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Formulation, Evaluation and Optimization of Sustained Release Tablets of Indapamide using Hydrophilic Matrix system

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Abstract: Different formulations of Indapamide 1.5mg sustained release tablets were formulated using wet granulation method using hydrophilic polymer. The tablets were subjected to physicochemical studies, in vitro release studies, kinetic modeling and stability studies to find out the best formulation. The *in vitro* release studies were conducted for 16 hours using USP 30 apparatus type I (Basket method) at pH 6.8 Phosphate buffer. The release mechanisms were then treated with zero order, higuchi, first order and Korsemeyer-Peppas equations. In vitro release patterns and kinetic results of different models were compared with the innovator brand. All formulations along with innovator brand followed zero order release pattern. According to Korsmeyer-Peppas equation release mechanisms of all formulations were super case II transport. All the kinetic treatments and comparison with innovator brand showed that F-5 was the most successful formulation. The optimized formulation was subjected to stability studies and no significant changes were found in physicochemical properties and release pattern. The result of the study indicated the effect of hydrophilic polymers on the release of Indapamide drug from the sustained release matrix tablet.
Key words: Indapamide, sustained release, matrix tablet, hydrophilic polymer, release kinetics.

INTRODUCTION:

The relationship between blood pressure (BP) and cardiovascular risk is clearly established; hypertension increases the rate of cardiovascular. High systolic blood pressure (SBP) may be the main parameter involved in cardiovascular morbidity and mortality. The benefit of lowering BP, particularly with diuretics has been proven in many outcome studies.[1] Indapamide is a non-thiazide sulphonamide diuretic drug, generally used in the treatment of hypertension, as well as decompensated cardiac failure.[2]It has fully demonstrated its efficacy in the 2.5-mg immediate-release formulation.[3] In accordance with international recommendations on the need to decrease doses of antihypertensive drugs, a low-dose (1.5 mg) sustained-release (SR) formulation of indapamide was developed to optimize the drug's efficacy: safety ratio.[4] Then the efficacy of Indapamide SR 1.5mg at reducing blood pressure was studied and it was found that the low dose SR formulation of Indapamide confirmed its 24h

activity and met the FDA standard requirements.[5] The incidence of adverse effects was found very low in all studies with indapamide SR 1.5mg, such as, influence of Indapamide SR 1.5 mg/day on glucose metabolism, serum levels of lipids and uric acid, or renal function was evaluated and no deleterious effect was found.[6] This antihypertensive agent can be considered to be an attractive therapeutic choice for all patients with mild-to-moderate hypertension, including the elderly and patients with increased cardiovascular risks, i.e. those with LVH(Left Ventricular Hypertrophy).[7]

Hydrophilic polymers have been given considerable attention in the formulation of controlled release drug delivery systems for various drugs.[8] Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, does not disintegrate, but immediately after hydration develops a highly viscous gelatinous surface barrier which controls the drug release from and the liquid penetration into the center of the matrix system.[9] Hydroxypropylmethylcellulose (HPMC), a semi-synthetic derivative of cellulose, is one of the best choices as swellable and hydrophilic polymer. It has been widely used in the formulation of hydrophilic matrices for oral extended release drug delivery due to its key features and advantages including global regulatory acceptance, stability, ease of manufacture, versatility, suitability for various drugs and release profiles, and availability of the polymer.[10]

The aim of the present work was to formulate an optimum Indapamide sustained release matrix tablets using Hydrophilic polymer (Methocel K15M CR) by comparing with reference brand and to elucidate the release mechanisms.

MATERIALS AND METHODS:

MATERIALS:

Indapamide, Lactose Monohydrate (spray dried), lactose Monohydrate (Powder), Maize starch, Hypromellose (Methocel K15M CR premium), Colloidal anhydrous silica and Magnesium stearate were collected as gift sample from Healthcare pharmaceutical Ltd, Bangladesh. The solvents and reagents were of analytical grade.

PREPARATION OF INDAPAMIDE MATRIX TABLET:

Different formulations of Indapamide sustained release tablet were prepared using methocel K15M CR premium as release retarding material. The compositions of the tablet formulations were listed in table-1. All the formulations were prepared by wet granulation technique using varying proportion of polymer. Indapamide and Lactose monohydrate were blended for 5 minutes for each batch. Then Methocel K15 MCR Premium was added and blended to make a homogenous mixture. Then the blends were granulated with purified water. Then the wet mass were sieved through 16 mesh and dried into tray dryer to obtain the moisture contain 2 – 3%. Then the dried granules were again sieved through 16 mesh to get suitable size reduced granules. Finally dried granules were lubricated with colloidal anhydrous silica and magnesium stearate. Tablets (200mg) were compressed using a tablet compression machine (35 stations FETTY, Germany).

Table No. 1: Composition of Indapamide 1.5mg SR tablets.

Materials (mg/tablet)	F-1	F-2	F-3	F-4	F-5	F-6
Active Ingredient						
Indapamide	1.50	1.50	1.50	1.50	1.50	1.50
Excipients						
Lactose Monohydrate (Spray dried)	128.50	136.50	-	-	-	-
Lactose Monohydrate (Powder)	-	-	146.50	151.50	154.50	116.50
Hydroxy Propyl Methyl Cellulose (Methocel K 15 M CR)	68.00	60.00	50.00	45.00	42.00	40.00
Maize Starch	-	-	-	-	-	40.00
Colloidal Anhydrous Silica	0.60	0.60	0.60	0.60	0.60	0.60
Magnesium Stearate	1.40	1.40	1.40	1.40	1.40	1.40
Tablet Weight (mg)	200.00	200.00	200.00	200.00	200.00	200.00
Matrix Content (%)	34.00	30.00	25.00	22.50	21.00	20.00

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 DR. SCHLEUNIGER, Switzerland; Friability was tested using Friabilator, Taiwan and thickness was tested using digital thickness tester. Weight variation test was performed according to official method by using OHAUS Electronic balance, USA. Drug content for Indapamide was carried out by measuring the peak area of standard and sample at 242nm using HPLC method (HPLC-UV detector, Water, USA).

***IN VITRO* DISSOLUTION STUDIES:**

The *in vitro* dissolution studies were carried out using USP 30 dissolution apparatus type I (Basket method) at 100 rpm in an ERWEKA dissolution tester, Germany. The dissolution was conducted for a total period of 16h using 900ml phosphate buffer (pH 6.8) at 37.0 ± 0.5º C. Samples were withdrawn from each vessels at 4, 8, 12 & 16hr from starting the amount of drug present was determined according to the USP monograph for Indapamide tablets using HPLC at 242nm.

KINETIC MODELING OF DRUG RELEASE:

Data from the *in vitro* drug release were analyzed by different kinetic models to find out the release pattern. Zero order ($Q_t = Q_0 + K_0t$), First order ($\ln Q_t = \ln Q_0 + K_1t$), Higuchi ($Q_t = K_ht^{1/2}$) models were fitted to the dissolution data using linear regression analysis. But these models fail to explain drug release mechanism due to swelling (upon hydration in contact with dissolution medium) along gradual erosion of the matrix.[11] Therefore, the dissolution data were also fitted to the well known exponential equation, Korsmeyer-Peppas equation ($M_t/M\infty = Kt^n$). According to Korsmeyer-Peppas equation a value of n=0.5 indicates case I (Fickian), 0.5< n <1 anomalous (non- Fickian) diffusion, n=1 case – II transport and n>1 super case II transport. Mean dissolution time (MDT) was calculated from dissolution data according to Mockel and Lippold, 1993 using the following equation[12]:

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

STABILITY STUDIES:

One selected formulation was packaged into ALU-ALU strip and kept for stability study at both room condition (30±2ºC / 65±5%RH) and accelerated condition (40±2ºC / 75±5 %RH) according to ICH Guideline [ICH Q1A (R2)].[13] Samples were withdrawn at 0, 1st, 3rd and 6th month for evaluation of physical condition, drug content and in vitro release and accelerated condition.

Table No. 2: Physical evaluation of Indapamide 1.5mg SR Tablets

Test Parameters	F-1	F-2	F-3	F-4	F-5	F-6
Weight (mg)	201.2±1.6	200±0.98	200.5±1.1	200.45±0.95	201.7±1.15	201.3±2.23
Average Hardness (Kg/cm^2)	9.5 ±0.07	9.2±0.08	9.7±0.10	9.3±0.08	9.6±0.11	10.2±0.18
Average Thickness (mm)	3.5±0.012	3.5±0.015	3.6±0.014	3.5±0.015	3.6±0.017	3.5±0.013
Friability (%)	0.07	0.09	0.06	0.08	0.07	0.06
Assay (mg)	1.5± 0.02	1.51±0.03	1.51±0.02	1.49±0.01	1.5±0.015	1.52±0.02

Table No 3: drug release of different formulations

Formulations	Average % of drug release of 6 tablets				
	0 hr	04 hrs	08 hrs	12 hrs	16 hrs
F-1	0.00	19.40	36.93	52.42	65.24
F-2	0.00	19.60	37.42	52.24	64.60
F-3	0.00	22.12	42.29	59.53	71.79
F-4	0.00	28.38	47.42	62.03	74.81
F-5	0.00	25.78	45.80	67.96	88.66
F-6	0.00	23.00	46.23	63.38	75.38
IB*	0.00	21.65	47.05	69.64	87.32

*IB = International Brand

Table No. 4: Kinetics of Indapamide Sustained release tablets

Formulation	Zero order		First order		Higuchi		Korsmeyer		MDT (hrs)
	K_o	R^2	K_1	R^2	K_h	R^2	n	R^2	
F-1	4.08	0.99	0.028	0.99	16.16	0.95	0.88	0.99	11.92
F-2	4.04	0.99	0.028	0.99	16.05	0.95	0.86	0.99	11.75
F-3	4.52	0.98	0.035	0.99	18.00	0.96	0.85	0.99	10.42
F-4	4.58	0.97	0.035	0.99	18.64	0.98	0.70	0.99	9.78
F-5	5.49	0.99	0.055	0.92	21.49	0.93	0.89	0.99	8.74
F-6	4.77	0.98	0.038	0.99	19.07	0.96	0.86	0.98	9.61
IB*	5.57	0.99	0.056	0.95	21.69	0.93	1.02	0.99	9.03

*IB = International Brand

Table No. 5: Stability study result of Indapamide SR Tablets (formulation F-5)

Storage period	**Condition**	**Average Hardness (Kg/cm^2)**	**Assay (mg)**	**Average % of drug release**			
				4^{th} hr	8^{th} hr	12^{th} hr	16^{th} hr
Initial	Room temperature	9.70	1.50	25.78	45.80	64.96	88.66
Three months	Room temperature	9.50	1.50	24.83	46.67	65.12	79.26
	Accelerated Condition	9.43	1.52	23.18	47.73	66.27	76.64
Six months	Room temperature	9.98	1.50	25.19	48.21	63.44	82.55
	Accelerated Condition	9.32	1.51	24.05	45.33	60.34	77.11

RESULTS AND DISCUSSION:

Physical properties like weight variation, hardness, thickness, friability of formulated matrix tablets were evaluated and were found to be satisfactory (Table No. 2). All tablets comply with pharmacopoeial specifications for weight variation and friability. Analytical testing for determining potency and dissolution were done according to official guideline by using HPLC machine. The formulation in all prepared batches contains Indapamide within 1.5 mg ± 5% of the labeled claim. Release of Indapamide from tablets was slow and extended over longer period of time. The results of potency and % release studies of formulation-1 (F-1), formulation-2 (F-2), formulation-3 (F-3), formulation-4 (F-4), formulation-5 (F-5), and formulation-6 (F-6) are shown in Table No 3.

The *in vitro* release of drug shows the effect of polymer concentration on the drug release. Drug release from the tablets was found to decrease with the increase of polymer concentration in the matrix. This may be due to the reason that the polymer in higher concentrations in the tablets might have produce dense matrix around the drug particles, providing more barriers for them to escape and dissolve.[14] The percentage of drug release after 16 hrs from METHOCEL K15M CR Premium based matrix tablet of formulations F-1, F-2, F-3, F-4, F-5 & F-6 are 65.24%, 64.60%, 71.79%, 74.81%, 88.66% & 75.38% respectively. From these release pattern correlations were found among polymer ratio and release rate. Release rate was decreased with increasing the percent of polymer concentration. F-5 and F-6 were found effective in sustaining the drug release after 16 hour. Hence formulation F-5 was selected as optimized formulation among them as it had created the best result. Drug releases of all formulations were then compared with International Brand (Natrilix 1.5mg SR tablet), so that the best formulation can be found out. All the drug release results are shown in the Table No. 3**.** As only drug release profile of F-5 has correlated with the reference brand, it can be called as the best formulation. But the established result can be found after stability study.

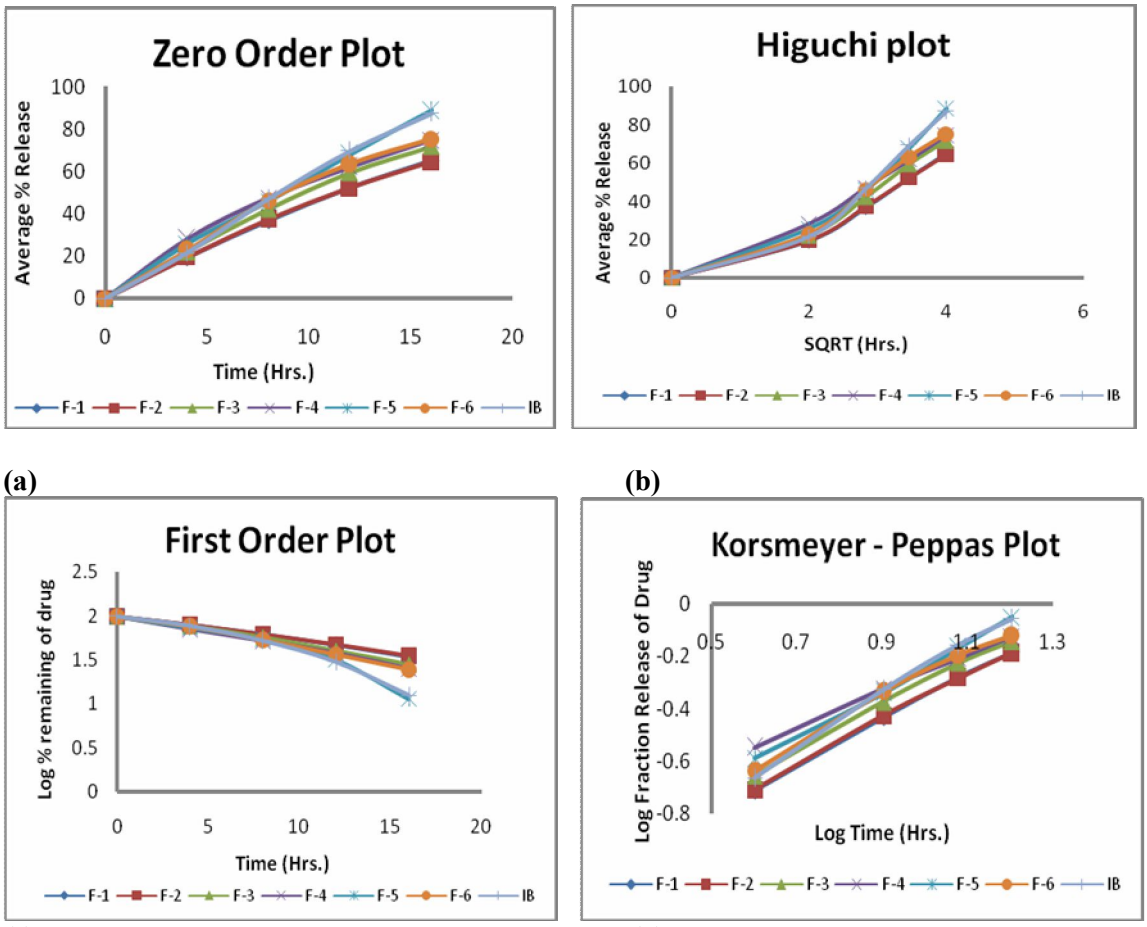

Fig: (a) Zero order plot (b) Higuchi plot (c) first order plot
(d) Korsmeyer-peppas plot manipulating of different formulations of Indapamaide SR tablets.

To find out the release mechanism all the formulation along with International Brand were treated with different kinetic models. Table No 4 shows data analysis of release profiles according to different kinetic models. The result of kinetic treatment reflected that all formulations followed zero order kinetics as it gave the highest linearity (R^2: 0.97-0.99). So simultaneous swelling and erosion might be the mechanism of drug release from these matrix tablets. To confirm the actual release mechanism all release results were extrapolated by Korsmeyer-Peppas equation. According to this model all formulations exhibited Super case II transport as 'n' value of all formulations were of > 0.85.

From all these release kinetics, correlations were found only between Innovator Brand (IB) and F-5. According to Zero order, First order, Higuchi and Korsmeyer-peppas equation, R^2 values of F-5 were almost as same as R^2 of IB value. According to zero order, R^2 of F-5(0.99) was similar to R^2 value of IB (0.99). Higuchi release also illustrated the same result (R^2 of F-5:0.93 and R^2 of IB: 0.93). Not only that, as per Korsmeyer and Peppas plot again F-5 gave the similar result (R^2 of F-5:0:0.99 and R^2 of IB: 0.99). In response to Fist order data analysis, R^2 value of F-5 (0.92) was the closest value to the R^2 value of IB (0.95). So F-5 is the best formulation as per reference standard.

MDT values were also found to be a function of polymer content, Polymer nature and manufacturing process. MDT values for F-1, F-2, F-3, F-4, F-5 and F-6 were 11.92, 11.75, 10.42, 9.78, 8.74 & 9.61 hrs respectively (Table No.4). It was found that MDT values were larger for those formulations which contain highest percentages of polymer. MDT value of IB (Natrilix) was also compared with all formulations and it was found that MDT value of F-5 had the closest result.

After finding of all kinetics and comparison with Innovator Brand (IB) it was clear that F-5 showed the best result as a purpose of sustaining drug release. That's why tablets of formulation F-5 were then decided to kept for stability study according to ICH guideline for 0, 3 & 6 months at both room condition (30±2°C / 65±5%RH) and accelerated condition (40±2°C / 75±5%RH). All data were evaluated (Table No.5) and no considerable changes were found.

Hydrophilic polymer promotes desired controlled drug release upon hydration, swelling and gel formation when interact with gastrointestinal fluid. Results of the present study reveal that hydrophilic polymer based formulation F-5 of Indapamide 1.5mg SR tablet has fulfils all the requirement of sustained release tablet and can be used for commercial purpose.

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