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Effect of Ethylcellulose and HPMC K100 M on In Vitro Release Rate of Metformin HCl from Carbopol 971P Matrix Tablets

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Abstract: Metformin hydrochloride is a highly water soluble biguanide derivative of oral antihyperglycaemic agent used in the treatment of type II non-insulin dependent diabetic mellitus. Metformin has problem of incomplete absorption with an absolute bioavailability of 40–60% (under fasting conditions) with rapid elimination and 20–30% of an oral dose which decreases as dose increases. Administration of sustained release Metformin Hydrochloride form could reduce the dosing frequency and improve patient compliance. The present study was based on direct-compressed matrix tablets of metformin Hydrochloride with combination of hydrophilic polymers HPMC K 100M, Carbopol 971P and effect of hydrophobic polymers Ethylcellulose 7cps. The resulting monolithic tablets were evaluated for hardness, thickness, weight uniformity, friability and drug content. *In vitro* release studies were carried out in 0.1N HCl for first 2h and followed by phosphate buffer at 6.8 over a period of 12hrs using USP type II dissolution apparatus. Applying different kinetic models, the mechanism of drug release from formulations was found to be followed Higuchi model. A combination of anionic polymer carbopol with non-ionic HPMC produce a synergistic increase in viscosity gave satisfactory results on the formulation while ethylcellulose controls diffusion of drug towards surface of matrices which was retard release.

Key words: Metformin hydrochloride, Ethylcellulose, Matrix Tablets

INTRODUCTION

Metformin hydrochloride is a biguanide derivative of highly water soluble oral antihyperglycaemic agent used in the treatment of type II non-insulin dependent diabetic mellitus[1,2]. Some high incidence of concomitant GI symptoms, such as abdominal discomfort, nausea, and diarrhea, may occur during the treatment[3]. Gastrointestinal absorption of metformin is incomplete with an absolute bioavailability of 40–60% (under fasting conditions) and in combination with rapid elimination and 20–30% of an oral dose is recovered in faeces[4,5,6]. It decreases as the dose increases, suggesting some form of saturable absorption or permeability/transit time-limited absorption[7]. Administration of sustained release Metformin Hydrochloride form could reduce the dosing frequency and improve patient compliance. Inspite of the clinical response and lack of significant drawback ,chronic therapy with Metformin Hydrochloride suffers problems of which high dose (1-3g/day) and enhancing the incidence of metallic taste, gastrointestinal tract i.e., lactic acidosis, to improve the pharmaceutical formulation of Metformin hydrochloride[8,9]. In order to achieve an optimal therapy, the effort mainly focus on formulation of a sustained release matrix tablet of Metformin hydrochloride dosage forms.

The primary benefit of a sustained release dosage form, compared to a conventional dosage form, is the uniform drug plasma concentration and therefore uniform therapeutic effect[10,11,12]. Over the past two decades, sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Matrix devices were used due to their chemical inertness, drug embedding ability and drug release character, have gained steady popularity for sustaining the release of a drug. Preparation of sustain release formulation by matrix technique is commonly employed method because of ease of preparation, flexibility and cost efficiency[11,12,13,14].

The objective of this study was to prepare sustained release matrix Metformin HCl tablets using hydrophilic anionic carbopol 971P and nonionic HPMC K100 M and hydrophobic ethylcellulose (EC), to study the effect of HPMC and EC on the *in vitro* release characteristics and to predict and correlate the release behavior of metformin HCl from the matrix.

MATERIALS AND METHODS

Materials:

Metformin hydrochloride was obtained as gift sample from BlueCross

Pharmaceuticals Ltd, Nashik. HPMCK100 was obtained as gift sample from Colorcon, Mumbai. Ethylcellulse (7cps) and Carbopol 971P were obtained as gift Sample from Glenmark Pharmaceuticals Ltd, Nashik.

Preparation of matrix tablet:

Matrix tablets containing 500mg of Metformin HCl along with various amount of polymers such as HPMC K100M, EC, Carbopol and other inactive ingredients were mixed and tablet were prepared by direct compression technique. In the first step, active and inactive ingredients (except magnesium Stearate) weighed accurately and were screened through a 40-mesh sieve. Required materials except lubricant were then combined and passed through 40-mesh sieve. In the screened powder following the addition of given amount of lubricant powder was again mixed. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate, and then desired amount of blend was compressed into tablets using rotary tablet compression machine (Rimek tablet machine, Minipress) equipped with 13 mm flat circular punch. All the preparations were stored in airtight containers at room temperature for further study.

EVALUATION OF TABLETS [14, 15, 16]

The compressed matrix tablets were evaluated for thickness, weight variation, hardness and drug content.

Thickness:

The thickness of tablet was determined using Vernier Calliper (Kayco, India). Six tablets from each batch of formulation were used and mean thickness value and SD was calculated for each formulation.

Hardness:

For each formulation, the hardness of six tablets was measured using the Pfizer hardness tester (Cadmach, Ahemadabad, India) and mean value and SD was calculated.

Weight variation:

To study the weight variation, 20 tablets of each formulation were weighed using an electronic digital balance.

Table 1: Table shows Formulation of Matrix Tablet

Ingredients	F1	F2	F3	F4	F5
Metformin HCl	500	500	500	500	500
Carbopol 971 P	200	160	120	80	120
HPMC K100 M	-	-	-	-	120
Ethylcellulose	-	-	120	160	-
Avicel PH 102	80	120	40	40	40
PVP-K-30	10	10	10	10	10
Talc	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5
Total	800	800	800	800	800

The average weight of each tablet was calculated and from that the percentage deviation in weight was calculated.

Friability:

For each formulation the friability of 6 tablets was determined using Roche Friabilator. (Remi Equipments).

Drug content:

Five tablets were weighed and powdered. Weigh accurately a quantity of the powder equivalent to 0.1 g of Metformin HCl shake with 50 ml of 6.8 pH phosphate buffer for 10 minutes, and add sufficient buffer to produce 100.0 ml and filter. After suitable dilution with solvent measure the absorbance of the resulting solution at the maximum at about 233 nm. Calculate the content of C4H11N5, HCl, at the maximum at about 233 nm.

***In vitro* drug release study:** [17, 18, 19, 20]

In vitro drug release studies of the prepared matrix tablets were conducted for a period of 12 hours by using an USP 24 Dissolution Apparatus type II (2000) (Labindia, Mumbai, India) at 37± 0.5° C. The agitation speed was 100 rpm.

Table 2: Table shows Evaluation of Tablets

Formulation code	Thickness (mm) (mean ± S.D)	Hardness (Kg/cm^2) (mean ± S.D)	Weight Variation (%)	Friability (%) (mean ± S.D)	Drug Content
F1	4.58± 0.060	7.5± 0.05	2.440	0.61± 0.060	99.93
F2	4.46± 0.030	7.8± 0.14	1.937	0.47± 0.035	100.15
F3	4.43± 0.010	7.6± 0.10	3.152	0.23± 0.028	98.84
F4	4.44± 0.060	7.5± 0.23	2.729	0.40± 0.060	99.75
F5	4.53± 0.030	7.8± 0.05	2.306	0.24± 0.035	98.25

Table 3: Table Shows Drug Release Profile of Matrix Tablets

Time (Hrs)	% cumulative drug release				
	Formulation code				
	F1	**F2**	**F3**	**F4**	**F5**
1	37.52± 0.31	38.96±1.28	35.49±0.18	30.46±1.48	34.49±0.40
2	45.39±2.07	48.82±1.31	44.64±1.45	38.73±2.56	42.98±0.64
3	58.68±1.20	55.24±0.49	55.57±1.87	50.15±1.63	52.87±1.95
4	67.22±0.29	68.60±1.06	64.35±1.26	58.30±1.06	60.07±1.57
6	81.90±0.45	85.48±0.32	78.32±0.83	72.79±0.84	72.88±0.34
8	96.84 ±1.52	99.19 ±1.41	88.66±0.34	84.73±0.47	85.37±1.56
10	-	-	92.74±1.70	91.89±0.75	95.82±0.31
12	-	-	97.16±0.73	96.25 ±0.97	-

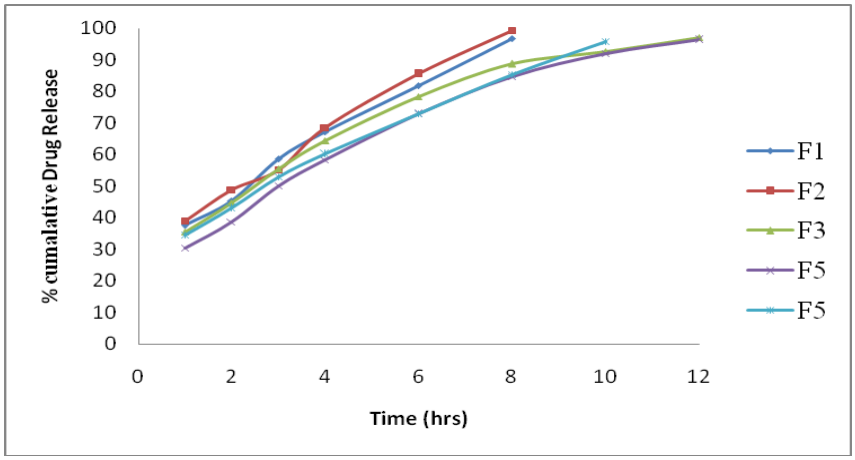

Fig 1: Dissolution profile of matrix tablets

Table 4: Table shows data treatments of matrix tablets

Formulation code	Coefficient of determination (r^2)				Korsmeyer plot n (release exponent)
	Zero order	First order	Higuchi	Korsmeyer plot	
F1	0.9907	0.9149	0.9827	0.9705	0.47
F2	0.9929	0.8382	0.9833	0.9722	0.10
F3	0.9345	0.9847	0.9943	0.9982	0.30
F4	0.9572	0.9808	0.9921	0.9864	0.42
F5	0.9905	0.9252	0.9964	0.9919	0.19

The Dissolution study was carried out in 900 ml 0.1N HCl at 37±0.5 ºC for first 2 hours and then in 900 ml of phosphate buffer (pH 6.8).5ml of the sample was withdrawn at regular intervals and the same volume of fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45 µ membrane filter and the drug content in each sample was analyzed after suitable dilution with a Shimadzu 2501PC UV/VIS spectrophotometer at 233 nm. The amount of drug present in the samples was calculated with the help of calibration curve constructed.

RESULT AND DISCUSSION

Evaluation of Tablets:

The **thickness** of all the formulations were varies within ranges from 4.43-4.58 mm. All the formulation showed uniform thickness. The **weight variation** test was carried out as per official method and it was found that all formulation to be within the limit (as per pharmacopoeial standard). The **content uniformity** test was also carried out as per official method and it was found that different batches shown good content uniformity. It was found that all batches shown percent drug content more than 98 %. The tablet **hardness** of all the formulations was determined and it was found sufficient in the range 7.5-7.8 kg/cm2. Another measure of tablet hardness was the **friability**. A compressed tablet that loses less than 1 % of their weight is generally considered acceptable. For all formulation tried here the weight loss was less than 1 % hence acceptable.

Invitro release study

The in vitro drug release characteristics were studied in 900 ml 0.1N HCl for a period of 2 hours and 6.8 pH phosphate buffer for Remaining 10 hrs using USP XXIII dissolution apparatus 2. According to the USP release pattern, the conventional formulation release not less than 70% in 45 minute. Various formulations were tried here and out of that F3 was the best formulation of the study.

Data treatment

Different kinetic treatments (zero order, first order, Higuchi's square root equation and (Korsmeyer treatment) were applied to interpret the release of Metformin HCl from different matrices. The data was given in (Table 4). The Korsmeyer Peppas kinetic treatment gave consistently higher values (0.9705 to 0.9982) for all formulations. First order kinetic treatment also gave higher values (0.8382 to 0.9847). Zero order kinetic treatment gives higher values (0.9345 to 9929). In order to determine the release mechanism of drug from different matrices different kinetic models was applied. The release profile was fitted into Higuchi model. This model was used to analyze the release from pharmaceutical dosage forms, where the release mechanism was well known or more than one phenomenon could be involved. The values of release exponent (n) and coefficient of determination (R2) were shown in table 4. The value of release exponent (n) was used to characterize the release mechanism from dosage form.

Effect of Carbopol

To study the effect of Carbomer on release of Metformin Hydrochloride, HPMC and Ethyl cellulose were replaced with Carbomer namely Carbopol 971P the degree of swelling of carbopol 971P less in acidic media, the dissolution medium can penetrate fast and deep into the glossy core and the drug is released faster. The gel layer around the tablet core acts as a rate-controlling membrane. F1 and F2 were formulated as shown in Table 1, Fig 1 shows that as percentage of Carbopol was increased, release of Metformin Hydrochloride was decreased. 25% & 20% of Carbopol 971P with respect to anhydrous drug produced sustained effect for eight hours as shown in Table 3. Although Carbopols sustained the drug release, rate of drug release 37.52% & 38.96% after 1hrs and 45.39% & 48.82% of the drug after 2 hrs respectively. The release rate of drug was slow as compared with HPMCK100M, which may be attributed to its swelling, which is greater than that of HPMC K100M indicating insufficient quantity of Carbopol 971P to form the gelatinous layer around the tablet core.

Effect of Ethylcellulose and HPMC K100 M on in vitro release rate of Metformin HCl from Carbopol 971P matrix tablets

The hydrophobic nature of ethyl cellulose seems to have contributed toward reduction in the penetration of the solvent molecules into the matrix. Increasing the concentration of ethyl cellulose shows more retardation in the release of the drug from the formulation F3 & F4 containing ethyl cellulose in combination with Carbopol 971P in the ratio 1:1, 1:2 respectively. F3 & F4 showed 35.92% & 30.46% after the 1hrs and 44.64 & 38.73 after the 2 hrs. The tablet formulation F5 (1:1 ratio of HPMC K100 M and Carbopol 971 P) showed that a combination of anionic polymer with non-ionic HPMC produce a synergistic increase in viscosity gave satisfactory results on the formulation, which was retard to upto 10 hrs.

Influence of addition of (1:1) Carbopol 971P and Ethylcellulose on in vitro release rate of Metformin Hydrochloride from matrix tablets.

In the batch of tablets, to control the initial burst release ethyl cellulose was included in the matrix in the ratio of 1:1 along with Carbopol 971P (F3) which resulted in extending the drug release for a period of 12 hrs indicating fair uniform drug release throughout the dissolution period was shown in Table 3. This may be due to a more rigid complex formed by hydrophilic polymers (HPMC K100 M and Carbopol 971P) in presence of ethyl cellulose, which helped in retaining the drug in the matrix and did not allow rapid diffusion of soluble drug from the matrix.

CONCLUSION

In the matrix drug delivery systems the characteristics of the matrix forming agent play an important role in the mechanisms of the drug. The swelling and gel able properties of hydrophilic polymer matrix like HPMC and carbopol which form protective barrier to influx of water and efflux of drug solution. A combination of anionic polymer carbopol with non-ionic HPMC produce a synergistic increase in viscosity gave satisfactory results on the formulation, along with ethylcellulose has no inert matrix with no physiological action controls diffusion of drug towords surface of matrices which was retard to upto 10 hrs. This may be due to a more rigid complex formed by hydrophilic polymers (HPMC K100 M and Carbopol 971P) in presence of ethyl cellulose, which helped in retaining the drug in the matrix and did not allow rapid diffusion of soluble drug from the matrix and gives better retarding property to give desire dissolution profile.

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