International Journal of Pharmacology and Clinical Research (IJPCR)

IJPCR |Volume 2 | Issue 2 | July - Dec - 2018
www.ijpcr.net

Research article *Clinical research*

ISSN: 2521-2206

Formulation and invitro evaluation of floating matrix tablets of metformin

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ABSTRACT

The floating matrix tablets Metformin (MH) were prepared by using HPMC K15M, as release retarding polymer along with other polymeric substances. Final formulations were prepared using HPMC K15M and Eudragit RLPO as the release retarding polymers. The optimization of metformin floating matrix tablet was done by simplex centroid design (SCD) using HPMC K4 M (X_1), Eudragits (X_2), gas-generating agent, sodium bicarbonate (X_3), as independent variable. The floating lag time (Flag) and time required for 90% drug release were taken as dependent variables. All the tablets showed acceptable physicochemical properties. All the Formulations shown good drug release optimum having good floating lag time and also matching the desirability criteria for drug release

Keywords: Metformin, Floating matrix tablet, Eudragit RLPO.

INTRODUCTION

Metformin hydrochloride (MH) is an antihyperglycemic agent, belonging to biguanide class, and used for the treatment of non-insulin dependent diabetes mellitus [1]. The exhaustive literature research elucidates that several approaches have been tried for the preparation of gastro retentive metformin formulations

An important aspect for the development of gastro retentive dosage form is the selection of suitable hydrophilic polymer, which provides acceptable flotation characteristics and release of the drug substance [2]. The release mechanism of MH from the polymeric matrix has been explained by many researchers, but in most of the studies, hydroxy propyl mHPMC K 15 M (HPMC) is used as polymeric floating matrix system [3] Gastroretentive drug delivery system of MH can be developed successfully by using the combination of various release retarding polymers [4]. The combination of HPMC with other ionic and anionic polymeric substances [5] and their effect on the release of the drug has not been explored much.

EXPERIMENTAL WORK

Preparation of MH floating matrix tablets

Tablets containing 500mg of MH were made by direct compression technique [6]. The active ingredient, metformin, excipients, a gas forming

agent, $NaHCO_3$, were passed through sieve no. 20, individually. Different powder blends were prepared and mixed in a mortar and pestle for 10 minutes. Microcrystalline cellulose and magnesium stearate were then added to the mixed powders. Mixing was continued for another minute and the mixed blend was studied for pre- compression parameters. Finally, required quantity of mixture was weighed and fed into the die of Rotary tablet compression machine manually [6]. In another attempt, the effect of different viscosity grade HPMC polymers was checked on the Gastro retentive dosage form of metformin HCl [7]

Table 1 Composition (%) of metformin HCl Floating Matrix Tablets

Sr No	Ingredients	F1	F2	F3	F4	F5	F6
1	Metformin	50	50	50	50	50	50
2	HPMC K15M	18	18	18	18	18	18
3	Sodium bicarbonate	15	15	15	15	15	15
4	Sodium Alginate	10	-	-	-	-	-
5	udragit RLPO	-	10	-	-	-	-
6	Eudragit RSPO	-	-	10	-	-	-
7	Xanthan gum	-	-	-	10	-	-
8	Poloxamer 188	-	-	-	-	10	-
9	MCC	5	5	5	5	5	5
10	Magnesium Stearate	0.15	0.15	0.15	0.15	0.15	0.15
11	Aersosil	0.05	0.05	0.05	0.05	0.05	0.05

EVALUATION OF GASTRORETENTIVE FLOATING MATRIX TABLET OF MH

Weight variation

20 tablets were randomly selected and accurately weighed. The results were expressed in SD

Drug content

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet 1000 mg was extracted in 100 ml of 0.1N HCl. The solution was filtered through a cellulose acetate membrane (0.45 µm). The drug content was determined by UV spectroscopy at a wavelength of 230 nm after a suitable dilution with 0.1 N HCl [8].

Friability studies

According to the IP specifications, 10 tablets were randomly selected from each batch and placed in the drum of a tablet friability test apparatus. The drum was adjusted to rotate 100 times in 4 min [9]. The percentage friability of the tablets was calculated by measuring the weight loss by the tablets during the rotations, using following equation:

$$\% \text{ friability} = \frac{w1 - w2}{w1} \times 100$$

Where, W_1 is intital weight of 10 tablets and W_2 is weight of dusted tablets after 100 rotations.

Swelling ability (SI)

The swelling behaviour of the tablets was determined, in triplicate [10]. Briefly, a tablet was weighed (W1) and placed in the petridish with 20 ml of HCl 0.1 N, maintained at 37 ± 0.5 ºC. After 8 hours the tablets were removed from the petridish and the swollen tablet was then reweighed (W2) [11]. The swelling index (SI) was calculated using following formula.

$$\text{Swelling Ability} = \frac{(w2 - w1)}{w1}$$

Where, W2 is the weight of the swollen tablets, and W1 is the initial weight of the tablets. Size of

tablets, before and after swelling, was also measured.

In vitro buoyancy studies

The floating behavior of the tablets was visually determined, in triplicate, according to the floating lag time method described by Rosa et al. Briefly, a tablet was placed in a glass beaker, containing 200 ml of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 ºC. The floating lag time, ‘‘the time between tablet was placed in a glass beaker with HCl and its buoyancy” and total floating duration, ‘‘the time during which tablet remains buoyant”, were recorded.

Adhesion retention period

The adhesion retention period of the tablets was evaluated, in triplicate, by an *in vitro* method reported by Nakamura et al. Briefly, an agar plate (2%, w/w) was prepared in 0.1 N HCl (pH 1.2). A side of the tablet was wetted with 0.1 N HCl and attached to the centre of agar plate by applying a light force with a fingertip [1] Five minutes later, the agar plate was attached to a USP disintegration test apparatus and moved up and down in 0.1 N HCl (pH 1.2) at 37 ± 0.5 ºC (Fig. 4.1). The tablet adhered on the plate was immersed into the solution at the lowest point and got out of the solution at the highest point**.**

Drug release studies

Drug release studies of the prepared floating tablets were performed, in triplicate, in a USP Dissolution Tester Apparatus, type- II (Paddle method) at 37 ± 0.5ºC. The paddles were rotated at a speed of 100 rpm, as given in USP. The tablets were placed into 900 ml of 0.1N HCl solution (pH 1.2). Aliquots of 5 ml were withdrawn from the dissolution apparatus at different time intervals and filtered through a cellulose acetate membrane (0.45 µm). The drug content was determined spectrophotometrically at a wavelength of 230 nm, as mentioned before. At each time of withdrawal, 5 ml of fresh medium was replaced into the dissolution flask, to maintain the sink condition. The release of the prepared gastroretentive formulations was compared with the theoretical release of the drug using model independent method by calculating similarity and dissimilarity factor

RESULT AND DISCUSSION

Evaluation of preliminary batches

Physical properties of floating tablet

The batches prepared as per the table no. 2, were evaluated and the results indicated that all the formulations had acceptable physical characteristics. Hardness of all the batches was found to be in the range of 4-5.7 kg/cm^2 (Table 2).

Table 2 Results of the physical evaluation of preliminary batches of MH floating matrix tablets

Batch code	Weight variation	Hardness* (kg/cm^2)	Drug content* (%)	Friability* (%)
F1	Complies	5.7±0.95	98.56±1.25	0.25±0.09
F2	Complies	4.2±0.62	100.94±0.94	0.23±0.12
F3	Complies	4.0±0.28	98.73±1.37	0.13±0.10
F4	Complies	4.7±0.54	102.46±0.59	0.29±0.20
F5	Complies	4.6±0.65	100.98±0.94	0.44±0.16
F6	Complies	5.1±0.98	99.57±0.99	0.13±0.11

The assay for drug content indicated acceptable content uniformity in the prepared tablets. Drug content were found to be within the limits given in Indian pharmacopoeia (IP). The percentage friability for all batches was less than 1%, indicating good mechanical resistance.

In vitro buoyancy studies

All the formulations had floating lag time less than 31 seconds and floating time, more than 8hrs, as shown in Table 2. Previous literature has reported that viscosity of the gel-forming polymer influences the *in vitro* buoyancy[16]. Also, the earlier studies suggests that strength of gel layer changes with the increase in polymer proportion, which in turn will affect flotation of the tablet. In the present study, variation of the polymers used along with HPMC had no effect on the floating properties of the tablets. This indicates the flotation property of tablets is dependent on the amount HPMC K 15M and sodium bicarbonate. As the amount of these two was same in all the formulations, the floating properties were also similar.

Swelling Ability

The swelling indices of all the preliminary batches were found to be in range of 1.734 to 3.864, as shown in table 3. Formulation 2, with Eudragit RLPO exhibited highest swelling index, which was in agreement to the findings of Dorozynski et al., who revealed that application of mixtures of Eudragit and HPMC, increase the swelling capacity of HBS formulations and suggested that the combination can be directly utilized as a starting point in the development of various controlled release formulations [6]

Table 3 Results table for buoyancy, swelling ability and tablet retention period for preliminary floating matrix tablets of MH

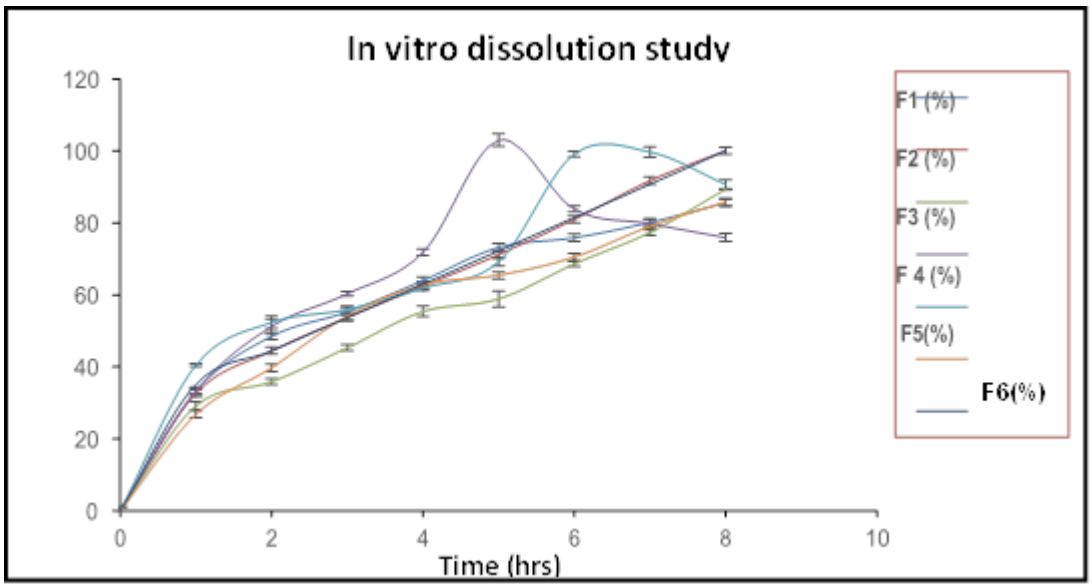
Formulation	Lag Time*(s)	Floating Time*(h)	Tablet adhesion retention period* (min.)	Swelling index (ratio)	Physical appearance of the tablet after swelling	
					8 h (width)	24 h
F1	15.25 ± 1.20	> 8	18.25 ± 2.41	1.734	Intact 2cm	intact
F2	**10.71 ± 2.36**	**> 8**	**93.50** ± 3.36	**3.864**	**2.2cm**	**deformed**
F3	30.50 ± 3.17	> 8	66.41 ± 3.42	2.755	1.8cm	deformed
F4	12.07 ± 1.70	> 8	42.12 ± 4.25	2.851	deformed	deformed
F5	15.65 ± 2.20	> 8	17.10 ± 2.45	2.501	deformed	deformed
F6	30.75 ± 4.96	> 8	21.41 ± 2.15	2.827	1.7cm	deformed

Drug release studies

Table 4.7 Results table for *in vitro* drug release and f_2 & f_1 values for preliminary batches of MH matrix tablets

Time (hrs)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	Theoretical release (%)
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	34.23±1.23	33.65±0.93	28.16±1.14	34.31±0.76	41.44±0.39	25.75±1.54	37.12±0.52
2	49.49±1.54	43.41±2.01	36.84±0.89	52.23±2.11	53.30±1.67	40.71±2.43	45.38±1.31
3	56.28±1.11	52.70±1.54	44.28±0.87	59.29±0.59	54.90±0.98	53.03±2.44	54.64±0.94
4	64.98±2.18	61.37±2.9	53.34±1.44	72.83±0.92	62.83±0.75	61.72±1.26	63.9±0.91
5	70.19±1.04	70.18±1.1	59.83±2.16	101.98±1.73	70.19±1.11	64.38±1.04	71.16±0.84
6	76.86±2.64	82.94±3.21	67.58±0.78	84.79±0.83	98.15±0.78	72.45±1.52	82.42±2.03
7	81.12±1.54	92.70±0.95	78.32±0.83	78.78±1.23	98.65±1.43	79.97±1.18	91.68±1.54

8	86.56±1.13	100.03±0.82	88.32±0.18	76.9±1.13	91.67±1.32	84.76±1.14	98.94±1.14
Similarity factor (*f*2) (%)	58	92	49	41	53	53	-
Dissimilarity factor (*f*1) (%)	7	1	15	17	10	11	-



CONCLUSION

The floating matrix tablets of metformin were prepared by direct compression technique. The preliminary batches of metformin floating matrix tablets were prepared using HPMC K15M, as release retarding polymer along with other ionic and anionic polymeric substances like, sodium alginate, Eudragit RSPO, Eudragit RLPO, xanthan gum, poloxamer 188. Prepared formulations were evaluated for swelling, floating adhesive period and drug release. All the tablets showed acceptable physicochemical properties but, the formulation F_2 (prepared with HPMC K15M and Eudragit RLPO) showed excellent floating properties, extended adhesion periods and sustained drug release characteristics with similarity factor as 92% on comparison with the theoretical release of the drug

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