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Formulation and Quality Determination of Indapamide Matrix Tablet: A Thiazide Type Antihypertensive Drug

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ABSTRACT

Purpose: The present study was explored to develop a sustained release matrix tablet of Indapamide, a low-dose thiazide-type diuretic, using hydroxylpropyl methylcellulose (Methocel K15MCR) in various proportions as release controlling factor.
Methods: The tablets were formulated using direct compression method. The powers for tableting were evaluated for angle of response, loose bulk density, tapped bulk density, compressibility index, total porosity and drug content etc. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability, and *in vitro* dissolution studies.
Results: The granules showed satisfactory flow properties, compressibility index, and drug content. All the formulated tablets complies pharmacopoeia specifications. The release kinetics of the drug decreased exponentially with the addition of polymer concentration. Indapamide release rate was observed to be the highest with the lowest concentration of polymer used. The release mechanism was explored with zero order, first order, Higuchi and Krosmeyer equations. Stability tests of the drug showed no notable changes in the rate of drug release, related substances and drug content.
Conclusion: In the context, it can be suggested that this formulation of sustained release Indapamide tablets can be marketed to treat patients with hypertension ensuring proper healthcare.

Introduction

Sustained release matrix dosage forms are designed to achieve a prolonged therapeutic action by continuous releasing medication over an extended period of time after administration of single dose. In order to achieve steady level of medication, biodegradable polymer may play a vital role due to their biodegradability.[1] 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. 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.[2] 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.[3] A wide array of 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.[2] 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.[4] Previous studies

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developed by Williams *et al*.[5] led to the conclusion that the type and level of excipients influence the rate and extension of drug release.

Indapamide is an orally active sulphonamide diuretic agent. Although some evidence appears to indicate that the antihypertensive action of indapamide is primarily a result of its diuretic activity, only a limited diuresis occurs with the usual antihypertensive doses of 2.5 mg daily, and *in vitro* and *in vivo* data suggest that it may also reduce blood pressure by decreasing vascular reactivity and peripheral vascular resistance. In mild to moderate hypertension it is as effective as thiazide diuretics and β -adrenergic blocking agents in lowering blood pressure when used as the sole treatment.[6] Indapamide has been successfully combined with β -adrenergic blocking agents, methyldopa, and other antihypertensive agents. While such findings need confirmation, it appears that indapamide shares the potential with other diuretic agents to induce electrolyte and other metabolic abnormalities, although it may do so with less frequency or severity.[6] The main purpose of our present study was to formulate sustained release matrix tablet of Indapamide using hydroxypropyl methylcellulose (Methocel[1]) and evaluate its quality and release profile as well to justify the formulation.

Materials and Methods

Materials

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

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

Name	Category	Source
Indapamide	Active Ingredient	Merck, Germany
Methocel K15M 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 Indapamide SR tablets

Name	Model	Source	Country
Sieve	-	Endecotts, Test Sieve	UK
Compression Machine	Manesty D type	-	UK
Electronic Balance	AR2140	OHAIS	Switzerland
Digital pH meter	pH 209	HANNA	Romania
Shaker	Power Sonic 505	Hwashin Technology	South Korea
Hardness tester	EH-01P	Electro Lab	India
Fribilator	EF-2	Electro Lab	India
Dissolution Tester	TDT-08L Plus	Electro Lab	India
UV-Spectrophotometer	UV-1800	SHIMADZU Corporation	Japan

Methods

Preparation of Matrix Tablet: Indapamide

The tablets were prepared by direct compression method. In all the formulations (Table 3), the weight of the active is 2.5 mg and the total weight of the tablet is 200 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 K15M CR and the filler or diluents lactose were mixed well. The next step was milling of the mixed ingredients. At the last stage of the method, microcrystalline cellulose, magnesium stearate and aerosil were added to the formulation. The tablets were prepared by compressing the tablets in using 5 punch compression machine with a 15.00×7.00 mm round punch and die set. The compression force was 10 ton. Before the compression the face of the die and punch were lubricated with purified talc.

Table 3. Formulation of Indapamide sustained release tablet.

Ingradients	F_1 mg	F_2 mg	F_3 mg	F_4 mg	F_5 mg
Indapamide	2.5	2.5	2.5	2.5	2.5
Methocel K15MCR	20	40	60	80	100
Aerosil	3.0	3.0	3.0	3.0	3.0
Microcrystalline Cellulose	4	4	4	4	4
Magnesium stearate	3.5	3.5	3.5	3.5	3.5
Lactose Monohydrate	167.0	147.0	127.0	107.0	87.0

Physical Characterization of Indapamide Tablets

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).[7] 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. 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 (W_1) 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 (W_2) and the loss in weight indicates the friability. The acceptable limits of weights loss should not be more than 1 percent.[8]

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

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.[7] 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 Indapamide

Preparation of Sample Solution: At first, 10 tablets of indapamide SR tablets from each formulation were weighed accurately and were grinded to a fine powder. Then 20 mg of powder was taken in a 100 ml volumetric flask and diluted with phosphate buffer up to the mark. Then 1ml solution was taken into another 100ml volumetric flask and diluted with buffer up to the mark. Then their absorbance was measured at 242 nm using a UV spectrophotometer (UV- 1800, UV-VIS spectrophotometer, Shimadzu, Japan).

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

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

Where,

A_{spl} =Absorbance of Sample
W_{std} =Weight of Standard
P_{std} =Potency of standard
A_{std} = Absorbance of standard
W_{spl} =Weight of sample

Dissolution Procedure: Dissolution studies were conducted by USP type II test apparatus (Electrolab, TDL-80L Plus, India) at a speed of 50 rpm and the temperature was maintained at 37° ± 0.5°C.

This operation was continued for 8 hours. At every 1-hour interval samples of 6 ml 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 242 nm for indapamide 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 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 (h) 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), and Korsmeyer-Peppas (log cumulative percentage of drug release versus log 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 *et al*.[9]

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

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.[2] Mean dissolution time (MDT) was calculated from dissolution data using the following equation.[2]

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

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

Results and Discussion

Drug Content and Physical Evaluation of Indapamide Matrix Tablets

After preparing the matrix tablets, all the tablets of the proposed formulations were subjected to various evaluation tests such as hardness, thickness, uniformity of weight, drug content and friability (Table 4).

Table 4. Physical properties of Indapamide

Formulations	Weight variations (mg)±SEM	Hardness (kg/cm^2)±SEM	Thickness (mm)	Friability (%)	Drug content (%)
F 1	200.45 ± 0.98	6.5 ± 0.21	4.2 ± 0.05	0.03	99.0 ± 1.2
F 2	200.51 ± 1.1	7.1 ± 0.35	4.3 ± 0.04	0.04	101.12 ± 0.97
F 3	200.43 ±1.3	7.9 ± 0.65	4.5 ± 0.04	0.02	99.23 ± 0.27
F 4	201.3± 0.95	8.1 ± 0.24	4.4 ± 0.03	0.03	100.52 ± 0.86
F 5	201.7 ± 1.12	8.0 ± 0.37	4.2 ± 0.04	0.02	98.33 ± 0.96

Here, n=10; SEM= Standard Error Mean

Polymeric Effect on Formulated Indapamide Tablets

For this study different matrix tablets containing Indapamide as active ingredient and Methocel K15MCR as the rate retarding polymer were prepared. The polymer concentrations were 10%, 20%, 30%, 40%, and 50% of the total tablet weight having the formulation codes F1, F2, F3, F4, and F5 respectively. After preparing the tablets the dissolution studies were conducted in paddle method at a speed of 50 rpm and the temperature was maintained at 37° ± 0.5°C. This operation was continued for 8 hours. Three tablets from each formulation were taken for the test. *In vitro* release kinetics and mechanisms are explained by zero order, first order, higuchi and korsmeyer models. The highest Methocel K15MCR containing formulation F5 showed the highest MDT and t_{50} value which indicates the rate retarding effect of Methocel K15MCR (Table 5). From Figure 1- 4, we can see the zero order, first order, Higuchi and Korsmeyer-Peppas release kinetics of the formulated drugs respectively.

Table 5. MDT and t_{50} value of the drug Indapamide

Formulation	t_{50} (hr)	MDT
F1	5.6663	4.67745
F2	8.6633	6.637662
F3	12.7643	11.63254
F4	15.754	14.76884
F5	23.6574	21.65762

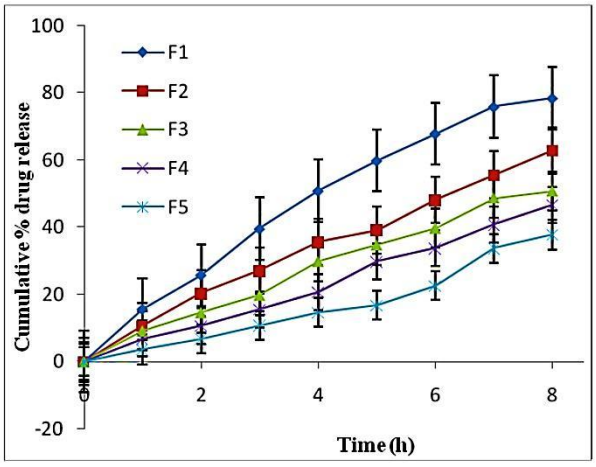

Figure 1. Zero order release kinetics of Indapamide from Methocel K15MCR matrices

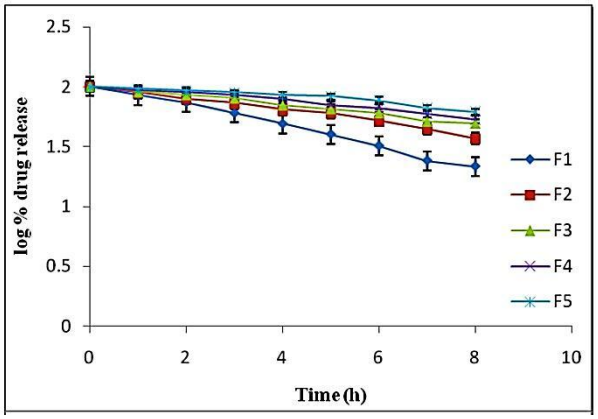

Figure 2. First order release kinetics of Indapamide from Methocel K15MCR matrices

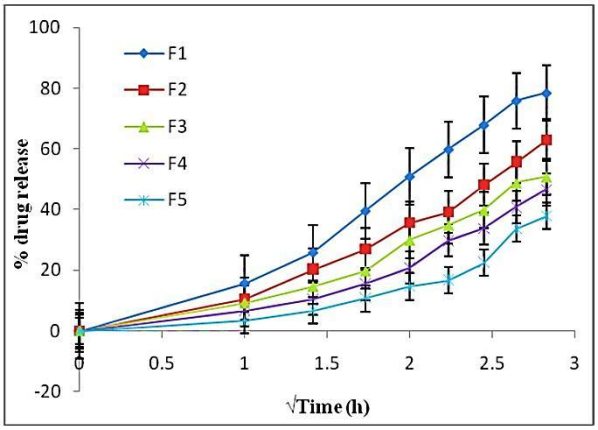

Figure 3. Higuchi release kinetics of Indapamide from Methocel K15MCR matrices

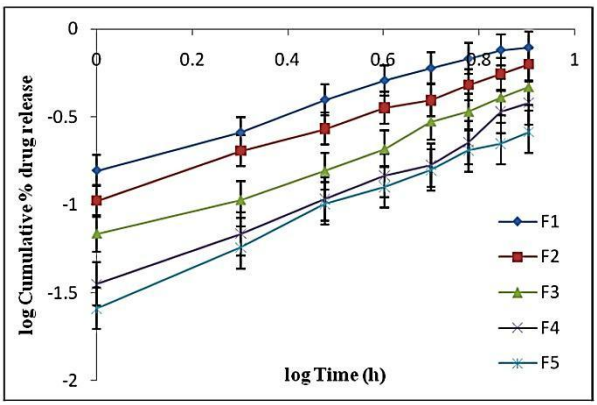

Figure 4. Korsmeyer- Peppas release kinetics of Indapamide from Methocel K15MCR matrices

Conclusion

The study reveals that it is possible to design sustained release solid dosage form with Methocel K15MCR polymer. 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. In fine, further investigation is required to establish *in-vivo-in-vitro* correlation to manifest the exact pattern of drug release *in-vivo* condition from this polymeric system.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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