Original Article

FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

Objective: Now a days as very few antidiabetic drugs are coming out of research and development and some existing drugs are showing several side effects when administered orally, multiple times in a day, hence change in the operation is a suitable and optimized way to make some drug more effective by slight alteration in the drug delivery. Matrix type drug delivery systems of an antidiabetic drug like Metformin Hydrochloride, is an interesting and promising option when developing an oral sustained release system

Methods: An appropriately designed controlled release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target sites. This research work is made in designing of sustained release dosage form of Metformin Hydrochloride by wet granulation method employing both Xanthan Gum and Hydroxy Propyl Methyl Cellulose (HPMC K4M) as a rate controlling polymer.

Results: The development of oral sustained release systems has been a challenge to formulation scientists due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. From all the formulation trial batches, formulation F7 shows the best results. It has been observed that HPMC K4M alone cannot give satisfactory drug release profile but the blend of HPMC K4M and Xanthan gum together give the best drug release kinetics.

Conclusion: The drug release mechanism from the matrix tablets follows Fickian diffusion with first order kinetics. Thus, sustained release matrix tablets of metformin hydrochloride can be expected to reduce the frequency of administration and decrease the dose dependent side effects

Keywords: Sustained release drug delivery, Matrix tablets, Diffusion, Rate limiting polymer, Anti-diabetic

INTRODUCTION

Diabetes is one of the major causes of death and disability in the world. Diabetes is a long-lasting health condition that affects how our body turns food into energy. If you have diabetes your body does not make enough insulin that cause serious health problems, like heart disease, vision loss and kidney disease. Diabetes mellitus are be classified into two main types. First is type I or juvenile diabetes which is also called as insulin dependent diabetes and second type is type I or non-insulin dependent diabetes mellitus, this Type II diabetes is most common type of diabetes. Oral drug delivery is the most widely utilized route of administration among all the routes [nasal, ophthalmic, rectal, transdermal and parenteral routes] that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe, due to its cease of administration, patient acceptance, and cost-effective manufacturing process [1-3].

Novel drug delivery systems are designed to achieve a continuous delivery of drugs at predictable and reproducible kinetics over an extended period of time in the circulation. The potential advantages of this concept include minimization of drug related side effects due to controlled therapeutic blood levels instead of oscillating blood levels, improved patient compliance due to reduced frequency of dosing and the reduction of the total dose of drug administered. Hence, the combination of both sustained release and control release properties in a delivery system would further enhance therapeutic efficacy [4, 5].

Controlled drug delivery systems have been developed 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 drug delivery or modified drug delivery system. A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient. Metformin Hydrochloride is the best drug of choice as a sustain release drug delivery system because a single dose of a Metformin we observe up to 12 h of therapeutic efficacy in our body. Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia [6-8].

In our research article we have developed Metformin sustain release formulation using both Xanthan Gum and Hydroxy Propyl Methyl Cellulose (HPMC K4M) as a rate controlling polymer. Xanthan Gum is a natural polymer it has been used as a rate controlling agent to reduce the release pattern of the drug in the dissolution [9, 10].

MATERIALS AND METHODS

Materials

Metformin hydrochloride was purchased from Aarti Drugs, Polyvinylpyrrolidone (PVP K-30), Microcrystalline Cellulose (PH101) Xanthan gum purchased from Loba Chemie and Hydroxypropyl methyl cellulose purchased from Anhui Sunhere Pharmaceutical Excipients Co. Ltd. Talc and Magnesium stearate purchased from Loba Chemie. All other chemicals, solvents and reagents used were of analytical grade.

Methods

Drug excipient compatibility study

To understand the physico-chemical characteristics of the active pharmaceutical ingredient (API) that is Metformin Hydrochloride, as well as inactive, drug excipients compatibility study is a very important process before going to design a prototype formula. Infrared spectra of pure drug and drug with polymers were recorded on a Fourier Transform Infra-Red Spectrophotometer available at Bengal School of Technology, Sugandha, Hooghly. The disc method was employed to study possible interactions between drug and polymers. Infrared spectrum was taken by scanning the sample in KBr (IR grade) disc and powder pellets produced were analyzed over a wave number range of 4000-400 cm^{-1}. Transmittance spectra were recorded [17].

Preparation of matrix tablets using drug substance, polymers and other excipients

Metformin hydrochloride matrix tablets were prepared by wet granulation method using Polyvinylpyrrolidone (PVPK30) as granulating agent. Different formula was designed using varying proportions of hydrophilic polymer alone and in combination. The composition of matrix tablet is given in table 1. Following steps were followed for preparation of granules:

Step 1 Sifting: Metformin hydrochloride was weighed accurately as per composition and sifted through 60#, Microcrystalline cellulose (PH101), Xanthan gum, Hydroxypropyl methyl cellulose (HPMC K4M) were weighed accurately as per composition and sifted through 40#.

Step 2 Dry mixing: Above sifted materials were collected in a polybag and mixed for 30 min to get a perfect homogenous mixture of drug and excipients. Here powder samples were collected after mixing to check the LOD of dry mix blend and also for blend uniformity.

Step 3 Preparation of binder solution: As per composition required quantity of purified water was taken in a beaker. Polyvinylpyrrolidone (PVP K30) was weighed accurately and added slowly to that beaker under stirring condition and continue stirring until it fully gets dissolved in purified water and form a clear translucent binder solution.

Step 4 Wet mixing: The binder solution next added slowly in dry mix blend in mix continuously until coherent wet mass is achieved. Granulation end point was determined by continuous visible observation on formation of granules.

Step 5 Wet sifting: Wet mass sifted through 10# to get uniform size particles.

Step 6 Drying: After wet sifting granules were kept for air drying for 10 min and then kept inside a tray dryer at 50 °C until target LOD was achieved.

Step 7 Dry screening: Dried granules sifted through 20# and collected in a double polythene lined container.

Step 8 Lubrication: Talc and Magnesium Stearate was weighed as per requirement and added to the above granules and mixed in a blender to get a lubricated blend.

Step 9 Compression: Tablets were compressed in a 10-station single rotary tablet press (Rimek Mini Press, IRM Enterprises Private Limited, Ahmedabad, India) equipped with 19.5 x 9.0 mm, capsule shaped punch, having break-line on one side and plain on other side. A constant compression force required to produce hardness of tablets about 5-7 kg/cm². All physical parameters were checked and tablets were stored in airtight containers for further use.

Table 1: Composition of matrix tablets of metformin hydrochloride

Ingredients per tablets (mg)	Composition (mg/s) of the prepared formulation						
	F1	F2	F3	F4	F5	F6	F7
Metformin HCl	500	500	500	500	500	500	500
Microcrystalline cellulose (PH 101)	150	140	120	115	115	115	110
Hydroxypropyl methyl cellulose (HPMC K4M)	180	180	200	200	100	100	100
Xanthan Gum	-	-	-	-	100	110	110
Polyvinylpyrrolidone (PVP K30)	10	20	20	25	25	25	25
Purified water	qs	qs	qs	qs	qs	qs	qs
Talc	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	10
Total weight	850	850	850	850	850	850	850

Pre-compressional evaluation

Angle of repose

Angle of repose helps to determine the effect of frictional force in a loose powder and cohesion between one particle to another. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Static angle of repose was determined by fixed funnel method or Fixed cone method. Angle of repose was calculated using following equation [11, 12].

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

Where θ = angle of repose, h= height of pile, r = radius of pile base

Compressibility Index

Powder flow property can be measured by Compressibility index also known as Carr's Index. So, it is defined by the equation [13]

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Bulk density}} \times 100$$

Where, Bulk density is the ratio of mass of powder to the bulk volume and Tapped density is the ratio of mass of powder to the tapped volume.

Table 2: Concentration v/s absorbance of metformin hydrochloride at 6.8 phosphate buffer

Concentration (μg/ml)	Absorbance
0	0
1	0.079
2	0.165
3	0.246
4	0.323
5	0.407
6	0.48
7	0.562
8	0.65

Evaluation of matrix tablets

Uniformity of drug content

From each formulation ten tablets were weighed and triturated in a mortar to a fine powder. Powder equivalent to 500 mg of metformin hydrochloride was extracted in 100 ml of pH 6.8 phosphate buffer and then the liquid was filtered using Whatman filter paper. Using UV-Visible spectrophotometer of Simadzu UV 1800 the drug content

was determined by measuring the absorbance at 233 nm, after proper dilution of the filtrate liquid with pH 6.8 phosphate buffer.

The drug content was determined using standard calibration curve [13, 14]
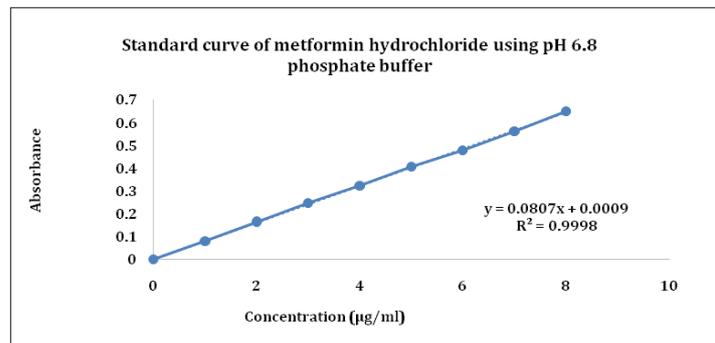

Fig. 1: Standard curve of metformin hydrochloride

In vitro dissolution study

The *in vitro* dissolution study of matrix tablets of metformin hydrochloride was performed using USP type II dissolution apparatus (LABINDIA) at a rotational speed of 50 rpm. In order to simulate gastrointestinal environment, the tablets were subjected to different dissolution media. The dissolution medium used were 900 ml of 0.1(N) HCl acidic buffer of pH 1.2 buffer for first two hours and then pH 6.8 phosphate buffer for next ten hours. The dissolution medium was maintained at a temperature of 37±0.5 °C. At predetermined time intervals, 5 ml of the sample solution was withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium to maintain sink conditions. The collected samples were filtered through a 0.45 μm membrane filter and the drug content in each sample was analyzed by measuring absorbance at 233 nm after suitable dilution using UV-spectrophotometer (SHIMADZU UV 1800). Cumulative percentage of drug release was calculated using equation obtained from a calibration curve [14, 17].

In vitro drug release kinetic study

To study the release mechanism of metformin hydrochloride from the sustained release matrix tablets, the invitro drug release data were fitted to the following the mathematical models [3, 4, 16].

- Zero order release model $Qt = Q_0 + K_0 t$

- First order release model $\log C = \log C_0 + Kt/2.303$

- Higuchi's model $Qt = K_h t^{1/2}$

- Kors Meyer–Peppas model $Qt/Q\alpha = K_p t^n$

- Hixon-Crowell cube root model $(W_0^{1/3} - W_t^{1/3}) = K_h t$

Where Q_0, Qt and $Q\alpha$ are the amounts of drug dissolved initially, at time t and at time infinite. C_0 and C are the concentrations of drug initially and at time t, W_0 and W_t are the amounts of drug in the pharmaceutical dosage form initially and at time t and K0, K1, K_h and K_p refer to the rate constants obtained from the linear curves of the respective models. n is the diffusional exponent that characterizes the mechanism of drug release. The values of the coefficient were calculated using regression analysis between $\log Qt/Q\alpha$ and log time. The diffusional exponent n value was obtained from the slope of the regression equation and K_p was calculated from antilog of the intercept value.

If the value of n for a cylinder is<0.45 it suggests the Quasi Fickian release (diffusion controlled), if n=45 it suggests Fickian diffusion, if 0.45<n<0.89 it suggests anomalous diffusion or non–Fickian release (diffusion and polymer relaxation), if n=0.89 it suggests Case II release (only relaxation and swelling) and IF n>0.89 it suggests super Case II release (relaxation and erosion) for swellable systems. For cylindrical systems like tablets, the n values of 0.45 and 0.89 represent pure diffusion or erosion release respectively [4, 16].

RESULTS AND DISCUSSION

Characterization of powder

For all the formulations the lubricated blend was evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and Angle of repose and their values were shown in table 2. The bulk densities and tapped densities were 0.77±0.01 to 0.80±0.03 g/cm3 and 0.87±0.02 to 0.95±0.01 g/cm3 respectively. Powder blend indicated fair to passable flow properties at the beginning and improve finally after increasing the concentration of lubricant. The values of angle of repose ranging from 27.65 °C to 38.29 °C. The Carr's compressibility index range for all the formulations were found to be 11.49% to 16.13%, which indicates that the powder mixture has good flow properties. Hausner's ratio was also calculated, the ration was ranged between 1.12 and 1.23.

Evaluation of physical parameters

By wet granulation technique Sustained release matrix tablets of metformin hydrochloride were prepared. Total seven formulations were prepared. The tablet weight variation, hardness, friability and content uniformity for each formulation are shown in table 3. The weight variation test indicated that the percentage deviation of all tablet formulations was found to be within pharmacopeial acceptable limit. The hardness of all the tablets was within the range of 5.65±0.43 to 6.59±0.37 kg/cm2. The percentage weight loss in the friability test was found to be below 1 % in all the cases indicated that all the tablets had good mechanical strength. The drug content in all the batches was determined by measuring absorbance of sample at 233 nm using double beam UV spectrophotometer (LAB INDIA). The content uniformity among different formulations was found to be higher and the drug content was more than 98% which indicates uniform drug distribution in all the formulations.

Table 3: Micromeritic properties of lubricated blend of all formulations

Formulation	Bulk density (g/cm³)*	Tapped density (g/cm³)*	Compressibility index (%)	Hausner's ratio	Angle of repose (°C)
F1	0.78±0.02	0.93±0.01	16.13	1.19	36.86
F2	0.79±0.01	0.90±0.03	12.22	1.23	38.29
F3	0.78±0.02	0.90±0.02	13.33	1.15	34.99
F4	0.80±0.03	0.95±0.01	15.79	1.19	35.94
F5	0.78±0.01	0.90±0.02	13.33	1.15	33.02
F6	0.78±0.02	0.92±0.01	15.22	1.17	32.00
F7	0.77±0.01	0.87±0.02	11.49	1.12	27.65

***All values are expressed as mean±SD (Standard deviation), n=3

Table 4: Physical properties of metformin hydrochloride sustained release matrix tablets of all formulation

| Formulation	Weight variation±SD (mg)	Hardness±SD (kg/cm²)	Friability (%)	Content uniformity (%)
F1	850.52±2.58	5.65±0.43	0.78	98.96
F2	850.35±2.47	6.32±0.46	0.65	99.02
F3	849.79±2.32	6.45±0.42	0.62	99.56
F4	850.30±1.97	6.59±0.37	0.54	100.56
F5	850.36±1.03	5.90±0.58	0.81	99.98
F6	850.86±2.52	6.00±0.59	0.89	101.23
F7	850.44±0.76	6.55±0.35	0.48	100.05

In vitro dissolution study

Release profile of Metformin hydrochloride from the matrix tablets was studied for first two hours in pH 1.2 buffer and the next ten hours in pH 6.8 phosphate buffer. Total seven formulations were made with HPMC K4M alone and combination of xanthan gum with HPMCK4 in different ratios [15]. The results of dissolution studies indicated that the first four formulations with hydrophilic polymer, HPMC K4M alone released 43.68%, 42.84%, 37.80% and 33.88% of drug at the end of 2 h and 71.683, 66.922 and 64.962% of drug at the end of 6 h. Formulations containing HPMCK4M in combination with Xanthan gum released 33.321, 30.241 and 27.721 % at the end of 2 h and 99.124, 100.524 and 101.084 % at the end of 12 h. Marketed formulation Bigomet 500 SR tablet from Aristo Pharma showed 23.24% at 2h and 98.48% at 12h. The comparative dissolution profile of all the formulations is given in fig. 1. The results shown in fig. 1 indicate that the release rate of metformin hydrochloride from all the sustained release matrix tablets was dependent on concentration of release retardant contained in the tablet. The drug release rate was decreased from the tablets as the concentration of release retardant was increase. HPMC K4M alone could not control the release of metformin hydrochloride from the tablets because burst release was observed due to high dose of drug. Hydroxyl propyl methyl cellulose could control the drug release when combined with high molecular weight xanthan gum up to 12 h. This may be due to the formation of thick gel layer around the tablets by quick hydration of xanthan gum. These results indicated that the Xanthan gum could control the release of metformin hydrochloride up to 12 h. When it combined with hydroxy propyl methyl cellulose (semi synthetic). Following graphs represents the drug release kinetics.

Table 5: Zero order drug release

Time (h)	Cumulative % drug release						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
2	43.681	42.841	37.801	33.881	33.321	30.241	27.721
4	54.882	55.722	49.842	47.322	44.801	46.202	45.362
6	71.683	71.683	66.922	64.962	63.842	62.722	62.442
8	90.443	88.483	82.603	82.323	80.083	78.963	80.643
10	99.124	97.724	94.644	93.524	91.844	91.844	95.204
12	101.364	100.524	103.044	99.964	99.124	100.524	101.084
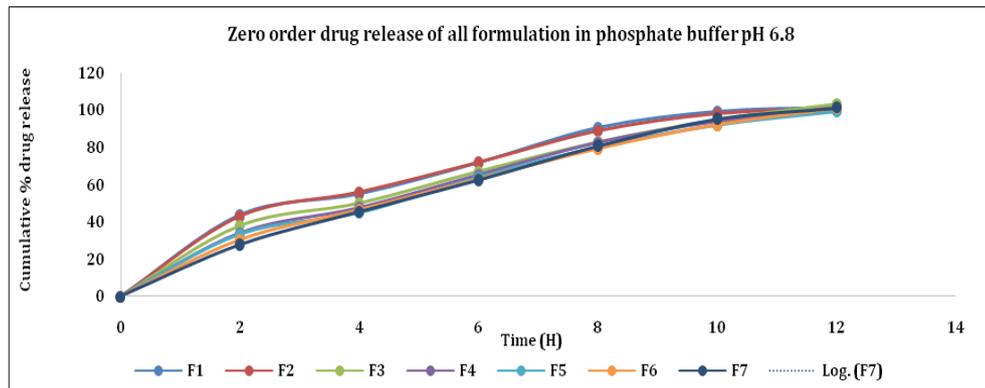
Fig. 2: Plot of zero order drug release

Table 6: First order drug release

Time (h)	Log % drug remaining						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
2	1.805	1.810	1.837	1.857	1.860	1.875	1.886
4	1.737	1.731	1.769	1.784	1.799	1.791	1.795
6	1.610	1.610	1.650	1.665	1.674	1.682	1.684
8	1.402	1.429	1.501	1.504	1.529	1.540	1.523
10	1.257	1.284	1.338	1.356	1.381	1.381	1.328
12	1.210	1.228	1.171	1.240	1.257	1.228	1.216
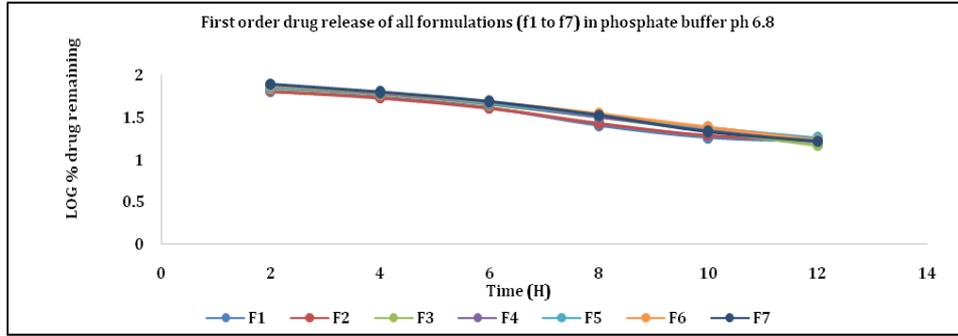
Fig. 3: Plot of first order drug release

Table 7: Higuchi plot

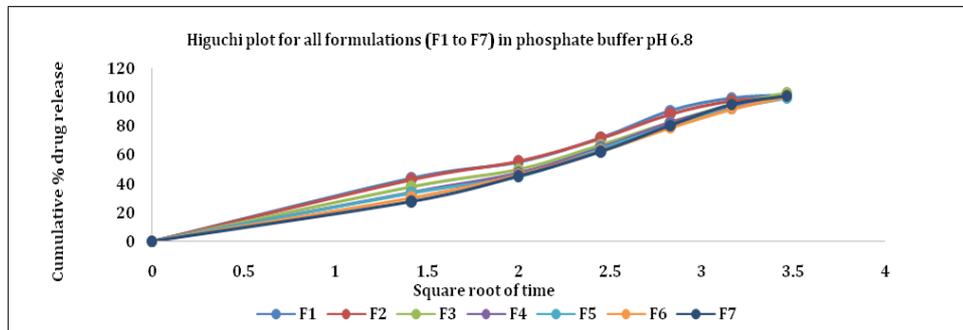| Sqrt time	Cumulative % drug release						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1.414	43.681	42.841	37.801	33.881	33.321	30.241	27.721
2	54.882	55.722	49.842	47.322	44.801	46.202	45.362
2.449	71.683	71.683	66.922	64.962	63.842	62.722	62.442
2.828	90.443	88.483	82.603	82.323	80.083	78.963	80.643
3.162	99.124	97.724	94.644	93.524	91.844	91.844	95.204
3.464	101.364	100.524	103.044	99.964	99.124	100.524	101.084

Fig. 4: Higuchi plot for all formulations

Table 8: Peppas plot for all formulation (F1 to F7) in phosphate buffer pH 6.8

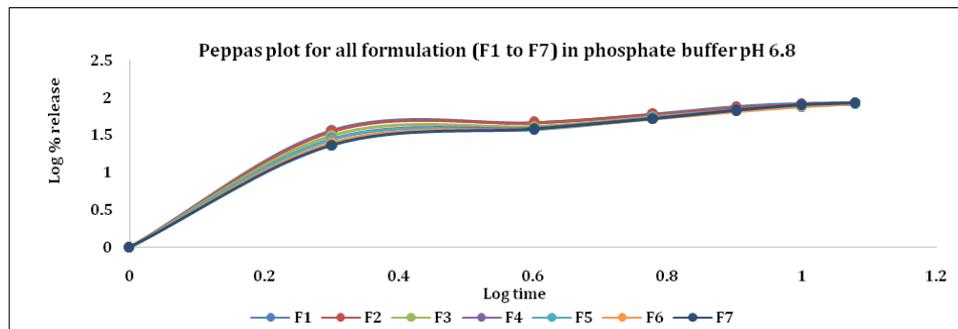| Log time	Log % drug release						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
0.301	1.557	1.549	1.494	1.447	1.439	1.397	1.360
0.602	1.656	1.663	1.614	1.592	1.568	1.581	1.573
0.778	1.772	1.772	1.742	1.729	1.722	1.7146	1.712
0.903	1.873	1.864	1.834	1.832	1.820	1.814641	1.823
1	1.913	1.907	1.893	1.888	1.880	1.880266	1.895
1.079	1.923	1.919	1.930	1.917	1.913	1.919486	1.921

Fig. 5: Peppas plot for all formulations

Table 9: Comparative dissolution study with BIGOMET SR500 tablet (Marketed product)

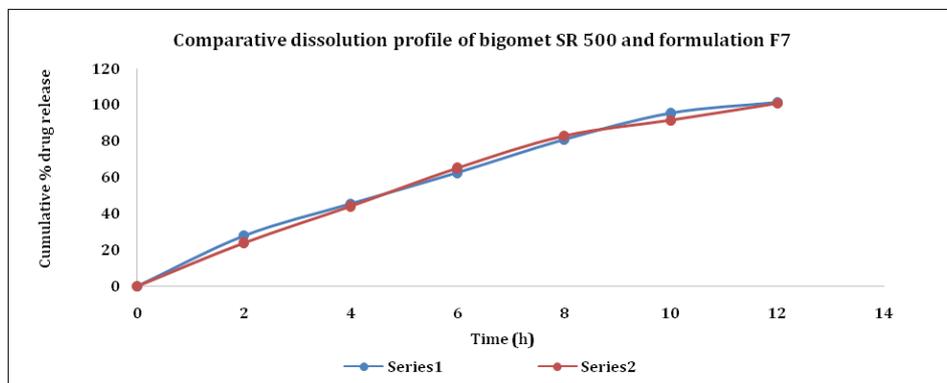| Time (h)	F7	BIGOMET SR 500
0	0	0
2	27.72122525	23.80105198
4	45.36200495	43.96194307
6	62.4427599	64.96287129
8	80.64356436	82.60365099
10	95.20420792	91.28403465
12	101.0844678	100.5244431

Fig. 6: CDP of bigomet SR 500 v/s formulation F7

The similarity factor (f2) as defined by FDA is the logarithmic reciprocal square root transformation of sum of squared error and is a measurement of the similarity in the percentage (%) dissolution between the two curves [3, 4].

$$f2 = 50 \log \{[1 + 1/n \sum_{n=1}^{n} (R_t - T_t)^2]^{0.5} * 100\}$$

Results of similarity factor (f2) is 55%

Where, f_2 is similarity factor, n is the number of observations, wt. is optional weight, R_t is average percentage drug dissolved from reference formulation and T_t is average percentage drug dissolved from test formulation.

The difference factor f1 calculates the percent (%) difference between the two curves at each time points and is the, measurement of the relative error between the two curves:

$$f1 = \{[\sum_{t=1}^{n} |R_t - T_t|]/[\sum_{t=1}^{n} R_t]\} * 100$$

Results of difference factor (f1) is 3.5%

CONCLUSION

Sustained release matrix tablets of metformin hydrochloride were prepared using HPMCK4M alone and in combination with Xanthan gum by wet granulation method. The results of the present study demonstrates that the HPMC K4M alone could not control the metformin hydrochloride release effectively for 12 h, whereas when combined with Xanthan gum and it could control the release of metformin hydrochloride from their matrices. It is concluded that sustained release of metformin hydrochloride over a period of 12 h was obtained with formulation (F5, F6 and F7) containing Xanthan gum and HPMCK4. Out of these three formulation F7 shows the best results. Both physical parameters and drug release kinetics showed satisfactory result in formulation F7. The drug release mechanism from the matrix tablets follows Fickian diffusion with first order kinetics. The comparative dissolution profile shows satisfactory results of similarity and difference factor of test product against the reference sample. Thus, Sustained release matrix tablets of metformin hydrochloride can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional metformin hydrochloride tablets. *In vivo* study of test product needs to be performed in future to study the *in vivo in vitro* correlation ship of test sample.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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