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ORAL SUSTAINED DELIVERY OF GASTROPROKINETIC DRUG MOSAPRIDE CITRATE FROM FLOATING MATRIX TABLETS-FORMULATION AND IN VITRO CHARACTERIZATION

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ABSTRACT

Floating drug delivery systems can significantly prolong the gastric residence time of drug providing continuous input and greater therapeutic efficacy of the drug. The aim of the present study was to formulate effervescent floating tablets of Mosapride citrate by direct compression method; using hydrophilic swellable carriers such as polyethylene oxide PEO WSR 1105, PEO WSR 301and PEO WSR 303 as a release retarding agent, Sodium starch glycolate as swelling enhancer and sodium bicarbonate as a gas generating agent. The effervescent floating tablet formulations were evaluated for physicochemical properties, in vitro buoyancy, drug release, rate order kinetics and stability studies. Result revealed that, F11 (WSR 303, 30 %) was selected as an optimized formulation based on its 12 hr drug release (80.3% at the end of 12 hr) with minimal floating lag time(0-0.2min), maximum total floating time (> 12 hr.) The optimized formulation followed zero order rate kinetics, non- Fickian diffusion mechanism. Furthermore, The accelerated stability studies, at 40^0 C / 75% RH, of the optimized formulation was carried out for three months and no significant changes were observed.

KEYWORDS: Mosapride citrate; effervescent Floating tablets; Polyethylene oxide; Release kinetics.

INTRODUCTION

Oral route is by far the most convenient and preferable for drug delivery due to its ease of administration, low cost of therapy, better patient compliance and flexibility in

formulation(Ummadi et al., 2013**).** However, this route has certain problems such as unpredictable gastric emptying rate, short gastro-intestinal transit time (8-12 hr) and existence of an absorption window in the gastric and upper small intestine for several drugs leading to low and variable oral absorption over shorter period of time(*Agyilirah* et al., 1991; *Hoffman* et al., *1983)*. Thus to increase the gastric retention time (GRT) of drugs, gastroretentive dosage forms (GRDFs) are developed which can remain in the gastric region for several hours(Garg et al, 2008). Various approaches are available to increase gastric retention time (GRT) of drugs in the stomach which includes floating systems(*Menon* et al.,1994; Whitehead et al.,1998), swelling and expanding (*Deshpande* et al., 1996; 1997) and other delayed gastric emptying devices (*Chawla* et al., 2003). Effervescent floating drug delivery systems generate gas (CO2),thus reduce the density (less than 1.0g/ml) of the system and remain buoyant in the stomach for a prolonged period of time and release the drug slowly at a desired rate, so that improves the bioavailability of the drug (Shah et al., 2011; Mayavanshi et al, 2008). Mosapride citrate is a prokinetic drug help to speed up the passage of food through the stomach, used for the treatment of acid reflux, non-ulcer dyspepsia, gastroparesis, also help with symptoms of bloating and feeling sick and gastric irritable bowel syndrome (Patel et al., 2007). In addition to these actions it has an anti-emetic action. The marketed conventional release products need to be given either 5mg or 10mg three times daily. The continuing effort to improve pharmaceutical formulation in order to optimize therapy and patient compliance, various efforts have been tried to develop a modified release.

In the present investigation, effervescent floating tablets of mosapride citrate were formulated to be retained in the stomach. Different concentrations and grades of polyethylene oxides (PEO), such as PEO WSR 1105, PEO WSR 301 and WSR 303 were utilized as swelling agent, as well as release retarding polymers, Sodium bicarbonate was used as gas generating agent which would improve the therapeutic efficacy and patient compliance**.**

MATERIALS AND METHODS

Mosapride citrate was kindly provided by Marcyrl Pharmaceutical Industries (Cairo, Egypt). Polyethylene oxide PEO grades were purchased from Aldrich (Germany). Sodium bicarbonate were from Kahira Pharm. (Egypt).Avicel PH200 (microcrystalline cellulose) was from Fluka (Switzerland). (Aerosil 200) (Degussa, Germany) and magnesium stearate were obtained from (Peter Greven Nederland, Germany). All other reagents and chemicals were of analytical grade.

Tablet Preparation

Each swellable effervescent matrix tablet containing 15 mg of mosapride citrate was prepared by direct compression method, employing different concentrations of water soluble polymer PEO as swelling matrix, sodium bicarbonate as gas generating agent, and sodium starch glycolate (SSG) as a swelling enhancer, Avicel PH200 was selected as filler. The composition of all formulations in their specified ratios as given in Table 1. weighed accurately passed through 425 µm sieve (mesh number 40). The above blend was passed through sieve #18 to break the agglomerates and was further mixed. Blending all ingredients was carried out simultaneously using polyethylene bag, Then, blend compressed using single-punched tablet machine(Single Punch Press Tablet Machine, Stokes-Merrill Model 511-7-A, USA) equipped with 7mm round, flat and plain punch. The force of compression was adjusted so that hardness of all prepared tablets ranged from 5.5-6.5 kg **(**Inez *et al*., 2008).

Evaluation of the prepared tablet mixture

1-Pre-compression evaluation

1.1 Angle of Repose

The angle of repose of powder blend was determined by the funnel method. A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10 gm of sample powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction. The height of the heap was measured by using scale. The value of angle of repose are calculated by using the following equation (Banker *et al*., 1991).

$\tan \theta = H / R$ Where, H and R are the height and radius of the powder cone.

1.2 Compressibility Index

The BD was determined by three tap method. An amount of powder equivalent to 10 g was accurately weighed, placed in a 100 mL measuring cylinder without compaction.Percent compressibility of granules as determined by the following formula (Carr's,1965).

Carr's Index (%)=[(TBD-LBD) x100]/TBD.)

1.3 Haunser's ratio

It is the ratio of bulk volume to tapped volume or tapped density to bulk density, the ratio is an important character to determine the flow property of powder and granules. This can be calculated by the following formula (Carr's,1965).

Hausner's ratio = Tapped density / Bulk Density

2-Post-compression evaluation

2.1-Tablet weight variation

Twenty tablets were selected randomly and weighed individually using Sartorius electronic balance. Average weight was calculated and compared the individual tablet weight to an average. The tablet pass the USP test if no more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit. Kg/cm2 (Castellanos *et al*., 1994).

Calculate the average weight of tablets = Total weight of tablets/ Number of tablets Average weight of tablets (X) = (X1+X2 +X3+…+ X20) / 20.

2.2-Thickness

Ten tablets were taken from each formulation randomly and their thickness was examined with vernier caliper (*Rao et al*., 2009).

The mean ± standard deviation values of thickness were calculated.

2.3-Hardness test

Tablet was placed in contact between the tester plungers, and the handle was pressed using Pharmatest hardness tester, the force of the fracture was recorded. The results were expressed as mean values ± SD (Irene *et al*., 2011**).**

2.4-Friability test

Twenty tablets were weighed accurately and placed in the tumbling chamber (Erweka friability tester) and rotated at 20 rpm for a period of 5 min(100 revolutions). The tablets were removed, dedusted and accurately weighed. The percent weight loss was calculated by using formula given below (Kumar *et al*., 2011**).**

Percent friability = Initial weight of tablets- Final weight of tablets /Initial weight of tablets ×100. (% friability of tablets less than 1% are considered acceptable).

2.5-Content uniformity

Twenty Tablets of each formula were weighed, crushed in a mortar and the weight equivalent to one tablet was transferred quantitatively into 100 ml glass-stoppered volumetric flask and extracted with 0.1N HCl using "temperature-controlled shaking water-bath (Lab-Line, USA) in 37 ±0.5°C °C for 30 min, volume was then completed to the mark and filtered through a cellulose acetate membrane filter (0.45 µm), Further appropriate dilutions were made and the

absorbance of the solution was then measured spectrophotometrically using a UV/Vis double beam spectrophotometer (Shimadzu, Tokyo, Japan) at λmax 272 nm against a blank 0.1 N HCl (Sathiyaraj *et al*., 2011**)**.

2.6-In vitro buoyancy studies

The lag time was inspected visually in beaker containing 100 ml 0.1 N HCl as a testing medium maintained at 37 ±0.5°C °C and the time required for the tablet to rise to the surface and float was determined as floating lag time (Merchant *et al*., 2006).

2.7-Duration of floating

A glass beaker containing 100 ml of 0.1N HCl was taken, in which a tablet was placed for visual observation. The total duration for which a tablet remained buoyant without disintegration was recorded as duration of floatation (including floating lag time). For better floating behavior, small FLT and long floating duration(>12 hours) were required (Shoaib *et al*., 2006).

2.8-Swelling studies

The ability of floating matrix tablets to swell in 0.1N HCl (pH 1.2) medium were determined by swelling them up to their equilibrium**.**The measurement of swelling rates of tablet were determined by placing the weighed tablet matrices (w1) in the basket of dissolution apparatus -I, in 900 mL of 0.1 N hydrochloric acid at 37 ± 0.5°C, rotated at 50 rpm. The tablets were removed periodically from the dissolution medium and blotted with tissue paper to remove the excess water and weighed, the swollen weight (w2). (Chaudhari *et al*., 2008).

Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation : WU% = w2– w1/ w1 × 100.

Where, w1 = initial weight of tablet w2= final weight after swelling of tablet

The mean ± standard deviation values of swelling index were calculated.

2.9-In vitro dissolution study

In vitro dissolution study was performed in USP dissolution apparatus type II (Hanson Research), in 900 mL 0.1 N hydrochloric acid (pH 1.2), maintained at 37± 0.5ºC at a speed of 50 rpm. At suitable time intervals, aliquots (10 mL) were withdrawn and immediately replaced with equal volume of fresh dissolution medium to maintain a constant volume for drug dissolution. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 272

nm using a shimadzu UV/Visible beam spectrophotometer. Cumulative percentage drug release was calculated(Sriamornsak *et al*., 2008; Siepmann *et al*., 2001).

2.10-Stability studies

The ICH guidelines have established that long term stability testing should have done at 25°C ± 2°C and 60% RH ± 5% RH. Stress testing should have done at 40°C ± 2°C and 75% RH ± 5% RH for three month. If significant change occurs at these stress condition, then the formulation should be tested at an intermediate condition i.e. 30°C±2°C and 65% RH±5% RH. The optimized tablets were placed in plastic tubes containing desiccant and stored at ambient humidity conditions, at room temperature(25°C ± 2°C) and oven temperature (40°±2.C).The samples kept for stability were evaluated for the physicochemical parameters appearance, hardness, friability, floating test, drug content and in-vitro dissolution at specified intervals of time(Kulkarni *et al*., 2004).

RESULTS AND DISCUSSION

1. Pre-compression parameters

1.1 Angle of repose (θ)

The values obtained for angle of repose for all formulations were tabulated in Table 2, parameters were within the range from 24°. 30’ to 29°.60’.Study indicated good flow property of the powder blend for direct compression.

1.2 Compressibility index

The values obtained from Compressibility index for all formulations were tabulated in Table 2 Compressibility index value ranges between 12.30% to 16.66% indicating that the powder blend have the required flow property.

1.3 Haunser’s ratio

The ratio was calculated by using bulk density and tapped density data and was found to be between 1.08-1.19 as shown in Table 2 indicating that flow properties of the blends were good.

2-Post-compression evaluation

The results of weight uniformity, thickness, hardness, friability as well as drug content are presented in Table 3.It was observed that all the formulations were obtained in the range, with acceptable weight variations as per USP specifications less than 10 percent difference.

The thickness of the tablets was found to have 2.5 mm to 2.9 mm. Hardness of the tablets was not less than 4kg/cm2 and friability of tablets was found to be <0.5%. The assay of the drug was >96%. Thus, all the formulations were found to be of good quality fulfilling all the official requirements.

2.1 Swelling studies

The swelling studies of the floating tablets were conducted for 12 hr. Swelling index of the all formulations was in the range of 55 -121 %.The results revealed that, the swelling of the floating tablet has been increased as the time proceeds till it reaches to almost saturation at particular time depends upon the type as well as concentration of polymer it has as shown in Fig.1.

2.2 In vitro evaluation

It was observed that the formula F1(10%WSR-1105) failed to float immediately and continuously; moreover, initial burst release with complete drug release in short period of time this may be due to the low concentration and insufficiency of the polymer to form a rigid gel barrier around the tablet ultimately leading to loss of matrix integrity while the tablet prepared with (20% w/w) maintained their matrix integrity, but the release of drug was too rapid.F3 (30% w/w) showed good floating properties and release with this polymer (lag time3-4minutes, duration 12 hr). F4 showed almost no difference. Another grade, PEO WSR301, having higher molecular weight, F5(10% w/w) showed initial burst release with more than 50% of the drug was released in 2hr.F7(30% w/w)showed better buoyancy properties and retarding properties(lag time 0- 0.5minutes), duration 12 hr. F8 showed almost no difference with maximum drug release at 12 hr. Another higher molecular weight of PEO (WSR303) exhibited higher retarding and excellent buoyancy properties than all other formulations. From all the above results it was concluded that the drug retardation is mainly depends on the molecular weight of the polymer which plays a major role in the drug retardation due to enlargement and increase in gel strength, as well as the concentration which induces the formation of a strong viscous gel layer that slowed down the rate of water diffusion into the tablet matrix, which may result in retardation of the drug release. There is however, a maximum concentration beyond which no significant change in release rate occurs, the order of the drug retarding capacity of the polymer F11(PEO -303) > F7(PEO -301) >F3(PEO -1105).

Release kinetics

Data obtained from in vitro dissolution studies were fitted in different models viz.zero order first order, Higuchi model and Korsmeyer- Peppas model to study the drug release kinetics. Results revealed that F1,F2,F5,F6, F9 and F10 followed first order rate kinetics with high regression values, while F3,F4, F7,F8, F11 and F12 followed zero order rate kinetics, It was also noted that the rate order kinetics depends upon the concentration of the polymer, as it increases rate order changed from first order to zero order and the release exponent 'n' was found to be in the range 0.5 and 0.9 indicating 'non-Fickian diffusion' Thus, drug release from matrix tablets depends upon the water penetration rate, swelling of polymeric chain, diffusion and relaxation mechanisms occurs.

Stability studies

The optimized floating tablet (F11) was selected for stability study on the basis of in vitro dissolution studies. The tablets were stored as per stress testing studies for 3 months. The results reveled that, there was no significant change in appearance, floating lag time, drug content, hardness, and in-vitro release.

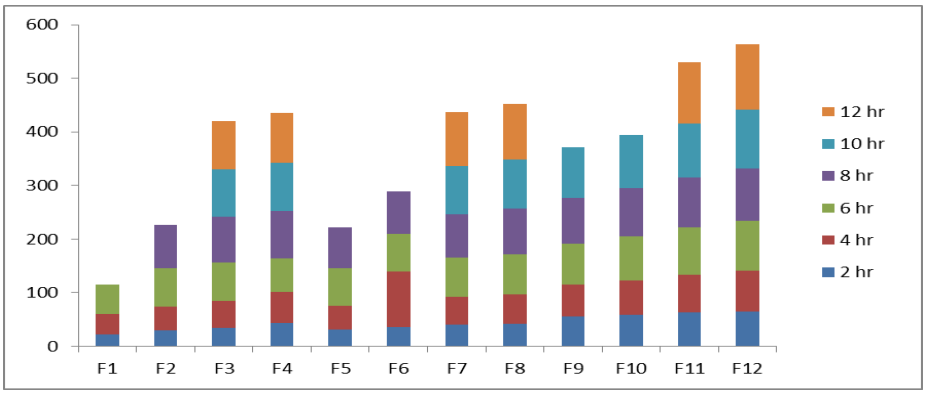

Fig 1: Swelling index of Mosapride citrate - polyethylene oxide formulations.

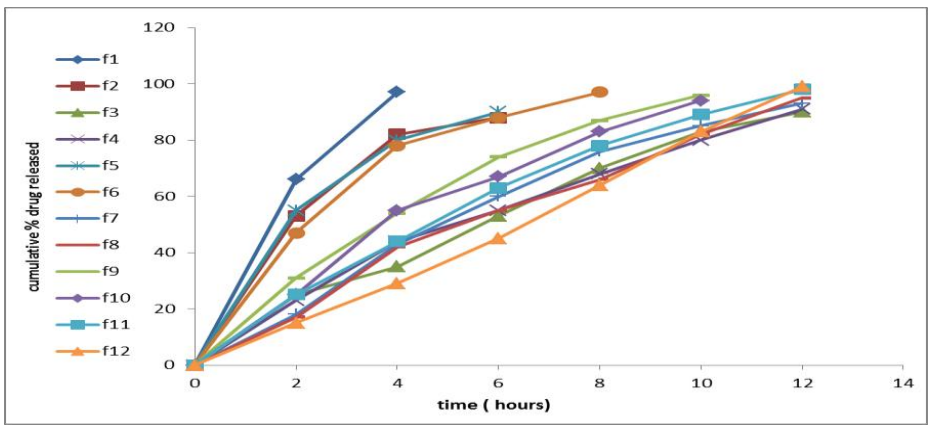

Fig. 2: Dissolution profile of Mosapride citrate- polyethylene oxide formulations.

Table 1: Composition of Mosapride citrate floating tablets.

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Mosapride citrate	15	15	15	15	15	15	15	15	15	15	15	15
PEO WSR 1105	10	20	30	40								
PEO WSR 301					10	20	30	40				
PEO WSR 303									10	20	30	40
NaHCO3	15	15	15	15	15	15	15	15	15	15	15	15
Mg stearate	10	10	10	10	10	10	10	10	10	10	10	10
Aerosol 200	5	5	5	5	5	5	5	5	5	5	5	5
S.S.G	10	10	10	10	10	10	10	10	10	10	10	10
Aviceel200	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight of tablet (mg)	100	100	100	100	100	100	100	100	100	100	100	100

Table 2: Pre-compression parameters.

Formulation Code	Angle of Repose (θ)	Compressibility Index (%)	Haunser's ratio
F1	26° 77	15.67	1.13
10F2	24° 30'	12.30	1.18
F3	25°22'	14.16	1.15
F4	25° 28'	14.48	1.16
F4	28° 56	16.66	1.18
F5	26°54'	15.56	1.13
F6	29° 60'	15.41	1.15
F7	24°36'	13.25	1.14
F8	25°22'	14.16	1.15
F9	29° 87	15.40	1.08
F10	27° 29'	12.45	1.19
F11	24° 30'	12.30	1.13
F12	25° 28'	14.48	1.15

Table 3: Post Compression parameters.

Formulation Code	% Drug Content	% Weight Variation	Thickness (mm) ± S.D	%Friability S.D	Hardness (Kg/Cm2) ± S.D.	Floating lag time (min)	Total Floating time(hr).
F1	98.42	1.5	2.56±0.03	0.39±0.05	4.4±1.1	8-9	> 4
F2	99.48	2.2	2.64±0.03	0.37±0.05	4.3±1.7	7-8	> 6
F3	96.64	1.4	2.91±0.04	0.28±0.06	6.4±1.3	3-4	> 11
F4	99.04	2.1	2.53±0.04	0.26±0.04	5.1±1.5	3-4	> 11
F5	99.32	2.4	2.86±0.02	0.35±0.04	5.6±1.2	0-0.5	> 6
F6	98.38	1.7	2.66±0.02	0.25±0.03	4.3±1.2	1-2	> 8
F7	97.23	1.7	2.56±0.03	0.45±0.04	6.4±1.3	0-0.5	> 11
F8	99.54	2.1	2.64±0.03	0.24±0.04	5.1±1.4	0-0.5	> 11
F9	97.56	1.8	2.76±0.03	0.39±0.05	5.1±1.4	1-2	> 10
F10	99.84	1.6	2.58±0.02	0.34±0.03	5.6±1.2	1-2	> 10
F11	99.91	1.4	2.67±0.02	0.37±0.05	4.5±1.1	0-0.2	> 12
F12	97.46	1.9	2.89±02..	0.24±0.04	6.4±1.3	0-0.2	> 12

CONCLUSION

It can be concluded that the effervescent floating sustained release tablets of Mosapride citrate using hydrophilic polymers of polyethylene oxide different grades with the aim of increasing the MRT in the stomach were successfully formulated. The optimized formula F11 containing Polyox WSR 303 (30 %) showed satisfactory results with respect to floating lag time, total floating duration, swelling ability, followed zero-order kinetic model with non-Fickian diffusion mechanism and was found to be stable at 40-C temperature and 75% RH for 3 months.

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