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Formulation and Evaluation of Gastric Floating Matrixtablets of Metformin Hydrochloride Using Pectin and Xanthan

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ABSTRACT

The present study is about the gastric floating matrix tablets prepared to increase the bioavailability of Metformin HCl with xanthan and pectin. Metformin HCl is anti-diabeticbiguanide with poor bioavailability and with absorption window at the upper part of gastro intestinal tract.Floating matrix tablets where prepared using different ratios of xanthan and pectin i.e. at 1:1, 1:2, and 1:5, at 2:1 and 5:1. Floating is achieved by adding sodium bicarbonate as a gas generating agent. HPMC K4M was also used in equal proportion in all the formulations. The floating lag time of the formulations F3 and F4 where rapid and are 2 min. 56 sec and 2 min. 48 sec. respectively. Formulation F3 had an optimum release of 100.1% drug release at 12 hrs. All the formulations had diffusion and they had better controlled efficiency in combination instead of individual concentrations.

Keywords: Pectin, Xanthan, Floating drug delivery systems, HPMC, MetforminHCl

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INTRODUCTION

Controlled release dosage forms have been extensively studies for the past few decades, these formulations are prepared to minimize the dosing frequency of drugs having frequent administration,low biological half life,to enable better dosing pattern with patient compliance and convenience. They are prepared to release the drug at a constant predetermined rate for a specified period of time and hence can exhibit better therapeutic results. Inspite of an effective controlled release system the drugs having absorption window in the stomach or upper part of small intestine and the drugs with low solubility at higher pH will have poor bioavailability[1]. This is because of the short transit time for the drug through upper parts of gastrointestinal tract.Hence gastro retentive drug delivery systems were developed for such drugs to retain in stomach or in upper small intestine until the drug is completely released for the intended period with increased bioavailability. Gastro retentive drug delivery systems enable greater and prolonged therapeutic effect with less frequent administration of doses, provide more effective treatment,solve local stomach complications, reduce the deterioration of drug at higher pH, thus giving increased gastric retention time.Over the last few decades various approaches have been developed to increase the retention of oral dosage forms in the stomach, like floating systems, bioadhesive systems, swelling and expanding systems, modified-shape systems,and high density systems [1].

Floating drug delivery systems (FDDS) have the capacity to float on gastric contents over a prolonged period of time. Prolonged retention of these delivery systems in stomach is due to a gas generating agent which enables the delivery system to float by decreasing the density and ensures the release of drug slowly at a controlled manner at predetermined rate. Based on the mechanism of buoyancy, two distinctly different technologies, non-effervescent and effervescent systems, have been utilized in the development of FDDS. In non effervescent systems intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms, in addition the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier. In effervescent systems a gas generating agent usually sodium bicarbonate or sodium carbonate is mixed with matrices prepared with swellable polymers, when the systems comes in contract with gastric fluids, the carbon dioxide is liberated by the acidity of gastric contents and the gas is entapped in the viscous hydrocolloid. Thus produces an upward motion of the system maintaining buoyancy. Floating drug delivery systems are retained in the stomach for a prolonged period of time by virtue of their floating properties. However the presence of food, is the most important factor affecting floating and increase Gastric Residence Time (GRT) of the delivery system. GRT is prolonged after a meal or fed state and it is shorter in fasting conditions[2]. Prolongation of the GRT by food will maximize drug absorption from a FDDS, longer residence at the most favorable sites of absorption will have increased dissolution of drug with absorption and hence greater bioavailability.

Metformin HCL is orally administered biguanide, which is widely used in the manifestation of type-2 diabetes, a common disease that combines defects of both insulin secretion and insulin action [3]. It improves hepatic and peripheral tissue sensitivity to insulin without the problem of serious lactic acidosis commonly found with its analogue, phenformin. It has three different actions, it shows the absorption of sugar in small intestine, it also stops liver from converting stored sugar into blood sugar, and it helps body use of natural insulin more efficiently. It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract and absolute bioavailability of a single 500 mg

dose is reported to be 50-60% [3]. An obstacle to more successful use of metformin therapy is high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea and diarrhea that especially occur during the initial weeks of treatment. Also the compound has relatively short plasma elimination half life of 1.5 to 4.5 [3]. Side effects and need for administration of two or three times per day when larger doses are required can decrease patient compliance. Sustained release formulations that would maintain plasma levels of drug for 8 to 12 hrs might be sufficient for once daily dosing for metformin. FDDS products with sustained release are needed for metformin to prolong its duration of action and to improve patient compliance [3]. Thus in the present study FDDS is prepared using pectin and xanthan as gelling hydrocolloids for Metformin HCl.

MATERIALS AND METHODS

Metformin HCl and HPMC K4Mwere obtained as gift samples from M/s Micro labs, Bangalore, India. Xanthan was procured as gift sample from M/s Unichem Laboratories, Goa, India. Sodium bicarbonate, Pectinwas purchased from LobaChemie, Mumbai, India, Where as Magnesium stearate and Talc were purchased from S.D. Fine Chemicals limited, Mumbai, India. All other chemicals and reagents used were of analytical grade and they were in good condition.

Experimental

Preparation of Floating Matrix Tablets

Formulations with compositions as given in Table 1 were prepared after initial trials. All the ingredients except xanthan and pectin were optimized and hence maintained constantly in all the formulations, different ratios of xanthan and pectin were used in the prepared formulations in such a way that overall tablet weight remains constant. The preparation of tablets is by wet granulation technique using 70% Isopropyl alcohol as granulating agent. All the ingredients, previously passed through sieve no. 60 were weighed except magnesium stearate and talc, and were mixed by geometrical dilution method to get uniform blend. The uniform blend was granulated using the granulating agent, the wet mass was passed through sieve no. 10 and the wet granules were dried at 50° C until residual moisture content of 2-3% w/w. The dried granules were passed through sieve no. 24 to make uniform sized granules, mixed with lubricants, magnesium stearate and talc. The granules equivalent to 500 mg of drug were weighed and compressed using sixteen station cadmach rotary punching machine, with caplet tooling, compression force was adjusted to obtain hardness in the range of 6-8 kg/cm^2.

Evaluation of Prepared Floating Tablets

All the prepared formulations were evaluated for hardness, weight variation, friability, drug content uniformity, floating lag time, duration of floating, *in vitro* dissolution studies and the results were as given in Table 2.

Hardness, Friability and Weight variation

Hardness of the prepared floating tablets wasdetermined using Monsanto Hardness tester. Weight variation was determined by weighing 20 tablets using an analytical balance and the deviation of individual tablet from the average weight of the tablets was determined. The friability was evaluated with 10 tablets by using Roche friabilator. The tablets were weighed initially and they were dropped from a height of 6 inches in Roche friabilator by setting a rotation of 25 r.p.m for 4 minutes. After 100

revolutions the tablets were dedusted and weighed for the loss in tablet weight to calculate the friability.

Drug content estimation

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added to 100 ml of 0.1 N hydrochloric acid, stirred for 30minutes. The solution was filtered through a 0.45 µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 232 nm using Systronics UV-Visible Spectrophotometer (Model-117).

Floating time and Floating lag time

In vitro buoyancy was determined by placing tablets in a beaker containing 0.1 N Hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time for which the dosage form constantly remained on the surface of medium was determined as the total floating time or duration of floating time [Fig. 1 and Fig. 2].

In Vitro Dissolution of Floating Tablets

Dissolution test was carried out using USP type-II (Paddle) dissolution test apparatus of model Disso 2000 of M/s Lab India at a stirring rate of 50 rpm., 900 ml of 0.1 N HCl (pH 1.2) was used as dissolution medium, maintained at 37 ± 0.5^{o} C. A 5 ml of sample volume was withdrawn periodically, appropriately diluted and analysed using systronics UV-Visible Spectrophotometer at 232 nm, 5 ml volume of fresh 0.1 N HCl maintained at the temperature of the dissolution basket was replaced after each sampling. Cumulative % drug released of all the formulations (Table 3 and Fig. 3) were determined and the data was fitted to popular mathematical models to know the drug release kinetics.

RESULTS AND DISCUSSION

Gastric floating matrix tablets were prepared by effervescent method using sodium bicarbonate as gas generating agent to increase gastric retention time of the drug to enhance its absorption and bioavailability. The effect of natural food grade polymers [4,5,6], such as xanthan and pectin on the floating and drug release were studied. Hence in the present study seven formulations were prepared according to the combinations given in the Table 1 after few preliminary studies for optimizing the floating time. Once floating is optimized the same concentration is used in all the formulations at different natural polymer combinations. The prepared tablets were then evaluated for tablet characteristics, floating lag time, total floating time and *in vitro* dissolution.

Hydro dynamically balanced single unit matrix floating tablets were prepared and they were evaluated for hardness, all the prepared formulations were in between 6-8 kg/cm^2. Thus the tablets found to be of good tensile strength to withstand the handling stress without break. All the formulations exhibited a weight loss of less than 1% and the loss was in the range of 0.14 to 0.76 %.It ensures that the tablets can withstand mechanical impacts during packing, transportation and other processing operations. There was no deviation of the tablet weights from the average weight beyond the pharmacopoeial standards. All the floating tablets weighed between 890.9 to 893.2 mg and none of the tablets deviated from the 5% allowance according to USP.

The drug content was found to be within the labeled amount and floating lag time, floating duration was determined by immersing the prepared floating tablets in a 500 ml simulated gastric fluid of pH 1.2 maintained at temperature of 37±0.5°C. All the tablets showed a floating lag time of 2 min. 48 sec. to 7 min. 21 sec. and total floating time of more than 24 hrs as shown in Fig. . The floating of prepared matrix tablets may be due to the viscous hydrocolloid formed immediately after coming in contact with aqueous medium by rapid hydration of the polymer and entrapping the gas which alters the density of the tablets. The prepared floating tablets were intact and had more than 24 hrs of buoyancy.

The prepared floating tablets F1 to F7 has different ratios of xanthan and pectin as given in Table 1, Formulation F1 is without pectin and similarly F7 is without xanthan. Other formulations were at the ratio of 1:1 (F4), 1:2 (F3, F5), 1:5 (F2, F6), in F4 both xanthan and pectin were at the same concentration. In formulation F2 and F3 xanthan and pectin were at a ratio of 5:1 and 2:1 respectively. Whereas F5 and F6 were prepared with pectin and xanthan at a ratio of 2:1 and 5:1 respectively. All the other ingredients were constant and the weight of the tablets was also kept constant. The formulations F3 and F4 had a good floating lag time of 2 min. 56 sec. and 2 min. 48 sec. respectively and with total floating time of more than 24 hrs. This may be due to higher xanthan concentrations which enabled the tablets to swell and entrap the gas generated efficiently. All other prepared tablets also had fair floating lag time except F7 with 7 min. 21 sec and it may be due to insufficient swelling and gelling property of pectin.

The in vitro dissolution data gave us more insight on the swelling and drug release capabilities of the selected two natural polymers. Formulation F1 released 99.6% in 8 hrs and more than 90% was released in 7 hrs, this may be due to lack of pectin in the formulation. As pectin concentration is increased from F2 to F4 along with xanthan the drug release was controlled and extended upto 12 hrs with 99.9, 100.1 and 100.8% respectively. Similar results were seen in other formulations, F7 showed a drug release of 99.9% within 6 hrs. This probably due to lack of enough gelling strength of pectin to control the drug release, xanthan at the same concentration in F1 could able to control up to 8 hrs and has better gelling strength. Formulations F5 and F6 with a decreasing and increasing concentration of xanthan and pectin respectively showed a drug release of 98.9% in 9 hrs and 100.4% in 8 hrs respectively. The neither xanthan nor pectin could control the drug release when they are alone, but when they are in equal or near to the equal ratio then they exhibited better controlling of the drug. Formulation F3 with 2:1 ration of xanthan and pectin was the most efficient formulation which sufficiently controlled the drug release till 12 hrs. The next best formulation was found to be F4 with 10 hrs. All the formulations in general had good control on the drug release this can be attributed partly to the concentration HPMC K4M in all the prepared formulations. When the dissolution data was fitted to popular mathematical models like zero order, first order, Higuchi and Hixon-crowell then they were found to exhibit similar mechanisms except in F7. F7 showed first order release with erosion, all other formulations showed zero order diffusion.

CONCLUSION

Based on the dissolution profiles the formulations can be arranged in the following order of their controlling efficiency as F3>F4>F2>F5>F1>F6>F7. Thus floating matrix tablets of xanthan and pectin can control the drug release and can reduce the fluctuations in plasma concentrations. However they are more effective in combination rather than alone, this can be due to the compensation of the deficiencies of each other to show a combined effect.

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Table 1: Composition of different floating matrix tablets of Metformin HCl

Ingredients (mg per tablet)	Formulation code						
	F1	F2	F3	F4	F5	F6	F7
Metformin HCl	500	500	500	500	500	500	500
Xanthan gum	150	125	100	75	50	25	0
Pectin	0	25	50	75	100	125	150
HPMC K4M	50	50	50	50	50	50	50
Sodium bicarbonate	130	130	130	130	130	130	130
Magnesium stearate	7	7	7	7	7	7	7
Talc	5	5	5	5	5	5	5
Total weight	892	892	892	892	892	892	892

Fig. 1: Before floating

Fig.2: After floating

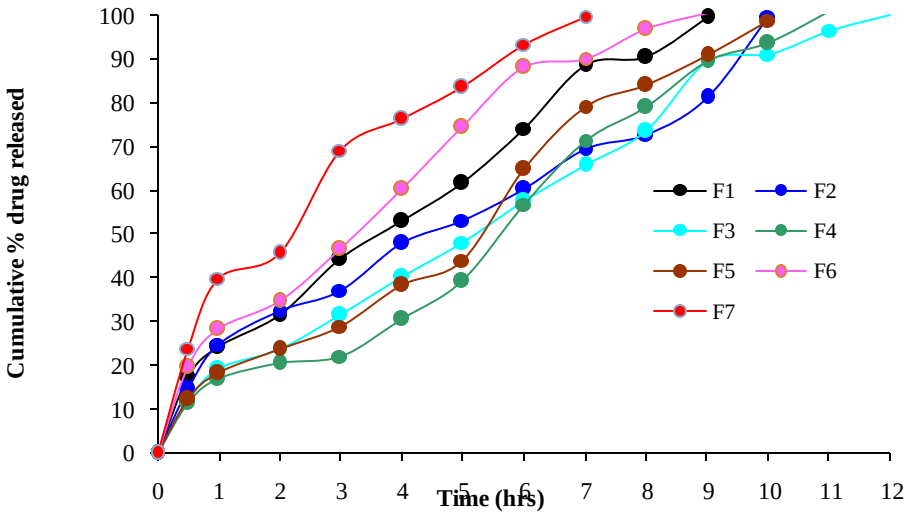

Fig. 3: Dissolution profiles of floating matrix tablets of Metformin HCl

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Table 2: Tablet characteristics of prepared floating matrix tablets (n=3)

Formulation	Weight (mg)	Drug content (%)	Hardness (Kg/cm^2)	Friability	Floating lag time	Duration of floating(Hrs)
F1	891.4±0.99	98.89±0.41	6-8	0.34	3 min 42 sec	>24 hrs
F2	890.9±1.12	97.69±1.98	6-8	0.21	4 min 09 sec	>24 hrs
F3	892.3±0.77	100.27±0.57	6-8	0.14	2 min 56 sec	>24 hrs
F4	893.2±0.12	99.79±0.51	6-8	0.57	2 min 48 sec	>24 hrs
F5	891.9±1.14	99.65±0.52	6-8	0.37	3 min 18 sec	>24 hrs
F6	890.9±0.94	97.56±1.73	6-8	0.22	3 min 52 sec	>24 hrs
F7	892.1±1.21	99.92±0.25	6-8	0.76	7 min 21 sec	>24 hrs

Table 3 Cumulative % drug release of prepared floating matrix tablets (n=3)

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
0.5	17.21±1.02	14.53±1.62	11.7±1.71	11.31±1.35	12.17±1.22	19.72±1.12	24.01±1.45
1.0	24.26±0.99	24.83±1.92	19.19±1.22	16.99±1.51	18.15±1.64	28.26±1.58	39.93±1.22
1.5	31.72±1.58	32.69±1.35	23.59±1.73	20.42±1.41	23.59±0.52	34.79±1.26	45.74±1.57
2.0	44.43±1.29	37.18±1.17	31.62±1.27	22.07±1.2	29.03±1.78	46.47±1.51	69.27±1.42
3	52.99±1.18	47.87±1.50	40.17±1.64	30.52±1.42	38.35±1.27	60.15±1.14	76.33±1.33
4	61.72±1.92	53.15±1.82	48.17±1.58	39.34±1.23	44.05±1.58	74.54±1.27	83.65±1.22
5	74.22±1.52	60.42±1.26	57.43±1.88	56.90±1.03	64.77±1.28	88.16±1.21	93.4±1.98
6	88.61±1.48	69.73±1.61	65.8±1.48	71.46±1.77	79.27±1.58	90.18±1.42	99.91±1.22
7	90.42±1.22	72.84±1.81	73.57±1.55	78.92±1.25	83.93±1.64	96.86±1.58	
8	99.61±1.25	81.21±1.77	89.44±1.41	89.47±1.17	90.92±1.33	100.46±1.91	
9		99.9±1.41	91.22±1.92	93.67±1.51	98.95±1.92		
10			96.62±1.14	100.87±1.23			
12			100.1±1.35				

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