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NOVEL METHYLDOPA EXTENDED RELEASE MATRIX TABLETS

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The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

The objective of the present study was to develop extended release (ER) matrix tablets of methyldopa using hydrophilic hydroxypropyl methylcellulose (HPMC) alone and in combination with hydrophobic ethylcellulose (EC), and to study the effect of some formulation variables (HPMC viscosity grade and combination with hydrophobic polymer in different ratio) on the properties of prepared tablets. Matrix tablets were prepared by wet granulation method, and prepared granules and tablets were subjected to suitable physiochemical studies. The *in-vitro* dissolution studies showed that formulation F1 containing 15% of HPMC K100M and formulation F6 containing EC:HPMC K4M (5%:10%) were selected as optimized formulations as they were able to sustain the release of methyldopa up to 24 hours. Drug release kinetics show that drug release mechanism from these two formulations was found to be anomalous diffusion in acidic medium, while in phosphate buffer medium methyldopa release mechanism was case II transport in formulation F1 and anomalous diffusion in formulation F6.

Keywords: Methyldopa; extended release; matrix tablets; hydroxypropyl methylcellulose; ethylcellulose; wet granulation.

1. INTRODUCTION

Over the past three decades, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention is being paid on development of these novel controlled release delivery systems which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue. Controlled release drug delivery systems are conveniently divided into four categories: delayed release, extended release, site-specific targeting, and receptor targeting.

Delayed release delivery systems release drug at a time later than immediately after administration while site specific targeting is a type of delayed release that are capable of targeting specific regions at the gastrointestinal tract e.g. the small intestine or colon. Extended release delivery systems are developed in order to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time [1,2,3]. These dosage forms are recognized to provide a better control of plasma drug levels, reduce side effects and increase effectiveness of the drug by reducing the dose required and hence improving patient compliance [4,5].

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In order to obtain oral extended release, matrix tablets are widely accepted because of their simplicity and easy formulation as it excludes complex production procedures such as coating and pelletization during manufacturing [6,7,8]. Gel-forming hydrophilic or swellable matrix systems are homogeneous or heterogeneous systems in which the drug is dispersed in a swellable hydrophilic polymer [9].

Methyldopa (3-hydroxy-α-methyl-L-tyrosine) is an antihypertensive agent which is regarded as first line, first choice of drug to treat hypertension during pregnancy [10,11]. Methyldopa has a short half life of about 2 hours and it is typically administered three or four times daily [12]. In order to overcome adverse side effects and poor patient compliance related to this short half life, an oral extended release dosage form of methyldopa is desirable. Methyldopa is slightly soluble in water [13], so judicious selection of release-retarding excipients is necessary to achieve a constant in vivo input rate of the drug. Hence, the aim of this present investigation is to develop a once-daily oral extended release tablets of methyldopa based on the matrix tablet technology using hydroxypropyl methyl cellulose (HPMC) alone and in combination with Ethylcellulose (EC) in different ratio.

2. MATERIALS AND METHODS

2.1 Materials

Methyldopa was obtained from Yarrow chemicals (Mumbai, India). Hydroxypropyl methylcellulose (Methocel K100LV, Methocel K4M, Methocel K100M) was obtained from Sigma-Aldrich (Steinheim, Germany). Ethyl cellulose (EC 7 CP) was obtained Zhejiang Haishen Chem Co., Ltd. and Polyvinylpirrolidone (PVP K30) was purchased from Otokemi (Mumbai, India). Talc, magnesium stearate and lactose were purchased from S.D. Fine Chem Ltd. (Mumbai, India). All other chemicals used were of analytical grade.

2.2 Methods

2.2.1 Preparation of tablets

Methyldopa extended release matrix tablets were prepared using wet granulation method. A 250 mg of methyldopa was mixed thoroughly with the required quantities of lactose and the used polymer and a sufficient quantity of binding agent (PVP K-30) was added slowly. Isopropyl alcohol was added drop wise till that a suitable mass for granulation was obtained.

After, the wet mass was sieved through 16 mesh. The granules were dried at 50±5°C for 1-2 hours in an oven until the required moisture level was obtained. The dried granules were homogenized by passing them through 20 mesh and lubricated with magnesium stearate by further blending for 3 mins and finally talc was added to the blend. The lubricated granules were compressed on single punch tablet machine into tablet each containing 250 mg Methyldopa and a total weight of 400±2 mg. Different formulations of methyldopa extended release tablets are listed in (Table 1).

2.2.2 Evaluation of granules

Granules were evaluated for particle size distribution, LOD, bulk density, tapped density, Carr's index and Hausner ratio.

Table 1. Composition of various formulations of methyldopa extended release matrix tablets (Weight in mg)

Ingredient	Formula code					
	F1	F2	F3	F4	F5	F6
Methyldopa	250	250	250	250	250	250
HPMC K100M	60	-	-	-	-	-
HPMC K4M	-	60	-	20	30	40
HPMC K100LV	-	-	60	-	-	-
Ethylcellulose	-	-	-	40	30	20
Lactose	64	64	64	64	64	64
PVP-K30	20	20	20	20	20	20
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Mg stearate	2	2	2	2	2	2
Talc	4	4	4	4	4	4

2.2.2.1 Determination of LOD

The percentage of moisture was calculated using IR balance. Three samples from each mixture (sample eight=100 mg) were placed in the moisture analyzer and the balance captures the initial weight. An infrared energy heater is used to heat the sample to 105°C. During the test the balance records the weight. When the sample no longer loses weight the instrument shuts off the heat and uses the final weight to calculate LOD percentage in the sample [14].

2.2.2.2 Loose bulk density (LDB)

A quantity of 2 g of granules from each formula was poured into a graduated cylinder. After the initial volume was noted, LBD was calculated using the following equation [15,16]:

LBD = weight of the powder/volume of the packing (1)

2.2.2.3 Tapped bulk density (TBD)

The volume was measured by tapping the powder for 100 times. Tapping was continued until the difference between successive volumes is less than 2%, and TBD was calculated using the following equation [15,16]:

TBD = weight of the powder/tapped volume of the packing (2)

2.2.2.4 Carr's index (% compressibility index)

The Compressibility index of the granules was determined by Carr's Compressibility. The compressibility index of the granules was determined using following equation [17,18]:

Carr's index (%) = [(TBD-LBD)/ TBD] x100 (3)

2.2.2.5 Hausner ratio

Hausner ratio is an indirect index of ease of granules flow. It is calculated by the equation [17,19]:

Hausner ratio= TBD/LBD (4)

2.2.3 Evaluation of tablets

2.2.3.1 Uniformity of weight

Twenty tablets of each formulation were weighed individually and collectively, then the average weight was determined. The percentage deviation from the average weight was calculated and checked for weight variation. The percentage difference in the weight variation should be within the permissible limits (±5%). The tablets meet the European Pharmacopeia (5th edition) weight uniformity test if not more than two of the individual weights deviate from the average weight by more than the percentage limit

2.2.3.2 Drug content uniformity

Ten tablets of each formulation were selected randomly and individually assayed for their content. Each tablet of was weighed individually and dissolved in HCl (0.1N). These solutions were filtered through 0.45 µ membrane and absorbance was observed at 280 nm in UV-Visible spectrometer according to the European pharmacopeia. The preparation complies with the test if each individual content is 85 to 115 percent of the average content. If one individual content is outside the limits of 85 to 115% of the average content but within the limits of 75 to 125%, the determination is repeated using another 20 dosage units. The preparation complies with the test if not more than three of the individual contents of the total sample of 30 dosage units is outside the range from 85 to 115% of the average content and none is outside the limits of 75 to 125% of the average content.

2.2.3.3 Hardness test

Hardness test was conducted for 10 tablets from each batch using hardness tester and the values were given in Kg/cm2 with their mean and standard deviation SD. The tablet hardness of 4 kg is considered as suitable for handling the tablet [19].

2.2.3.4 Friability test

Weighed amount of 10 dedusted tablets were subjected to rotating drum of friability test apparatus. The drum rotated at a speed of 25 rpm and the apparatus was operated for 4 minutes. At the end of test, tablets were dedusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

% Friability = (loss in weight/initial weight)*100 (5)

A maximum loss of not more than 1% is generally considered acceptable according to the European Pharmacopeia (5^{th} ed.).

2.2.3.5 Swelling study

The swelling of the polymers upon hydration by the test medium was determined by a method similar to the equilibrium weight gain method. The matrix tablets were weighed and placed in baskets. These baskets were then immersed in 900 ml of phosphate

buffer of pH 6.8 and rotated at 75 rpm at 37±0.5°C (USP XXIV basket method) [20]. At specified time intervals, the baskets containing the matrix tablets were removed, lightly blotted with tissue paper so as to remove excess water and weighed again. They were then placed back in the dissolution vessel as quickly as possible. The percent degree of swelling was calculated as follows [21,22,23]:

$$\text{Percent degree of swelling} = [(Ws - Wd)/Wd] \times 100 \quad (6)$$

Where Ws is the weight of the swollen matrix at time t and Wd is the weight of the dry matrix. The swelling study was done in triplicate for all samples tested.

2.2.3.6 In vitro drug release studies

The release of methyldopa from matrix tablets was carried out using USPXXIV Type II dissolution apparatus (basket method) at a rotation speed of 75 rpm, and a temperature of 37±0.5°C. In order to simulate the gastrointestinal transit conditions, the tablets were subjected to different dissolution media. Initially, the drug release was carried out for 2 hrs in 0.1 N HCl, and then in phosphate buffer pH 6.8 up to 24 hrs (900 ml). Samples were withdrawn at predetermined time intervals during 24 hours, filtered by passing through 0.45 µm membrane filters, diluted suitably and analyzed spectrophotometrically at 280 nm. Each test was conducted in triplicate (6 tabets in set) for each formulation.

2.2.3.7 Drug release kinetics

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first order (log cumulative percentage of drug released versus time), Higuchi (cumulative percentage of drug release versus square root of time).In order to further determine the mechanism of drug release, dissolution data were also fitted according to the well-known exponential equation (Korsmeyer equation); which is often used to describe the drug release behavior from polymeric systems:

$$\log (Mt/Ma) = n.\log t + \log K \quad (7)$$

Where, Mt is the amount of drug release at time t, Ma is the amount of drug released 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 [24].

2.2.3.8 Statistical analysis

A one way analysis of variance (ANOVA) was used to analyze both the swelling and dissolution data obtained for each batch of formulation. ANOVA was determined using SPSS software (Version 12, SPSS Inc., USA), and confidence limit of $P < 0.05$ was fixed.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Evaluation of granules

The loose densities and tapped densities for all the batches were found in the range of 0.569 to 0.681 g/cm3 and 0.658 to 0.741 g/cm3 respectively. Compressibility index values were ranging from 11.38% to 14.759%. Generally, compressibility index values up to 15 % and Hausner's ratio ranged from 1.129 to 1.173. LOD of all formulations ranged from 3.22% to 5.63% as shown in (Table 2).

3.1.2 Evaluation of tablets

3.1.2.1 Physical parameters

The tablets of the proposed formulations were evaluated for weight variation, drug content, friability and hardness (Table 3). The average percentage deviation of 20 tablets of each formula was less than 5%. Drug content in different batches of tablets ranged from 96.17±1.63% to 102.43±1.41% of the average content.

The hardness of tablets of each batch ranged between 0.22 5.68 and 8.25±0.42 kg/cm^2, and Friability value of all formulations were less than 1%.

3.1.2.2 Swelling study

Swelling study was performed for all the batches up to 12 hr. As time increases, the swelling index also increased. Figs. 1 and 2 show the relationship between swelling index and polymers level and type.

3.1.2.3 In vitro drug release studies

The release profiles of different formulations (F-1 to F-3) of methyldopa extended release matrix tablets are shown in Fig. 3. Formulation F1, F2, F3 released 26.208%, 52.289% and 71.396% of methyldopa, respectively, at the end of 2 hours; and 98.517%, 97.211% and 96.852% of the drug at the end of 24 hours, 10 hours and 5 hours, respectively.

Table 2. Granules properties of different formulations of methyldopa extended release matrix tablets

Batch code	LBD* (g/cm3)	TBD* (g/cm3)	Hausner's ratio	Carr's index (%)	Moisture content* (%)
F1	0.618±0.17	0.725±0.012	1.173±0.063	14.759±0.651	5.63±0.18
F2	0.599±0.002	0.683±0.028	1.140±0.018	12.299±0.019	5.46±0.14
F3	0.607±0.015	0.685±0.024	1.129±0.04	11.38±0.23	4.61±0.18
F4	0.584±0.005	0.671±0.033	1.149±0.009	12.966±0.371	3.08±0.22
F5	0.587±0.028	0.668±0.032	1.14±0.011	12.24±0.386	4.95±0.12
F6	0.569±0.036	0.658±0.029	1.158±0.014	13.61±0.519	3.72±0.27

**All the values are expressed as mean ± standard deviation*

Table 3. Tablets properties of different formulations of methyldopa extended release matrix tablets

Batch code	Weight** (mg) (n=20)	Hardness** (Kg/cm2) (n=10)	Friability (%) (n=10)	Uniformity content** (%) (n=10)
F1	03992±1.75	8.25±0.42	0.27	101.53±3.569
F2	03987±1.55	8.12±0.36	0.44	96.17±2.091
F3	03983±2.58	7.53±0.79	0.69	98.44±1.632
F4	0.4004±4.18	5.68±0.22	0.89	98.18±3.272
F5	03971±3.55	7.23±0.39	0.57	102.23±3.151
F6	03992±2.38	7.96±0.37	0.39	97.38±2.165

***All the values are expressed as mean ± standard deviation*

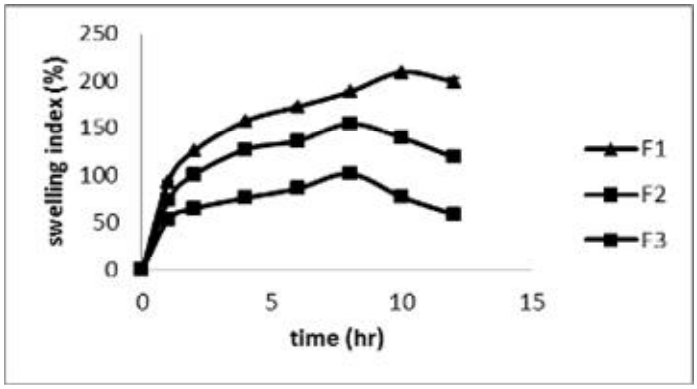

Fig. 1. The effect of HPMC viscosity on swelling index of matrix tablet
(F1: 15% HPMC K100M, F2:15% HPMC K4M, F3: 15% HPMC K100LV)

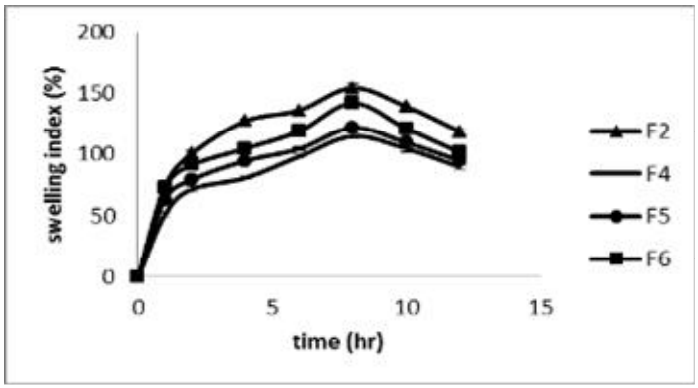

Fig. 2. The effect of EC on swelling index of matrix tablets
(F2: 15% HPMC K4M, F4: (10% EC: 5% HPMC K4M), F5: (7.5% EC: 7.5%HPMC K4M), F6: (5% EC: 10% HPMC K4M))

Besides, The dissolution profile of methyldopa matrix tablets containing combinations of a hydrophilic polymer HPMC K4M with a hydrophobic polymer EC in the different HPMC/EC ratio (1:2, 1:1 and 2:1) in formulations F4, F5 and F6, respectively while keeping the total polymer concentration 15% are shown in Fig. 4. Formulations F4 and F5 released 46.806% and 37.893% of methyldopa, respectively, at the end of 2 hours, and released 96.782% and 98.852% of the drug at the end of 12 hours and 16 hours respectively. Formulation F6 released 28.818% of methyldopa at the end of 2 hours and was able to sustain drug release up to 24 hours (97.542% of methyldopa was released at the end of 24 hours).

3.1.2.4 Drug release kinetics

The drug release data obtained were extrapolated by Zero order, First order, Higuchi and Korsmeyer-Peppas equations in order to define the pattern of drug release from the matrix tablets. Correlation coefficients R2 according to each equation for all of the formulations are presented in Table 4.

3.2 Discussion

3.2.1 Evaluation of granules

The results of Compressibility index and Hausner's ratio indicated that the granules possessed satisfactory flow properties and compressibility. Moreover, LOD of all the formulations was also found to be satisfactory.

3.2.2 Evaluation of tablets

3.2.2.1 Physical parameters

Results of weight variation, drug content, friability and hardness ensures good handling characteristics for all batches, and indicates that tablet surfaces were strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed.

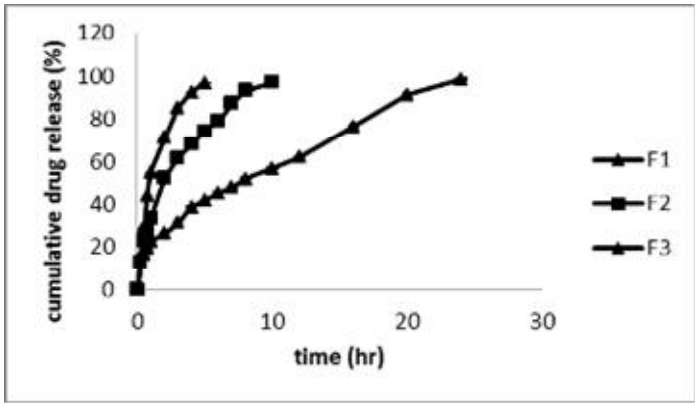

Fig. 3. The effect of HPMC viscosity on release profile of methyldopa extended release matrix tablet
(F1: 15% HPMC K100M, F2:15% HPMC K4M, F3: 15% HPMC K100LV)

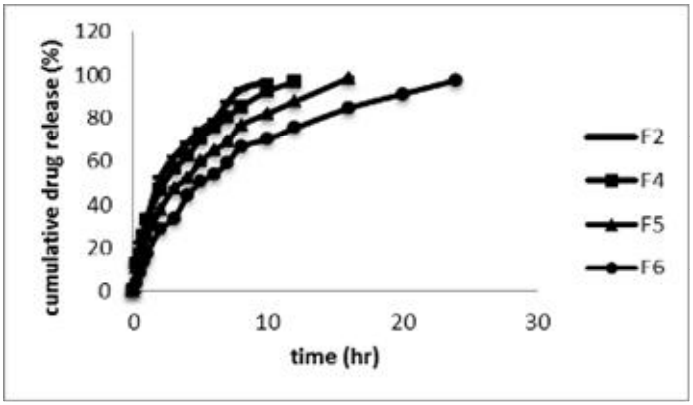

Fig. 4. The effect of EC on release profile of methyldopa from HPMC matrix tablets
(F2: 15% HPMC K4M, F4: (10% EC: 5% HPMC K4M), F5: (7.5% EC: 7.5% HPMC K4M), F6: (5% EC: 10% HPMC K4M))

Table 4. Kinetics of drug release from methyldopa matrix tablets

Formulation	Correlation coefficient (R^2)				Release exponent (n)	Mechanism
	Zero order	First order	Higuchi	Korsemeyer & Peppas		
F1	0.9516	0.9356	0.9951	0.9969	1.0532	Case II transport
F2	0.9047	0.9665	0.9831	0.9776	0.5801	anomalous diffusion
F3	0.8806	0.9947	0.9612	0.9583	0.5502	anomalous diffusion
F4	0.9013	0.9797	0.9859	0.9836	0.5319	anomalous diffusion
F5	0.9023	0.9185	0.9909	0.9902	0.5602	anomalous diffusion
F6	0.8609	0.9681	0.9776	0.9785	0.6413	anomalous diffusion

3.2.2.2 Swelling study

As time increases, the swelling index also increased, this is because weight gain by tablet was increased proportionally with rate of hydration up to certain limit. Later on, it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution Medium [25,26].

The direct relationship was observed between swelling index and polymer viscosity grade (HPMC). With increase in viscosity of HPMC, swelling index was found to show statistically significant increase (p<0.05) as shown in Fig. 1. In formulation F3 containing HPMC K100LV, swelling index increased up to a maximum level in 8th hr. and then onwards it started decreasing. This may be due to the low viscosity grades of HPMC that results in loss of matrix integrity and hence rapid erosion. The formulation F1 that contains HPMC K100M, swelling index was increased up to 10 hr. This may be due to the high viscosity grade that resulted in more hydration and gel formation around the surface of the tablet, attributing to high swelling index. Due to high viscosity, matrix integrity is maintained for a longer duration leading to least erosion [27,28].

It was also observed that tablets containing combination of HPMC K4M-EC blends swelled significantly less than (p<0.05) that of formulations containing HPMC K4M polymer alone (Fig. 2). This could be due to presence of non-swellable hydrophobic EC, which minimized the swelling of the matrix tablets as it limits the infiltration of medium in to the matrix as well as confine the development of gel layer on the outer surface of matrix as compared to the hydrophilic HPMC [29,30].

3.2.2.3 In vitro drug release studies

HPMC present on the surface of matrix tablets initially hydrates during dissolution and forms an outer gel layer on matrix tablet surface. Progressive contact with the medium leads to subsequent bulk hydration of the matrix. Eventually, this leads to HPMC chain relaxation, followed by erosion of the matrix. The drug release rate and mechanism is controlled by the matrix swelling, diffusion of drug through the gel layer and/or matrix erosion HPMC [31,32].

3.3 Effect of HPMC Viscosity Grade

To evaluate the effect of different HPMC viscosity grades on methyldopa release**,** formulations F1,F2,F3 were prepared using 15% of HPMC K100M, HPMC K4M and HPMC K100LV, respectively. With the increase of HPMC viscosity, the release rate had a tendency to decrease. It was probably due to more polymer entanglement, stronger gel strength and also less effective molecular diffusional area at higher viscosity. Besides, as the viscosity grade of HPMC increase, the swelling of its side chains undergoes faster to form a very strong gel, which had more ability to resist the drug diffusion and gel erosion, thus decreasing the drug release rate.

Results of previous studies showed that the formulations containing the same amount HPMC with different viscosities exhibited the discrepant release profiles. The release rates of drug from the formulations using HPMC with low viscosity (K100LV) were faster than those using HPMC with high viscosities (K4M, K15M and K100M) (P<0.05) [33,34].

3.4 Effect of EC Incorporation in HPMC Matrix Tablets

When compared to formulation F2 (containing 15% of HPMC K4M alone) which sustained drug release up to 10 hours, incorporation of EC in HPMC matrix was able to sustain methyldopa release more than using HPMC K4M alone. One study showed that HPMC K100M when combined with EC could slow down the release of metformine HCl more effectively than using HPMC K100M alone [35]. Another study demonstrated that combination of hydrophilic and hydrophobic polymers in equal ratios could be

successfully employed for formulating sustained release matrix tablets of Stavudine [36]. This release retardant effect of EC is most likely due to its hydrophobic nature which restrict the penetration of medium inside the matrix thus retarding the dissolution and subsequent release of the drug [37].

For the purpose of studying the influence of varying EC to HPMC ratio on drug release, formulations F4, F5 and F6 were compared between each other. It was observed that as the concentration of EC increased in these formulations, drug release was shown to increase and formulation F6 containing the less amount of EC was able to sustain the release of methyldopa up to 24 hours. The reason of this result might be that the EC large hydrophobic molecules imposed a discontinuity in the gel-structure leading to formation of a weaker barrier than the HPMC gel alone. Moreover, hardness test showed that hardness of tablets was decreased as EC level increased in formulation F4, F5 and F6 so the harder tablets in F6 will be less tortuous and as a result will restrict medium penetration into matrix.

3.4.1 Drug release kinetics

As shown in Table 4, the in vitro release profiles of drug from formulations F1, F2, F4, F5 and F6 could be best expressed by higuchi's equation , as the plots showed high linearity (R2: 0.9612 to 0.9951). Higuchi equation is followed usually when the release follows diffusion mechanism. Formulation F3 released methyldopa according to first order kinetic (R12=0.9797) which may be due to using of very low viscosity grade of HPMC K100LV that form low viscosity gel barrier that is more tortuous (compared to that formed with high HPMC viscosity grades) so it fasters the penetration of dissolution medium into the matrix and the drug (which is soluble in both dissolution medium 0.1N HCl and phosphate buffer) diffuses more easily out of this tortous matrix according to first order kinetic. To confirm the mechanism of diffusion, the data were fit into Korsmeyer-Peppas model. All the formulations showed highest linearity (0.9583 to 0.9969) with slope (n) values ranging from 0.5139 to 0.6413 which indicates that the release mechanism was non-Fickian or anomalous release ($0.45 < n < 0.89$). It can be inferred that the release from about all formulations was dependent on both drug diffusion and polymer relaxation, which appears to indicate a coupling of two occurring simultaneous mechanisms: diffusion and erosion so called anomalous diffusion. But formulation F1 showed Case II transport release (n=1.0532) which means that drug release was controlled by only polymer relaxation.

4. CONCLUSION

The study was undertaken with an aim to formulation and evaluation of sustained release matrix tablets using various polymers like HPMC K100M, HPMC K4M, HPMC K100LV and Ethylcellulose.

Results showed that the release rate was decreased as the viscosity of HPMC was increased. Besides, incorporation of EC in HPMC matrix system was found to decline the release rate.

Diffusion coupled with erosion might be the mechanism for the drug release from hydrophilic and hydrophobic polymer based matrix tablets. Among the various formulations, formulation F1containing 15% of K100M and formulation F6 containing 5% EC with 10% HPMC K4M showed satisfactory results because the release of drug could be sustained over 24 hours to give once daily dose.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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