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Original Article

FORMULATION AND EVALUATION OF PROCHLORPERAZINE MALEATE SUSTAINED RELEASE FLOATING TABLET

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ABSTRACT

Objective: The objective of this study was to formulate once daily sustained oral release floating tablet of prochlorperazine maleate, this floating tablet has many advantages like reduction in dosing frequency, increase bioavailability, enhance patient compliance, and improve drug solubility.

Methods: The prochlorperazine maleate floating tablets were formulated by using hydrophilic swellable polymer and gas generating agent. In this study, 15 formulas were prepared with many variables in order to achieve an optimum dissolution and floating behaviour for the floating tablet. The all prepared formulas were tested for bulk density, tap density, angle of repose, Carr's Index, thickness, weight variation, hardness, friability, drug content, *in vitro* dissolution test, *in vitro* buoyancy, and swelling index.

Results: Formula (F2) that contain 55% (w/w) hydroxypropyl methylcellulose k4M (HPMCK4M), 5 % (w/w) sodium bicarbonate ($NaHCO_3$) have acceptable flow properties and compressibility index and good physical properties with floating lag time (16±0.57) seconds and total floating time (32±0.29) h with 100% release of prochlorperazine maleate at the end of 24 h. Fourier transform infrared spectroscopy (FTIR) study of optimum formula (F2) showed no chemical interaction between the drug and the excipients that used in the formula.

Conclusion: It can be concluded that that the selected formula (F2) can be a promising formula for the preparation of gastro retentive floating drug delivery systems of prochlorperazine maleate.

Keywords: Prochlorperazine maleate, Floating tablet, Sustained release, Hydroxypropyl Methylcellulose k4M (HPMCK4M), Sodium bicarbonate ($NaHCO_3$)

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INTRODUCTION

Oral route of drug administration for the majority of therapeutic applications remains the most favored preference with obvious benefits including ease of administration, flexibility in formulation and patient compliance [1].

Effective oral drug delivery may depend upon the factors such as gastric emptying process, drug release from the dosage form, gastrointestinal transit time and site of drugs absorption [2]. An important factor for a complete drug absorption in the gastrointestinal tract (GIT) is the transition time of the dosage form [3]. Incomplete drug release from the drug delivery system may result from the relatively short gastric emptying time (GET) in humans which is normally about 2-3h, leading to reduced administered dose efficacy [4]. The easily absorbed drugs from the gastrointestinal tract (GIT) and drugs show short half-life are eliminated rapidly from the systemic circulation [5]. To overcome this physiological problem, many types of research and patent literature illustrated attempts of creating new dosage forms that are able to prolong the time that required for the dosage form to leave the stomach [6].

Floating drug delivery systems are low-density systems which have the adequate buoyancy to float above the gastric contents and stay for a long period of time in the stomach without affecting the gastric emptying rate" [7].

While the system is floating on the gastric contents, the drug is gradually released from the system at the desired rate and the residual system is emptied out of the stomach. This cause an increased gastric residence time (GRT) and preferable control of the fluctuations in plasma drug concentration [8]. Prolonged gastric retention dosage form improves bioavailability, improves solubility for drugs that are less soluble in a high pH environment (e. g., cinnarizine and chlordiazepoxide), and reduces drug waste [9].

Prochlorperazine, a phenothiazine derivative; it is known as typical antipsychotic medication, whose effect through blocking dopamine receptors. Prochlorperazine and its salts are in general utilised in the avoidance and treating of nausea and vomiting resultant of radiotherapy, chemotherapy, surgery and acute migraine [10]. The half-life of prochlorperazine maleate is 4 to 8 h and has about 12.5% oral bioavailability [11].

The aim of the study was to prepare once daily sustained release of prochlorperazine maleate effervescent floating matrix tablet in an attempt to improve drug solubility, bioavailability and patient compliance.

MATERIALS AND METHODS

Materials

Prochlorperazine maleate was obtained from Furat pharmaceutical industries (Iraq), hydroxypropyl methyl cellulose (HPMC) HPMCK4M, HPMCK15M, HPMCK100M, carbopol 934, carbopol 940, avicel PH 101 (MCC) were obtained from Jiangsu yew pharmaceutical co. limited (china), sodium bicarbonate ($NaHCO_3$) was obtained from Samara drug industry (Iraq), spray dried lactose, talc, magnesium stearate was obtained from Middle east laboratories co limited (Iraq); mannitol was obtained from Provizerpharma (India).

Methods

Formulation of prochlorperazine maleate floating tablet

Different formulas (15 formulas) of prochlorperazine maleate floating tablets were formulated as shown in the table (1). All formulas were compressed into tablets using direct compression method. The previously weighted ingredients (the drug, polymer, diluent and gas generating agent) were passed through sieve

(No.45) together and blended for 15 min in order to achieve a homogenous mixture of powder blend. Then a known weight of the blended powders of different ingredients was mixed with a calculated amount of talc and magnesium stearate powder for 3 min then compressed to tablet by using 9 mm biconcave punch tablet machine [12].

Table 1: Composition of different formulas of prochlorperzine maleate floating tablets

Ingredient(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Prochlorperazine maleate	15	15	15	15	15	15	15	15	15
HPMCK4M	90	110	130	-	-	-	-	-	-
HPMCK15M	-	-	-	90	110	130	-	-	-
HPMCK100M	-	-	-	-	-	-	90	110	130
Carbopol 934	-	-	-	-	-	-	-	-	-
Carbopol 940	-	-	-	-	-	-	-	-	-
$NaHCO_3$	10	10	10	10	10	10	10	10	10
AvicelPH 101 (MCC)	82	62	42	82	62	42	82	62	42
Spray dried lactose	-	-	-	-	-	-	-	-	-
Mannitol	-	-	-	-	-	-	-	-	-
magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1
Total weight (mg)	200	200	200	200	200	200	200	200	200

Ingredients (mg)	F10	F11	F12	F13	F14	F15
Prochlorperazine maleate	15	15	15	15	15	15
HPMCK4M	-	-	110	110	110	110
HPMCK15M	-	-	-	-	-	-
HPMCK100M	-	-	-	-	-	-
Carbopol 934	90	-	-	-	-	-
Carbopol 940	-	90	-	-	-	-
$NaHCO_3$	10	10	5	20	10	10
Avicel PH 101 (MCC)	82	82	67	52	-	-
Spray dried lactose	-	-	-	-	62	-
Mannitol	-	-	-	-	-	62
magnesium Stearate	2	2	2	2	2	2
Talc	1	1	1	1	1	1
Total weight (mg)	200	200	200	200	200	200

Evaluation parameters

Pre-compression parameters

The angle of repose, Bulk density, Tapped density, Carr's compressibility index, Hausner ratio was determined to find the flow of powders during formulation.

Post-compression parameters evaluation

Thickness test

The thickness of tablets was determined using vernier caliper. Three tablets from each formula were used, and average values were calculated±standard deviation (SD)[13].

Hardness test

The hardness of the tablets (Kg/cm^2) was determined using electrical hardness tester. In which three tablets from each formula were tested and the average reading±SD was recorded [14].

Weight variation test

The weight variation of the prepared floating tablet was determined by weighing twenty prepared floating tablets individually, and then calculate its average weight and comparing the weight of each tablet to the average weight. The prepared floating tablets meets the USP test if no more than 2 prepared tablets are outside the ratio limit and if no tablet differs by double the percentage limit, as shown in the table (2):[15].

Table 2: Weight variation according to the USP

Average weight of the tablets (mg)	Maximum difference % allowed
130<	10
130–324	7.5
>324	5

Friability test

Weigh twenty tablets and placed them in the friabilator and the device was rotated at 25 rpm for (4 min). After revolutions, the tablets then de-dusted and weighed again. The acceptable percentage weight loss or % friability should be <1% . The percentage friability was determined by using the following formula: [16].

$$\% \text{ Friability} = \left[\frac{\text{initial weight} - \text{final weight}}{\text{initial weight}}\right] * 100$$

Content uniformity test

Ten tablets of an equal weight of the prepared tablet were selected and powdering using mortar and pestle. Then powder equivalent to the average weight of the prepared tablet was weighed and dissolved in HCl solution (pH1.2).

The solution was filtered and about (1 ml) of the filtrate was appropriately diluted and analysed for prochlorperazine maleate content spectrophotometrically at 254 nm [17].

The requirements for content uniformity of the prepared floating tablet are met if the amount of active ingredient in each tablet lies within the range of 85% to 115% of the label claim and the standard deviation is less than 6% [18].

In vitro buoyancy studies

In vitro buoyancy of the prepared floating tablet was obtained by determine the floating lag time (FLT) and the total floating time (TFT). The test was done by placing the tablet in 100 ml beaker containing HCl solution (pH1.2), and the temperature of the medium is maintained at 37±0.5 °C. The time between the introduction of tablet and its buoyancy in HCl solution (pH1.2) is the floating lag time, while the time during which the tablet remains buoyant in the solution is the total floating time [19].

Swelling index studies

The swelling index of tablets was determined by placing the tablets in 100 ml beaker of HCl solution (pH1.2) and the temperature of the medium is maintained at 37±0.5 °C. And then after 1, 2, 3, 4 and 5 h, each beaker containing tablet was withdrawn and blotted with tissue paper to get rid of the excess water and weighed on the analytical balance. The swelling behaviour of the tablet was determined by measuring the difference in weight of the tablet before and after placing it in HCl solution (pH 1.2). Swelling index was calculated by utilise the following equation [20].

$$\text{Swelling index} = \frac{Wt - W0}{W0} \text{ X } 100$$

Where W_t is the weight of tablet at time t, and W_0 is the initial weight of the tablet.

In vitro dissolution test

In vitro dissolution of the prepared prochlorperazine, maleate tablets were performed utilising USP type II apparatus (paddle) at 37±0.5 °C in 900 ml dissolution medium HCl solution (pH1.2) at 50 rpm. Five milliliters samples were withdrawn periodically at (0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 12, 16, 20, and 24) hours intervals and each sample was substituted with an equal volume of new dissolution medium. Then, the withdrawn samples were filtered and analysed spectrophotometrically at 254 nm. Each test was done in triplicate [21].

Variable affecting prochlorperazine maleate behaviour and release from floating tablets: Effect of polymer type

Five different types of polymers; (hydroxypropyl-methylcellulose K4M (HPMCK4M), HPMCK15M, HPMCK100M, Carbopol 934, and Carbopol 940) in different concentration were utilised to study the influence of polymer type on the floating and drug release properties of prochlorperazine maleate floating tablet as in formulas 1 to 11.

Effect of polymer concentration

Formulas 1 to 9 were made to study the influence of polymer concentration on the floating properties and drug release of prochlorperazine maleate floating tablet in which formulas 1, 2, and 3 contain HPMCK4M 90 mg, 110 mg, and 130 mg respectively, formula 4, 5, and 6 contain HPMCK15M 90 mg, 110 mg, and 130 mg respectively, formulas 7, 8, and 9 contain HPMCK100M 90 mg, 110 mg, and 130 mg respectively.

Effect of the effervescent agent concentration

Formulas 2, 12, and 13 which contain 10 mg, 5 mg, and 20 mg of sodium bicarbonate ($NaHCo_3$) respectively were utilised to study the influence of the concentration of effervescent agent on the release profile and floating properties of floating tablet.

Effect of diluent types

Formulas 2, 14, and 15 were utilised to study the influence of types of diluent on the release profile and floating properties of floating tablet in which avecil PH 101(MCC) in formula 2 was replaced by Spray dried lactose in formula 14, and by mannitol in formula 15.

Drug-excipients compatibility studies

Physicochemical compatibility between prochlorperazine maleate and different excipients were tested using fourier transform infrared spectroscopy (FTIR). The pure drug powder (prochlorperazine maleate) and the optimum formula (F2) were analysed individually by using (Shimadzu 8300, Japan) according to potassium bromide disk method. About 2-3 mg sample was mixed with dried IR grade potassium bromide powder and analysed by FTIR spectroscopy at 4000-400 cm^{-1}[22].

Studies of *in vitro* drug release kinetic

The kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to determine the precise mechanism of prochlorperazine maleate release from the prepared floating tablets, drug release data was analysed according to first order, Higuchi square root, zero order, and Korsmeyer-Peppas models. The criteria for selecting the most suitable model were chosen on the basis of goodness of fit test. The data were treated for regression analysis utilising MS EXCEL statistical function [23].

Statistical analysis

All data were presented as mean±SD. Statistical analysis was performed by applying GraphPad Prism Version 7 by choosing one-way ANOVA, followed by Tukey's test (pairwise comparisons) at 95% significance* ($p<0.05$).

RESULTS AND DISCUSSION

Pre-compression evaluations

The measured values of angle of repose, bulk density, tapped density, Carr's index and Hausner ratio with their corresponding type of flow for each formula for the prepared powder mixtures are illustrated in table (3).

Table 3: Pre-compression parameters for powder blend

Formula number	Angle of repose (Degree)	Bulk density (g/cm3)	Tapped density (g/cm3)	Carr's Index	Hausner Ratio	Type of Flow
F1	33.07±2.31	0.314±0.02	0.366±0.02	14.2±0.99	1.16±0.08	Good
F2	32.96±1.64	0.337±0.01	0.39±0.02	13.56±0.68	1.15±0.05	Good
F3	37.12±2.41	0.372±0.02	0.462±0.03	19.48±1.26	1.24±0.08	Fair
F4	36.03±2.16	0.351±0.02	0.422±0.025	16.82±1	1.2±0.07	Fair
F5	31.43±1.26	0.37±0.015	0.425±0.02	12.94±0.52	1.15±0.05	Good
F6	32.27±2.26	0.384±0.02	0.443±0.03	13.32±0.93	1.15±0.08	Good
F7	28.22±1.41	0.341±0.02	0.38±0.02	10.26±0.51	1.11±0.06	Excellent
F8	29.43±1.18	0.323±0.01	0.36±0.01	10.27±0.41	1.11±0.04	Excellent
F9	32.91±1.97	0.321±0.02	0.365±0.02	12.05±0.72	1.14±0.07	Good
F10	41.63±2.29	0.373±0.02	0.473±0.03	21.14±1.16	1.27±0.07	Passable
F11	43.15±1.73	0.38±0.01	0.483±0.02	21.32±0.85	1.27±0.05	Passable
F12	32.27±0.3	0.328±0.02	0.378±0.03	13.22±0.92	1.15±0.08	Good
F13	38.23±1.91	0.358±0.02	0.427±0.02	16.16±0.8	1.19±0.06	Fair
F14	43.26±2.6	0.35±0.02	0.445±0.03	21.34±1.3	1.27±0.08	Passable
F15	36.87±2.95	0.371±0.03	0.45±0.04	17.55±1.4	1.21±0.1	Fair

Data represent mean (±SD) (n=3)

The angle of repose of all formulations was between 28.22 ° to 43.26 °, while the result of the Carr's index and Hausner ratio was between 10.26% to 21.34%, and 1.11 to 1.27 respectively. The results indicated that the prepared powder mixtures have acceptable flow properties and compressibility.

Post-compression evaluations

The thickness of prepared prochlorperazine maleate tablets was in the range of (3.82±0.015 to 3.89±0.017 mm) it was found that all prepared tablets had a uniform thickness**.**

The hardness of prepared floating tablets was in the range of (3.32±0.17 to 6.26±0.15 kg/cm^2) which indicated good mechanical strength.

The total weight loss of the prepared tablets due to friability was found in the range of (0.186% to 0.687%), which indicated to be less than 1%.

The weight variation of prepared floating tablets was in the range of (198.2±1.8 to 200.2±0.57) in which none of the formulas was exceeding the limits of (±7.5%) specified by USP.

The content uniformity of the prepared tablets was in the range of (96.4±4.3 to 99.8±1.76), which reveal a good content uniformity. No tablets lie out of the range of 85-115% of the label claimas shown in the table (4).

Determination of the floating lag time and total floating time

The results of floating lag time (FLT) and total floating time (TFT) for all the prepared prochlorperazine maleate floating tablet formulas are shown in the table (5).

Most of the prepared floating tablet formulas had acceptable (FLT) and (TFT) due to the presence of the gas generating agent within the formulas, when this agent become in contact with the acidic dissolution media (HCl solution, pH1.2) it generates carbon dioxide gas (CO_2) which entrapped within the gelling layer of the hydrophilic polymer. Furthermore owing to the swelling of the hydrocolloid particle on the surface after exposure to the aqueous gastric fluids, this sequentially results in an increase bulk volume and provides buoyancy to the floating tablet dosage forms [24].

Table 4: Post compression parameter of prochlorperazine maleate floating tablets

Formula Number	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Content uniformity (%)
F1	3.85±0.015	3.62±0.37	0.402	199.3±1.08	98.4±3.45
F2	3.86±0.011	4.01±0.15	0.387	199.4±0.87	99.2±2.41
F3	3.86±0.011	4.16±0.23	0.377	198.9±1.22	98.5±3.54
F4	3.87±0.015	3.93±0.35	0.374	199.2±0.99	99.4±2.12
F5	3.87±0.02	4.1±0.2	0.352	200.2±0.57	98.5±3.13
F6	3.85±0.036	4.27±0.15	0.350	198.8±1.45	99±1.52
F7	3.83±0.011	5.86±0.12	0.245	198.5±1.3	98.5±2.34
F8	3.85±0.042	6.06±0.31	0.227	199±0.64	99.6±1.23
F9	3.82±0.015	6.13±0.4	0.186	199.1±0.76	99.8±1.76
F10	3.88±0.025	6.26±0.15	0.235	198.5±1.18	96.4±4.3
F11	3.89±0.017	6±0.25	0.247	198.2±1.8	97.6±3.62
F12	3.85±0.04	3.9±0.26	0.354	200±0.56	97.5±2.22
F13	3.83±0.02	3.8±0.2	0.369	198.3±1.1	99.7±1.56
F14	3.83±0.061	3.43±0.15	0.687	198.3±0.73	96.5±4.31
F15	3.83±0.045	3.32±0.17	0.602	199.1±0.83	98±4.21

Data represent mean (±SD) (n=3)

Table 5: Floating lag time and total floating time

Formula number	Floating lag time (seconds)	Total floating time (H)
F1	8±0.57	26±0.28
F2	16±0.57	32±0.29
F3	130±3.51	45±2.08
F4	10±1	28±0.87
F5	19±1.53	33±1.76
F6	142±7.76	47±0.50
F7	23±1.53	44±0.87
F8	257±4.16	64±1.42
F9	298±7.64	66±2.15
F10	Not float	Not float
F11	Not float	Not float
F12	568±6.81	45±1.53
F13	4±0.58	26±0.88
F14	8±1.53	31±2.08
F15	6±0.58	27±1.53

Data represent mean (±SD) (n=3)

The floating lag time and total floating time are prolonged with increase Hydroxypropyl methylcellulose (HPMC) concentration and viscosity. An increase in lag time can be attributed to increases tablet integrity and formation of a stronger gel layer with increasing the polymer concentration and/or viscosity, thus more time is required to hydrate the tablet. Additionally, as the polymer concentration and/or viscosity increased, the tablet can retain CO_2 for a longer period of time and thus shows longer floating time periods [25]. On the other hand, the formulas that are containing Carbopol 934 and Carbopol 940 (F10and F11 respectively) did not float due to high carbopol affinity towards water, which promotes penetration of water into floating tablet matrices, leading to increased tablet density and hence decrease in its floating capacity [26].

It was found that as the concentration of sodium bicarbonate ($NaHCO_3$) increased, the floating lag time and total floating time decreased this behavior can be attributed to the fact that as amount of $NaHCO_3$ increases the result of effervescence amount increases too, which in turn causes pore formation, and that led to rapid hydration of the HPMCK4M polymer matrix and therefore cause decrease tablet floating time [27].

The effect of diluent type on floating properties found that formula 2 which contain avicel Ph101(MCC) showed longer floating lag time and total floating time than F14 which contains spry dried lactose (SDL) and this show longer floating lag time and total floating time than F15 which contains (mannitol) due to that both lactose and mannitol are water soluble in nature, while MMC is hydrophobic in nature, this property accelerates the penetration of dissolution medium to matrix lead to floatation of the prepared floating tablet in a short period of time [28].

Determination of the swelling index of the floating tablets

The swelling index of the prepared tablet is calculated with respect of time. As the time increase the swelling index of the prepared tablet increase. Because the weight gain of prepared tablet increased proportionally with the rate of hydration. Afterwards, it decreased gradually due to the dissolution of the external gelling layer of the prepared tablet in the dissolution medium [29]. There is a linear relationship between the concentration and viscosity of the polymer and swelling process as shown in the table (6), which illustrate the swelling index of the prepared prochlorperazine maleate floating tablets.

Formulas (10 and 11) was excluded from the study due to bad floating properties.

Drug release

Fig. (1,2, and 3) show the effect of polymer type on drug release in which as the polymer viscosity increases the rate of drug release was decreased significantly*, This behavior may be elucidated by the relation between the polymer viscosity and the disentanglement concentration (the critical concentration of polymer below which the polymer chains separate and detach from a qualified matrix). The higher polymer viscosity makes greater chain entanglement, so it becomes harder for longer chains to dissolve [30].

This lead to the formation of thicker gel and the ability to hold liberated gas for a longer time, and not allow fast diffusion of the drug from the tablet matrix [31].

Table 6: Study of swelling characteristics of floating tablets of prochlorperazine maleate

Formula Number	Time in hours (swelling %)				
	1h.	2h.	3h.	4h.	5h.
F1	62.5±3.2	74±4.3	83.33±4.8	92.5±4.6	85.66±3.6
F2	85.33±5.7	98±4.9	104±7.5	110.25±7.4	117±4.4
F3	100.5±6.3	107.66±6.4	111±6.7	121±7.3	134.5±5.6
F4	77.5±3.1	89±6.9	96±5.3	101.33±4.0	102.5±4.1
F5	92.5±6.4	99±5.5	108±4.9	115.83±6.2	127±7.3
F6	110±6.1	118.83±7.6	123.5±6.7	134±5.3	139.33±8.5
F7	109.5±5.3	113±4.9	124.5±7.5	130±7.5	138.5±7.3
F8	116.33±7.3	128±4.6	136.5±8.8	142.92±3.9	149.66±5.6
F9	120.5±4.2	131.33±7.8	139±6.4	148.5±5.2	155.58±8.7
F12	78.58±3.9	84.5±5.7	91±5.8	97.5±4.8	107.5±5.7
F13	92.5±2.8	101.25±5.3	109±4.9	101.5±6.5	96.42±2.4
F14	67.5±3.6	76.5±3.3	87.5±6.5	91.83±5.7	84.33±3.1
F15	62±3.1	78±4.2	89.17±4.4	82.83±3.1	73±4.7

Data represent mean (±SD) (n=3)

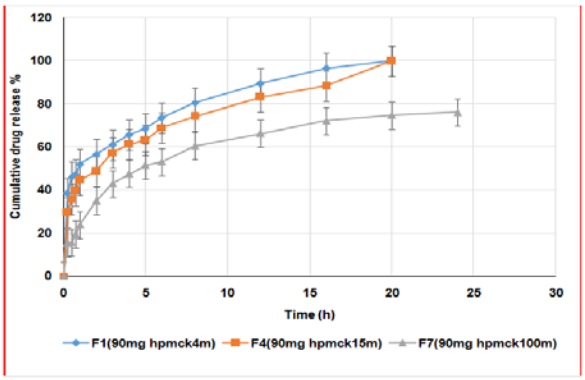

Fig. 1: The effect of polymer type on the release of prochlorperazine maleate floating tablets in pH 1.2 HCl solution at 37 ℃ temp (use 90 mg polymer concentration), Data represent mean (±SD) (n=3)

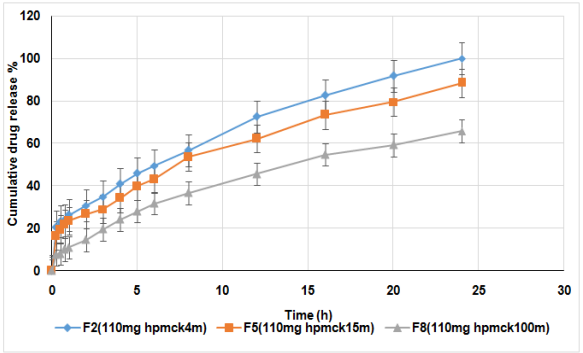

Fig. 2: The effect of polymer type on the release of prochlorperazine maleate floating tablets in pH 1.2 HCl solution at 37 ℃ (use 110 mg polymer concentration), Data represent mean (±SD) (n=3)

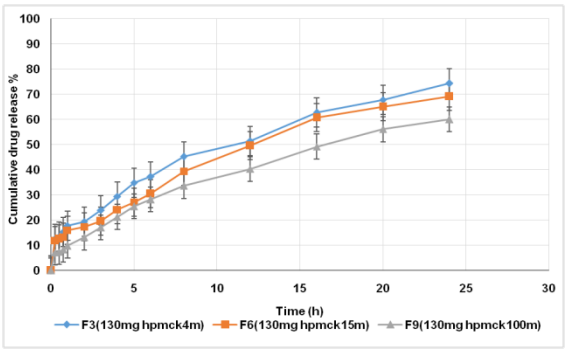

Fig. 3: The effect of polymer type on the release of prochlorperazine maleate floating tablets in pH 1.2 HCl solution at 37 ℃ (use 130 mg polymer concentration), Data represent mean (±SD) (n=3)

While fig. (4, 5, and 6) shows the effect of polymer concentration on drug release in which as the concentration of polymer in the formula increases, the rate of drug release decrease significantly*, This indirect relationship between polymer concentration and drug release is due to the fact that higher polymer concentration will forming a stronger viscous gel layer that decrease the rate of water diffusion into the floating tablet matrix, which cause decrease drug release [32].

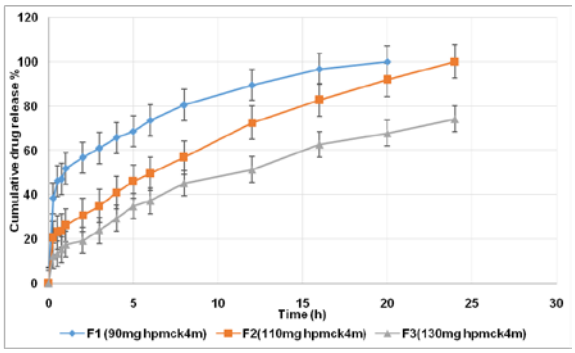

Fig. 4: The effect of HPMC K4M polymer concentration on the release of prochlorperazine maleate floating tablets in HCl solution pH1.2 at 37 ℃, Data represent mean (±SD) (n=3)

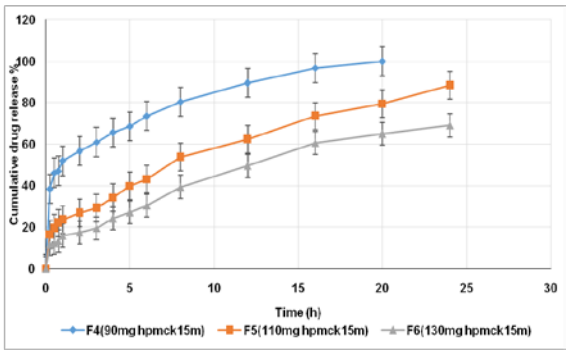

Fig. 5: The effect of HPMC K15M polymer concentration on the release of prochlorperazine maleate floating tablets in HCl solution pH1.2 at 37 ℃, Data represent mean (±SD) (n=3)

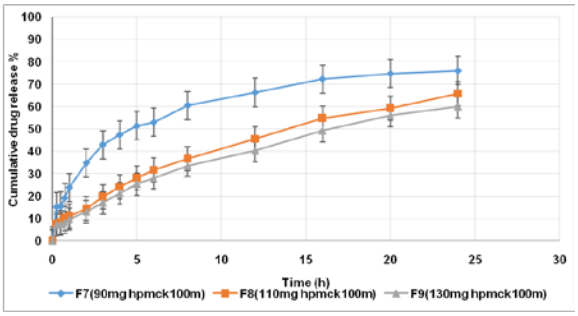

Fig. 6: The effect of HPMC K100M polymer concentration on the release of prochlorperazine maleate floating tablets in HCl solution pH1.2 at 37 ℃, Data represent mean (±SD) (n=3)

The effect of effervescent agent concentration on drug release showed in fig. (7) in which as the concentration of effervescent agent in the formula was increased, the rate of drug release was significantly* increased. This direct relationship was due to the porous nature of the $NaHCO_3$ containing tablet, and also, the high amount of $NaHCO_3$ that created channels for prochlorperazine maleate drug release by increase the pore size of the polymer matrix and increase the pressure of gas inside the polymer matrix [28].

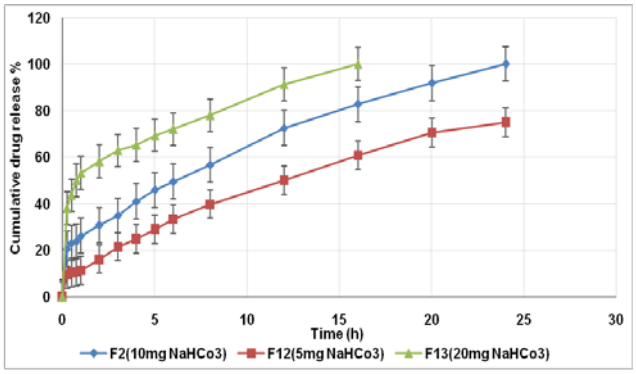

Fig. 7: The effect of sodium bicarbonate concentration on the release of prochlorperazine maleate in HCl solution pH 1.2 at 37 ℃. Data represent mean (±SD) (n=3)

The *in vitro* release of prochlorperazine maleate from floating tablet was significantly* increased in F14 and F15 which contain SDL and mannitol respectively in comparison with F2 which contain MCC as shown in fig. (8). These results may be due to that formulas 14 and 15 have a faster rate of hydration than F2 owing to SDL and mannitol higher water solubility than that of MCC. Alternatively, MCC is a water-swellable and hydrophobic polymer and thus remains swelling for a long time. Thus, it showed larger swelling diameter as compared to those contain lactose and mannitol. On the other hand, lactose and mannitol dissolves and leaves more pores to be filled with water hence results in more water penetration into the matrix [33].

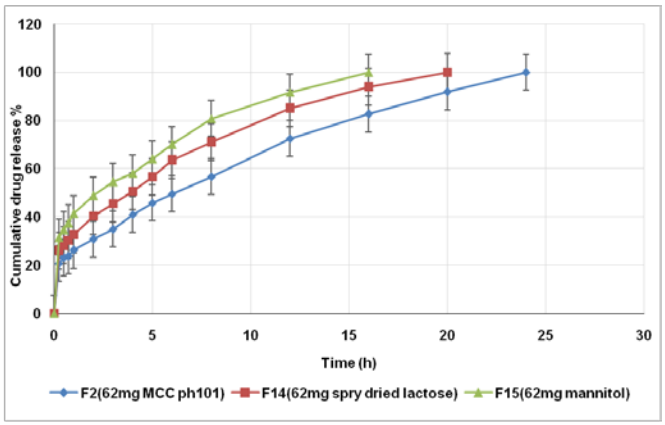

Fig. 8: The effect of diluent type on the release of prochlorperazine maleate floating tablets in solution HCl pH1.2 at 37 ℃, Data represent mean (±SD) (n=3)

Drug-excipients compatibility studies

The Fourier transform infrared spectroscopy (FTIR) spectrum for the pure prochlorperazine maleate as shown in fig. (9) displayed band at 3435 cm^{-1} attributed to the hydroxyl (OH) in the maleate group, while the band 3026 cm^{-1} assigned to the (C-H) aromatic rings in the backbone of the prochlorperazine. The (C-H) of aliphatic groups (CH_3 and CH_2) appeared in the expected area for the stretching vibration at 2974 cm^{-1}. The bands appeared at 1693 cm^{-1}and1620 cm^{-1} attributed to the (C=O) stretching of two carboxylic groups of maleate structure [34].

The band appeared at 1568 cm^{-1}attributed to (C=C) of the aromatic ring. The band appeared at 1089 cm^{-1} attributed to (C-Cl) stretching in the benzene ring. While the fingerprint area showed the bending bands of the drug.

The FTIR spectrum of prochlorperazine maleate after formulation in floating tablet dosage form as shown in the fig. (10) displayed same functional groups band with small shifting indicating the compatibility and uniformity of excipients with the drug without any chemical modification of the drug.

Determination of the Release Kinetics of optimised formula (F2)

The drug release data of optimised formula was fitted to models representing first order kinetic, zero order kinetic, Korsmeyer-peppas release kinetic and Higuchi releases kinetic to identify the release mechanisms of the drug.

The data were treated for regression analysis by MS-EXCEL statistical function as shown in the fig. 11, 12, 13, and 14.

The results of the study shows the *in vitro* release of the drug could be best expressed by Higuchi's equation as the optimised formula showed good linearity (R2: 0.9889) and that indicates the diffusion is a dominant mechanism of drug release with this formula.

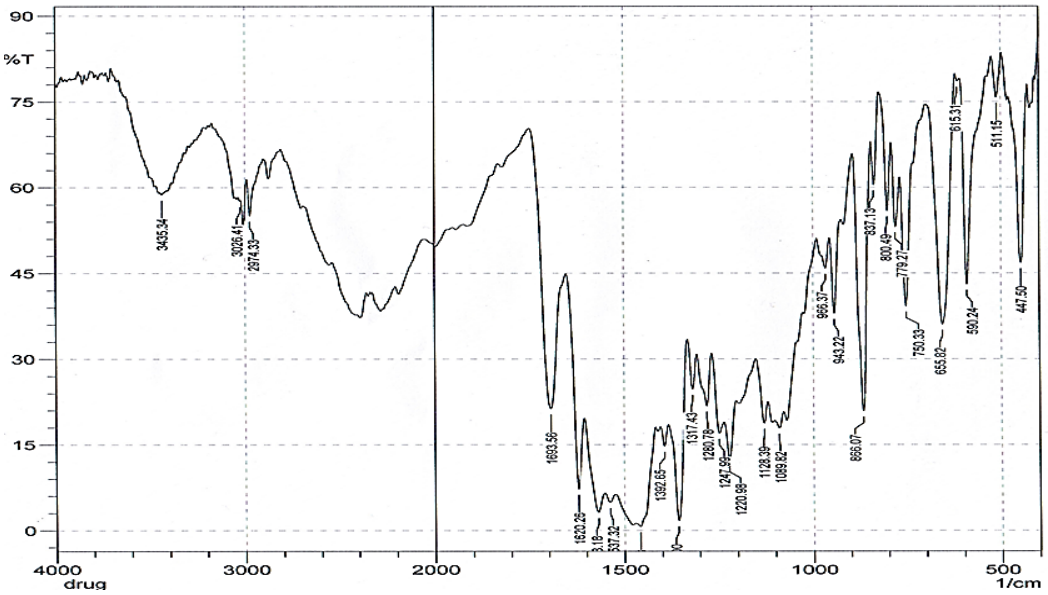

Fig. 9: FTIR spectra of prochlorperazine maleate pure powder

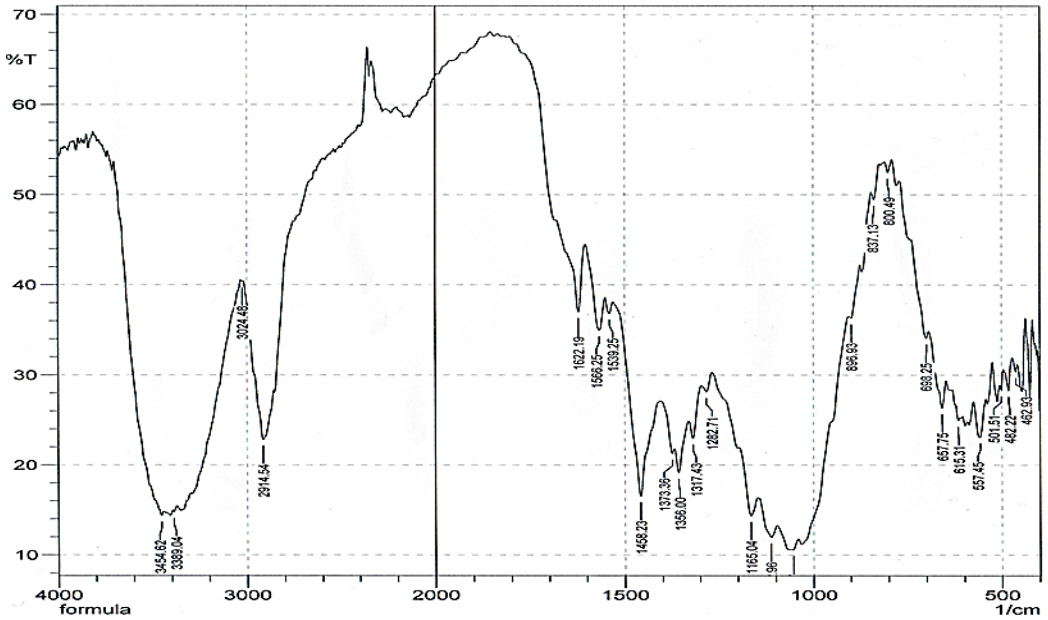

Fig. 10: FTIR spectra of prochlorperazine maleate with physical mixture (F2)

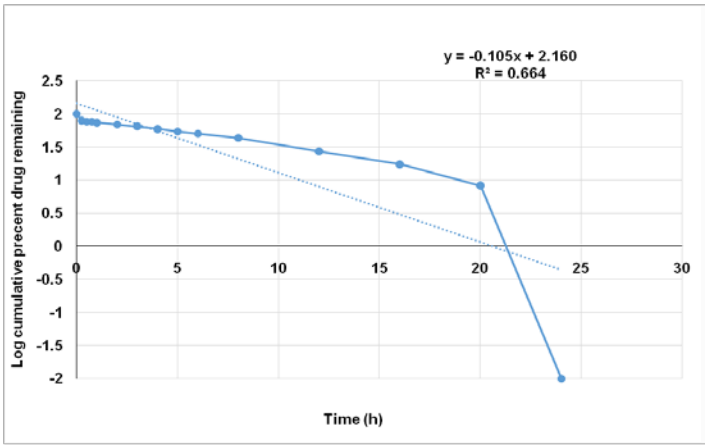

Fig. 11: First order release kinetics of optimised formula (F2)

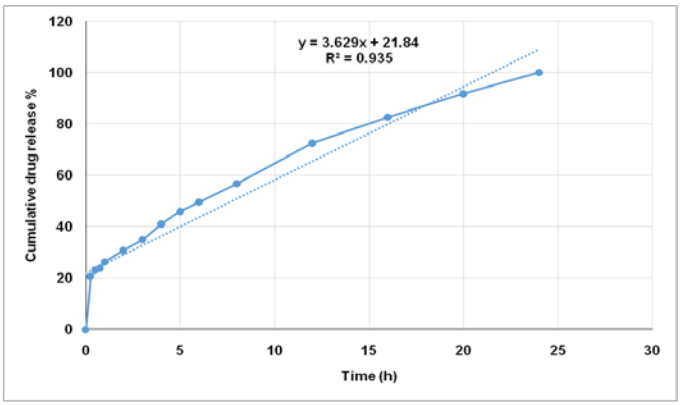

Fig. 12: Zero-order release kinetics of optimised formula (F2)

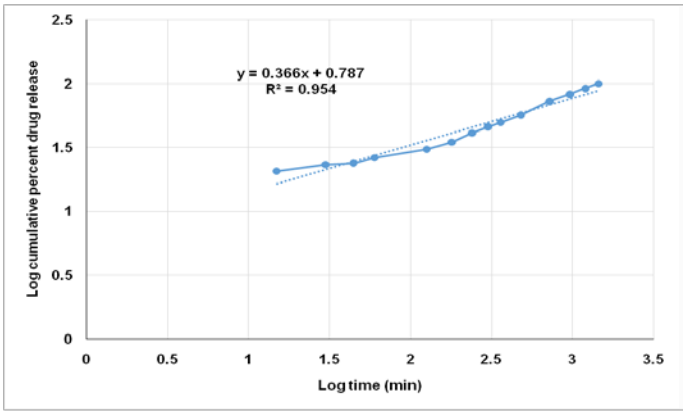

Fig. 13: Korsmeyer-peppers release kinetics of optimised formula (F2)

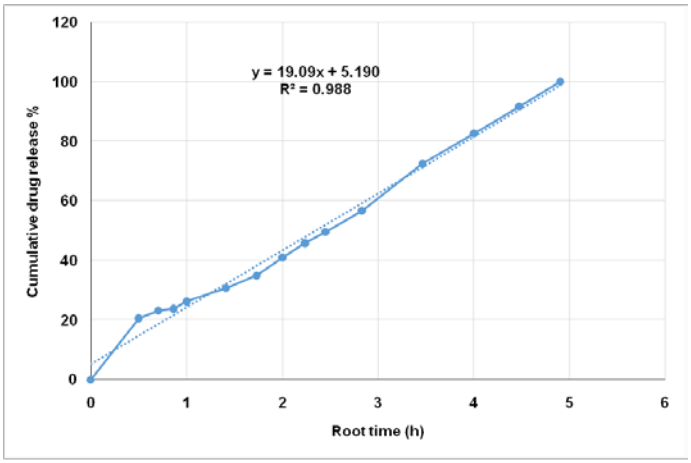

Fig. 14: Higuchi release kinetic of optimised formula (F2)

CONCLUSION

The formulation of sustained release (24 h) floating tablet of prochlorperazine maleate (15 mg) was successfully achieved, which can be taken once daily thereby controlling limitations accompanied with ordinary immediate release dosage form of the drug (5 mg of prochlorperazine maleate) which taken up 3-4 times daily resulting in an improvement in patient compliance (as the number of giving doses was decreased) and more efficient treatment for prolonged period of time (longer half-life and higher bioavailability).

CONFLICTS OF INTERESTS

Declared none

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