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Original Article

FORMULATION, *IN-VITRO* RELEASE KINETICS AND STABILITY INTERPRETATION OF SUSTAINED RELEASE TABLETS OF METFORMIN HYDROCHLORIDE

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ABSTRACT

Objective: The objective of the present study was to formulate, study the *in-vitro* release kinetics and stability of sustained release tablets of metformin hydrochloride.

Methods: Sustained release formulations that would maintain the plasma level for 8 – 12 h might be sufficient for daily dosing of metformin. The granules of metformin hydrochloride were prepared by wet granulation method using polymers such as ethyl cellulose (EC) and hydroxyl propyl methyl cellulose E15 (HPMC E15).

Results: The granules were evaluated by determining the angle of repose ($26.01^0 \pm 0.11^0$ to $31.95^0 \pm 0.10^0$), bulk density, tapped density, Hausner ratio and Carr's index. It shows satisfactory results. The tablets were subjected to measurement of thickness (4.78 ± 0.07 to 5.20±0.13 mm), weight variation (within limit), drug content (98.08±0.20 to 99.22±0.22%), hardness (9.27±0.16 to10.30±0.97 kg/cm^2), friability (0.2to 0.3%w/w), and *in-vitro* release studies.

Conclusion: It was found that as the concentration of HPMC increased the drug release rate declined due to formation of viscous layer. The release can be fine tuned by adding a hydrophobic polymer like EC in the hydrophilic matrix of HPMC. The release mechanisms were analyzed and were found that the release data was best fitted with Higuchi equation although there is no significant difference between the correlation coefficients of Zero-order and Higuchi model. The result also shows different parameters of stability studies and compare with initial results of different batches.

Keywords: Metformin Hydrochloride, Sustained release, HPMC E15, EC, Release kinetics, Stability.

INTRODUCTION

Now-a-days conventional dosage forms of drugs are rapidly being replaced by the novel drug delivery systems. Among, these the sustained release dosage forms have become extremely popular in modern therapeutics. Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. The main advantages of sustained release tablets are uniform release of drug substance over time and reduction of frequency of intake [1].

Metformin hydrochloride is an orally administered biguanide derivative, which is widely used in the management of type – II diabetes mellitus, ~~in~~ particularly in overweight and obese people and those with normal kidney function. Limited evidences suggest metformin may prevent the cardiovascular and possibly the cancer complications of diabetes. Metformin has an oral bioavailability of 50–60% under fasting condition, and is absorbed slowly. Peak plasma concentration (C_{max}) is reached within one to three hours of taking immediate-release metformin and four to eight hours with extended-release formulations [2]. The plasma protein binding of metformin is negligible, as reflected by its very high apparent volume of distribution (300–1000 lit after a single dose). Steady state is usually reached in one or two days [3]. Many researchers investigated or formulated metformin hydrochloride tablets using various natural, semi-synthetic and synthetic polymeric materials. Hence, in the present work, our attempt was to formulate metformin hydrochloride sustained release tablets using combination of two polymers such as hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC) or their mixture to evaluate *in-vitro* release characteristics and to predict the release pattern with kinetic equations.

MATERIALS AND METHODS

Materials

Metformin HCl was obtained as gift samples from Drakt Pharmaceutical Pvt Ltd., Baroda, Gujrat. Ethyl cellulose (EC), hydroxy propyl methyl cellulose E15 LV Premium (HPMC-E15), talc and magnesium stearate were purchased from Loba Chemie Pvt. Ltd (Mumbai). Starch was procured from Nice Chemicals (Cochin). Microcrystalline cellulose, di-sodium hydrogen phosphate and potassium di-hydrogen phosphate were purchased from Merck Specialties Pvt. Ltd., Mumbai, All those chemicals or reagents were used as supplied without any further purification.

Study of physical interaction between drug and polymer [4]

Differential Scanning Calorimetric (DSC) was carried out by scanning the samples of pure drug (Metformin HCl**)**, mixtures of two polymers (HPMC and EC), and the formulation, using DSC (Pyris Diamond TG/DTA, PerkinElmer, SINGAPORE) at nitrogen atmosphere (150 ml/min). Platinum crucible was used with alpha alumina powder as reference.

Preparation of granules [5]

The tablets, each containing 500 mg of Metformin HCl, were prepared by wet granulation technique. The composition of various formulations of the tablets with their codes is listed in table 1. The composition with respect to polymer combination was selected on the basis of trial and error method of tablets. A batch of 20 tablets was prepared with each formula. The drug (Metformin HCl), polymers (HPMC and EC) and other excipients were mixed. The granulation was done manually with a starch solution (5%).

The wet mass was passed through a 22 mesh sieves and the wet granules produced were first air dried for 30 minutes and finally at 45-50^0 C in for 60 minutes. The dried granules were sized by a sieve. Then magnesium stearate and talc were added as a lubricant and glidant respectively. Compression was carried out using single punch tablet compression machine (B. D. Instrumentation, Gujarat) at a constant compression force. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristic.

Table 1: Composition of sustained release Metformin HCL tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metfromin HCL	500	500	500	500	500	500	500	500	500
HPMC E15 LV Premium	0	100	200	250	300	350	400	450	500
EC	500	400	300	250	200	150	100	50	0
MCC	75	75	75	75	75	75	75	75	75
Starch	5%	5%	5%	5%	5%	5%	5%	5%	5%
Mg. Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5

Evaluation of granules flow characteristics [6, 7]

Bulk density

A known quantity (m) of granules was poured into the measuring cylinder carefully. The granules were leveled without compacting, if necessary and read the unsettled apparent volume (V), to the nearest graduated unit. The bulk density was calculated and expressed in gm per ml, by the formula m / V.

Tapped density

A known quantity of granules were taken in a measuring cylinder and tapped on mechanical tapping apparatus for 5 mins. The initial and final volumes were noted.

$$\text{Tapped density} = \frac{\text{Weight of Granules}}{\text{Final volume after tapping}}$$

Angle of repose

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. This is done by funnel method. The value of angle of repose is calculated by using the following formula:

$$\tan \theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

Where, θ = Angle of repose, h = height of the heap and r = radius of the heap

Compressibility index and Hausner ratio

The compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting granules flow characteristics. The compressibility index and Hausner ratio were determined by measuring both the Bulk density and tapped density of granules.

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{X } 100$$

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluations of tablets

a) Average weight [8]**:** Twenty tablets were randomly selected and individually weighted (E. G Kantawalla Pvt. Ltd, Pune). The average weight of the tablets was calculated and compared with individual weight.

b) Hardness and friability [8]**:** The hardness and friability were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Indian equipments, Kolkata, India) respectively.

c) Thickness [8]**:** The thickness of the tablets was determined by using Vernier slide calipers.

d) Drug content [8]: 20 tablets were taken in a mortar and crushed to make powder. Powder equivalent of 500mg was weighed accurately and transferred in a beaker. The drug was extracted with three volumes of 10 ml water. The extracts were pooled and after appropriate dilution the drug content was analyzed by measuring the absorbance of standard and samples at **λ**= 233 nm using UV spectrophotometer with photodiode array detector (SA165, Elico).

e) *In-vitro* release study [9]**:** The release rate of metformin hydrochloride tablets was determined using USP dissolution test apparatus (paddle type). The dissolution test was performed using 900 ml of 0.1 (N) HCl for the first 2 hrs followed by pH 6.8 phosphate buffer solution for 6 hrs at 50 rpm. The temperature of the dissolution medium was maintained at 37±0.5^{0}C. The withdrawn samples were replaced with fresh dissolution medium. The samples were analyzed at **λ**= 233 nm by UV Spectrophotometer (SA165, Elico).

f) Drug release kinetic study [10]**:** The data obtained from the in vitro release study were analyzed using linear regression method according to the following equations:

i. Zero order

$$Q_t = K_0 t$$

Where, Q_t = Amount of drug release in time t

K_0 = Zero order rate constant expressed in unit of concentration / time

t = Release time

ii. First order

$$\log Q = \log Q_0 - kt/2.303$$

Where, Q_0= is the initial concentration of drug, k= is the first order rate constant,

t = release time

iii. Higuchi model

$$Q = kt^{1/2}$$

Where, k = Release rate constant, t = release time

iv. Hixson-crowell model

$$W_0^{1/3} - W_t^{1/3} = \kappa t$$

Where, W_0 = initial amount of drug in the pharmaceutical dosage form, W_t = remaining amount of drug in the pharmaceutical dosage form at time t and κ = rate constant incorporating the surface volume relation

v. Korsmeyer-peppas model

$M_t / M_\infty = Kt^n$

Where, M_t = amount of drug released at time t

M_∞ = amount of drug released after infinite time

M_t / M_∞ = fraction solute release

t = release time, K = kinetic constant incorporating structural and geometric characteristics of the polymer system, n = diffusion exponent that characterizes the mechanism of the release of traces.

g) Stability study [11]**:** The stability study was performed as per ICH guidelines. The formulated tablets were stored at 40^{o}C/ 75% RH conditions for a period of three months.

RESULTS AND DISCUSSION

The preformulation study of drug-excipient interaction was carried out by DSC, which showed no interactions of the drug molecule and polymers.

Metformin is showing its characteristic peak approximately at 230^{0}C in both pure form (A) and in dosage form (C). The results are shown on fig. 1.

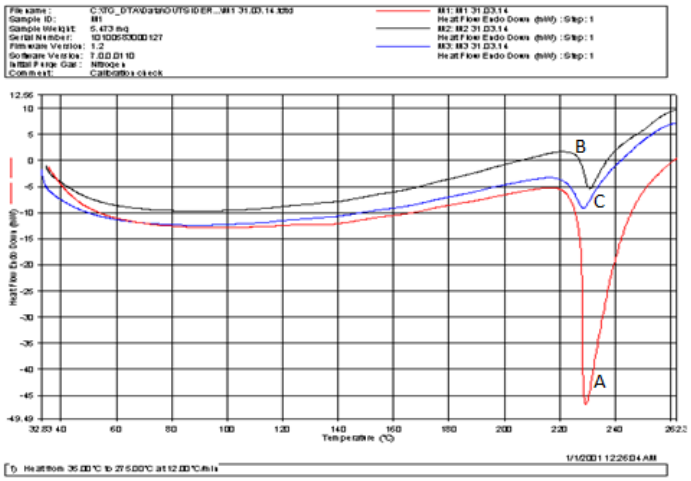

Fig. 1: DSC study of pure (A) Metformin Hydrochloride, (B) Metformin Hydrochloride, HPMC and EC (1:1:1 ratio), (C) Tablets Formulation

A total number of nine formulations were prepared by wet granulation method. The bulk densities of the granules of different batches (F1 to F9) were found between 0.2123±0.003 to 0.4029±0.007 gm/cm^3, tapped densities within 0.2725±0.002 to 0.4720±0.003 gm/cm^3, Carr's indices within 0.1192±0.010 to 0.2988±0.008 %, Hausner ratio within 1.1700+0.030 to 1.4268±0.017, angle of repose within 26.01±0.110 to 31.95±0.100^0, which are shown in table 2. All the data were in triplicate and expressed as mean ± standard error of mean, and expressed with 95% confidence. The above values of pre compression parameters show the prepared granules having good flow property. Hardnesses of tablets of all formulations were found between 9.27±0.16 to 10.30±0.97 kg/cm^2, weight variation was within 1079.42±6.04 to 1080.87±5.03 mg, friability range between 0.2 to 0.3%, thickness was 4.78±0.07 to 5.20±0.13 mm and Drug contents were found between 98.08±0.20 to 99.22±0.22 % (vide table 3).

Table 2: Pre compression parameters of granules

Formulation code	Bulk density*	Tapped density*	Carr's index*	Hausner ratio*	Angle of repose*
F1	0.3179±0.010	0.3843±0.006	0.1732±0.017	1.2105±0.025	27.18±0.240
F2	0.3547±0.006	0.4235±0.006	0.1624±0.012	1.1944±0.017	26.01±0.110
F3	0.3220±0.004	0.3765±0.007	0.1442±0.022	1.1700±0.030	26.36±0.678
F4	0.4029±0.007	0.4720±0.003	0.1464±0.009	1.1719±0.013	27.67±0.236
F5	0.3307±0.001	0.3903±0.003	0.1527±0.007	1.1803±0.010	26.88±0.465
F6	0.3171±0.015	0.4219±0.006	0.2476±0.044	1.3378±0.074	27.36±0.628
F7	0.3179±0.003	0.4534±0.002	0.2988±0.008	1.4268±0.017	30.10±0.166
F8	0.2468±0.003	0.2804±0.006	0.1192±0.010	1.1356±0.012	31.95±0.100
F9	0.2123±0.003	0.2725±0.002	0.2207±0.012	1.2839±0.020	28.11±0.543

* All value are express as Mean±(t x SEM), n=3 [t = $t_{(\propto/2,df)}$ =0.9647 at 95 % confidence level,df = (n-1)].

Table 3: Evaluation of tablets

Formulation code	Hardness (kg/cm^2)*	Friability (%)*	Weight variation**Ψ**	Drug content (%)*	Thickness(mm)*
F1	9.86±0.58	0.259±0.001	1080.45±4.79	98.66±0.16	5.01±0.02
F2	10.25±0.63	0.271±0.003	1080.06±3.73	98.69±0.23	4.78±0.07
F3	10.06±0.82	0.268±0.010	1080.84±4.64	99.22±0.22	5.10±0.03
F4	9.27±0.16	0.259±0.006	1080.87±5.03	99.07±0.14	5.10±0.06
F5	9.51±0.16	0.265±0.004	1080.34±2.48	98.16±0.18	5.10±0.09
F6	9.65±0.26	0.264±0002	1080.85±4.12	98.68±0.22	5.05±0.10
F7	9.71±0.38	0.278±0.006	1080.25±3.96	98.84±0.11	5.08±0.11
F8	9.79±0.51	0.243±0.005	1079.59±4.49	98.08±0.20	5.26±0.07
F9	10.30±0.97	0.252±0.005	1079.42±6.04	98.95±0.17	5.20±0.13

* All value are express as Mean± (t X SEM), n =3. **Ψ** All value are expressed as Mean± (t x SEM), n =10. [t = $t_{(\propto/2,df)}$ =0.9647 at 95 % confidence level, df = (n-1)].

The release obtained from formulation code F1 to F9 are mentioned in fig. 2A. The percentage of the drug released up to 6 hours for F1 to F9 was 85.86%, 74.85%, 65.47%, 61.41%, 54.91%, 51.89%, 46.78%, 42.02%, 37.82% respectively. Fig. 2B shows the time taken for 30% of drug release (t_{30}). The tablets containing only EC (F1) produced a t_{30} of 108 min because EC is not soluble in water. Therefore, it did not

create a viscous layer over the tablet core and the tablet matrix rapidly absorbed water compared to F9 containing higher amount of HPMC. Thus tablets containing combinations of EC and HPMC (F2 to F9) showed 30% of release of drug at 94 min, 103 min, 109 min,125 min,141 min,158 min,172 min,209 min respectively.

In the fig. 2C % drug released is plotted against HPMC: EC ratio (0, 0.2, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1.0). From this fig. it is evident that at 30 mins the release patterns were approximately same in all the formulations. As time increased, it was found that HPMC was getting dissolved quickly in the dissolution medium and was forming a viscous layer over the tablet matrix. This viscous layer reduced the movement of durg molecule from the inner core to the surface. This phenomenon is evident from the graph obtained from the release characteristics of 6 hrs (fig. 2C). With highest HPMC ratio in F9 the release was slowest (i. e. 37.8%). As the EC content in the matrix increased it was found that the release also increased. The release rate of metformin was found to be reduced with increasing amount of HPMC due to formation of viscous layer [12]. This information will help in designing formulations of metformin with desired release rate. It is evident from the in vitro dissolution data that increase in hydrophilic polymer concentration decreases the release rate this might be due to increase in diffusional path length, which the drug molecule may have to travel [13].

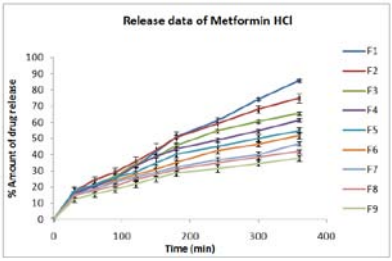

Fig. 2A: Comparative release profile of formulation F1 to F9

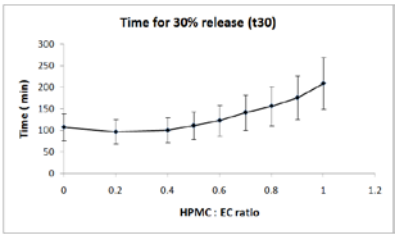

Fig. 2B: Time taken to release 30% of drug from all formulations (F1 to F9)

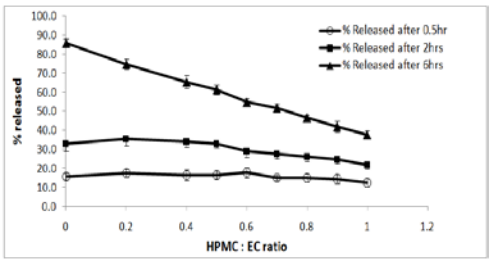

Fig. 2C: Percentage of drug released of all formulations (F1 to F9) after 0.5hr, 2 hrs and 6 hrs

The dissolution data of all the formulations were fitted to zero order, first-order, Higuchi, Hixon – Crowell and Korsemeyer-Peppas models. The model that best fitted the release data was evaluated by correlation coefficient (R^2). R^2 values for all formulations in various models were given in table 4. Comparing the average of the R^2 values of all the formulations Zero-order and Higuchi model showed the better fitting of data having 0.975 and 0.984 respectively.

***Table* 4: *In- vitro* drug release kinetics studies data of all formulations**

F. Code	Zero order*		First order*		Higuchi Model*		Hixon Crowell*		Korsmeyer-Peppas*	
	K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	K_{KP}	R^2
F1	65.74±0.66	0.990±0.001	-0.0006±0.0001	0.936±0.011	41.95±0.37	0.967±0.009	0.630±0.287	0.964±0.012	-0.0039±0.0002	0.976±0.006
F2	53.38±3.66	0.986±0.003	-0.0005±0.0002	0.918±0.010	37.13±1.72	0.982±0.003	0.314±0.004	0.950±0.008	-0.0035±0.0001	0.962±0.006
F3	46.40±0.56	0.964±0.010	-0.0005±0.0001	0.917±0.028	30.07±0.21	0.986±0.001	0.266±0.010	0.929±0.023	-0.0032±0.0002	0.977±0.010
F4	41.33±4.24	0.977±0.004	-0.0004±0.0002	0.910±0.019	26.96±0.99	0.988±0.001	0.251±0.008	0.940±0.008	-0.0030±0.0001	0.974±0.006
F5	34.49±0.96	0.964±0.001	-0.0003±0.0003	0.917±0.005	21.80±0.36	0.986±0.003	0.197±0.006	0.929±0.001	-0.0023±0.0001	0.977±0.001
F6	33.79±0.99	0.985±0.003	-0.0004±0.0001	0.930±0.003	21.91±0.65	0.992±0.003	0.225±0.009	0.949±0.004	-0.0027±0.0002	0.979±0.001
F7	27.56±2.23	0.981±0.002	-0.0004±0.0002	0.942±0.012	17.55±1.26	0.978±0.017	0.190±0.021	0.959±0.010	-0.0024±0.0003	0.963±0.009
F8	25.13±0.98	0.964±0.009	-0.0004±0.0001	0.882±0.016	16.61±0.47	0.988±0.002	0.200±0.006	0.923±0.015	-0.0027±0.0002	0.963±0.004
F9	22.94±0.35	0.967±0.002	-0.0004±0.0002	0.884±0.004	15.02±0.09	0.991±0.001	0.182±0.012	0.928±0.001	-0.0024±0.0002	0.957±0.006
Mean		0.975		0.915		0.984		0.941		0.969

* All value are express as Mean $\pm$ $t_{(\alpha/2,df)}$x SEM where α = 0.05 and n = 3.

Table 5: Evaluation of different parameters of all formulations of Metformin HCL SR Tablets after 3 months stability checking

Formulation Code	Hardness (kg/cm2)		Friability (%)		Weight Variation		Drug Content (%)		Thickness (mm)		% of release after 6 hrs	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
F1	9.86	10.75	0.2586	0.282	1080.45	1079.41	98.66	98.43	5.01	5.01	85.86	84.74
F2	10.25	9.29	0.2707	0.257	1080.06	1080.58	98.69	98.49	4.78	4.95	74.85	74.01
F3	10.06	9.17	0.2676	0.267	1080.84	1079.42	99.22	98.65	5.10	4.93	65.47	65.13
F4	9.27	10.72	0.259	0.267	1080.87	1079.11	99.07	98.61	5.10	5.11	61.41	61.47
F5	9.51	10.56	0.265	0.264	1080.34	1079.2	98.16	98.96	5.10	5.22	54.91	55.28
F6	9.65	10.62	0.2637	0.27	1080.85	1080.51	98.68	98.48	5.05	5.09	51.89	52.12
F7	9.71	10.01	0.2779	0.263	1080.25	1080.95	98.84	98.92	5.08	4.93	46.78	46.09
F8	9.79	10.56	0.2434	0.269	1079.59	1079.13	98.08	98.5	5.26	5.06	42.02	41.47
F9	10.3	10.73	0.2525	0.255	1079.42	1080.92	98.95	98.83	5.20	4.94	37.82	37.01
n =	9	9	9	9	9	9	9	9	9	9	9	9
P =	0.080		0.370		0.252		0.716		0.395		0.956	
Inference:	Not significant		Not significant		Not significant		Not significant		Not significant		Not significant	

A comparison of the R^2 values of the formulations for Zero-order and Higuchi model by t-test and the difference was found to be not significant (P = 0.062 which is > 0.05).

However, Higuchi model produced greater correlation (R^2=0.984) than Zero order (R^2 = 0.975), therefore the mechanism of release of drug from the HPMC: EC matrix can be concluded to follow Higuchi model.

Release of drug from the matrix tablet generally follows diffusion for water soluble drug and erosion or relaxation for water insoluble drug. Diffusion is related to transport drug from the dosage matrix into the in vitro study fluid depending on the concentration gradient between dosage form and in vitro fluid. As gradient varies, the drug is released and the distance for diffusion increases [14].

All formulations were packed and stored at 40°C/ 75% RH for three months. At the end of the months the samples were analyzed for their physical properties, drug content and release properties. Under each parameter the 'before' and 'after' data were compared by t-test and the P values are shown in table 5. All the statistical calculations were conducted by Statgraphics plus software. All the P values are greater than 0.05. It shows that there are no significant ($P<0.05$) changes in drug content, weight variation, hardness, thickness, friability and percentage of drug release.

CONCLUSION

Metformin tablets were formulated as matrix tablets with two polymers, HPMC as the hydrophilic one and EC as the hydrophobic polymer. Nine formulations were prepared with varying ratio of HPMC: EC and constant drug amount of 500mg. Tablets were tested for various physical properties like tablet thickness, hardness, weight variation, friability, drug content, *in-vitro* drug release and stability study. Present study demonstrates that HPMC alone or EC alone could not control the metformin HCL release effectively in sustained form for 6 hours while the combination of HPMC with EC can be successfully employed for formulating sustained-release tablets. The release rate of metformin was found to be reduced with increasing amount of HPMC due to formation of viscous layer. The drug molecules had to pass through the tortuous pathway through the meshworks of hydrophilic polymer chains of HPMC. The release can be fine tuned by adding a hydrophobic polymer like EC in the hydrophilic matrix of HPMC. Based on mathematical data revealed from the models, it was observed that the release data was best fitted with Higuchi equation although there is no significant difference between the correlation coefficients of Zero-order and Higuchi model. The results also showed different parameters of stability studies and the initial and final results after 3 months from different batches were compared and no significance difference was found. Therefore, it may be considered stable even after 3 months. Therefore, long term stability study and clinical trial is required for future development of this dosage form. The release rate may be controlled according to the requirement in the maintenance dose of a sustained release product.

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CONFLICT OF INTERESTS

Declared None

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