies on formulated batch 5 tablets

Parameter	Initial tablets	Blister pack at 40°C with 75% RH	
		90 days	180 days
Drug content (%)	98.33 ± 0.96	97.98 ± 0.97	97.86 ± 0.99
t_{50} (h)	5.10	5.10	5.05
t_{90} (h)	10.00	10.10	10.05

Results are the mean ± S.E.M. of three independent experiments. Other values represent an average of two experiments.

CONCLUSIONS

In the present study, the formulation and production technology of indapamide (1.5 mg) hydrophilic matrix tablets have been developed which produced SR formulation with good physical characteristics, predictable and reproducible drug release profiles similar to the reference product. This study demonstrated that Methocel K15 MCR provides reliable sustained release matrix formulation recommendations for low dose, low solubility drugs such as Indapamide.

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