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Effervescent floating tablets of metformin HCl developed by melt granulation. Part I: Effect of hydrophilic polymer on biopharmaceutical properties

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Abstract

In the present study which the aim to evaluate the effect of hydrophilic polymer on the biopharmaceutical properties of metformin hydrochloride floating tablets, we have prepared floating systems using melt granulation, according to effervescent approach. Two hydrophilic polymers are used at various concentrations (10, 12.5, 15 and 17.5%), Acacia gum and hydroxypropylmethylcellulose (HPMC) at three viscosity grades (K4M, K15M and K100M). In addition to the satisfactory physical parameters, the evaluation of buoyancy and *in vitro* dissolution of floating developed systems revealed that the biopharmaceutical performances of these systems depended on the nature of the polymer. Unlike the acacia gum which did not produce floating systems, the HPMC matrixes had good buoyancy properties: fast buoyancy time (240±30 to 360±30 sec) and total flotation time more than 24 hours with matrix maintained integrity. In addition, in the case of HPMC, a significant influence of viscosity grade on MTH kinetics has been demonstrated. Indeed, the observed results showed that at 17.5% of HPMC, as the viscosity grade increases, the dissolution kinetics of metformin HCl was extended. The formulations F8 (HPMC K15M) and F12 (HPMC K100M) have exhibited the drug release rates of about 92 and 80% respectively at the end of 8 hours dissolving. These formulations followed Korsmeyer-Peppas/Higuchi release kinetics according to a Non-Fickian mechanism. Finally, the melting granulation process of MTH with stearic acid, in the case of HPMC K100M, used at high concentration (17.5%), has allowed the development of extended-release effervescent floating tablets (> 8 h).

Keywords: Metformin HCl; Effervescent floating tablet; Melt granulation; HPMC; Acacia gum; Stearic acid

1. Introduction

The oral route is the most convenient for administering the drugs. However, it has certain limitations for several active ingredients: unpredictable gastric emptying, rapid gastrointestinal transit and the existence of a narrow absorption window in the upper intestine. In order to overcome these physiological problems, the researchers chose to design delivery systems that would remain in the stomach for an extended period of time. This is the case with GRDDS: Gastro-Retentive Drug Delivery System, whose design can improve the oral bioavailability of drugs by extending the absorption phase [1-5]. Several approaches to these systems are described in the literature [6-13].

For this study, metformin hydrochloride (MTH) was selected chosen as the molecule candidate. It is an oral antihyperglycemic agent of the biguanide class. Although its solubility in water is relatively high, the oral bioavailability of metformin hydrochloride is about 50-60%. This is mainly due to its low permeability (BCS III). Its narrow and limited

absorption window at the upper part of the small intestine means that it is slowly and incompletely absorbed by the gastrointestinal tract [14-18].

The aim of this work devoted to development floating effervescent tablets of MTH, using a simple process, melt granulation, is to study the effect of hydrophilic polymers on the biopharmaceutical performances of the developed floating matrixes. For its realization, we have prepared floating systems using a simple manufacturing technique, solvents-free (aqueous or organic) and without drying step [19], melt granulation with a hydrophobic agent, stearic acid, according to an effervescent approach. The sodium bicarbonate was therefore introduced into the formulation of these systems as a carbon dioxide generating agent. A natural polysaccharide, Acacia gum and hydroxypropylmethylcellulose (HPMC) at three viscosity grades (K4M-K15M-K100M) were selected as hydrophilic polymers and were used at various concentrations (10, 12.5, 15 and 17.5%) for the preparation of floating systems.

2. Material and methods

2.1. Chemicals

Metformin hydrochloride (metformin HCl or MTH) (free sample) provided by Shangai Pharmaceutical, China, lot N° A-21411205109. Stearic acid supplied by Transmare Antwerpen N. V., Belgium. Hydroxypropylmethylcellulose: Methocel HPMC K4M supplied by Wolff Cellulosics Bayer, lot N° 30100513, Methocel HPMC K15M obtained from Colorcon, Royaume-Uni, lot N° ZK11012N03 and Benecel HPMC K100M received from ASHLAND, Germany, lot N°425718. Acacia gum received from Axo Pharma, Belgium, lot N°602.302. Sodium bicarbonate supplied by Sigma-Aldrich, Germany, lot N° 80370. Microcrystalline cellulose pH 102 (CMC) received from JRS Pharma, France, lot N° 5610262715. Talc and magnesium stearate supplied respectively by Guangxi Longguang Talc (lot N° 2015034 G), Development CO., Ltd., China and Anhui Sunhere Pharmaceutical Excipients CO, Ltd., China (lot N° 1514163).

2.2. Characterization of metformin HCl

The maximum of absorbance (λ max) is determined by scanning the spectrum of metformin hydrochloride solution 0.1N HCl (pH 1.2) at 200-400 nm using a UV-visible spectrophotometer (WPA Light II 7120 V 1.80). The metformin hydrochloride's calibration curve is performed by using twelve standards (5 to 60 mg/l) prepared by successive dilutions of a 1000 mg/l metformin HCl stock solution with 0.1N HCl (pH 1.2). The results are the average of three trials.

2.3. Preparation of metformin HCl floating tablets

Table 1 Formulation of Metformin hydrochloride's effervescent floating tablets

Formulation Code	Composition of developed formulations (mg)									
	MTH	Stearic Acid	NaHCO$_3$	HPMC K4M	HPMC K15M	HPMC K100M	Acacia Gum	CMC	Talc	Mg Stearate
F1	250	100	50	50	-	-	-	Qs 500	7.5	2.5
F2	250	100	50	62.5	-	-	-	Qs 500	7.5	2.5
F3	250	100	50	75	-	-	-	Qs 500	7.5	2.5
F4	250	100	50	87.5	-	-	-	Qs 500	7.5	2.5
F5	250	100	50	-	50	-	-	Qs 500	7.5	2.5
F6	250	100	50	-	62.5	-	-	Qs 500	7.5	2.5
F7	250	100	50	-	75	-	-	Qs 500	7.5	2.5
F8	250	100	50	-	87.5	-	-	Qs 500	7.5	2.5
F9	250	100	50	-	-	50	-	Qs 500	7.5	2.5
F10	250	100	50	-	-	62.5	-	Qs 500	7.5	2.5
F11	250	100	50	-	-	75	-	Qs 500	7.5	2.5
F12	250	100	50	-	-	87.5	-	Qs 500	7.5	2.5
F13	250	100	50	-	-	-	50	Qs 500	7.5	2.5
F14	250	100	50	-	-	-	62.5	Qs 500	7.5	2.5
F15	250	100	50	-	-	-	75	Qs 500	7.5	2.5
F16	250	100	50	-	-	-	87.5	Qs 500	7.5	2.5

MTH: Metformin HCl, NaHCO$_3$: Sodium bicarbonate, HPMC: Hydroxypropylmethylcellulose, CMC: Microcrystalline cellulose

The effervescent metformin hydrochloride floating tablets were prepared by melt granulation of stearic acid in the presence of hydrophilic polymers, Acacia gum and three viscosity grades of HPMC (K4M, K15M and K100M), used at various concentrations and an effervescent agent, sodium bicarbonate. The tablets were prepared according to the formulations shown in table 1. Stearic acid is melted at 58°C (near its melting point) in a mortar placed on an Ikamag RET heating plate. All the powders were accurately weighed (Sartorius ED153-CW balance) and passed through a sieve (800 μm). Except magnesium stearate and talc, all other ingredients were blended uniformly, before being mixed in the melted stearic acid in the mortar. The resulting mass is allowed to solidify at laboratory temperature. Then, this solidified mass was calibrated (1000 μm sieve) and lubricated (addition of talc and magnesium stearate) then compressed using a Frogerais Type A 307 alternative press equipped with a double set of flat punches and a 12 mm diameter die. The obtained tablets have the following characteristics: average weight, 500 mg, and diameter, 12 mm.

2.4. Pre-compression evaluation

Prior to the compression, a rheological study is carried out on the granules according standard procedures [20]. The granules were therefore evaluated for angle of repose, bulk and tapped densities, compressibility index (Carr's index) and Hausner's ratio.

2.5. Post-compression evaluation

The formulated tablets were evaluated for quality control tests like drug content, weight variation, hardness, friability and thickness [20, 21].

2.6. *In vitro* buoyancy study

The *in vitro* buoyancy is carried out according to the method described by Rosa et al., [22]. The tablet is placed in a 250 ml glass beaker, containing 200 ml of 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float is called floating lag time (FLT). This delay should be as short as possible. The results are expressed in seconds and represent the average of 3 tests. The duration of time by which the tablet remained floating represents the total floating time (TFT). This period must be as long as possible. The results are expressed in hours (hrs.) and represent the average of 3 measures.

2.7. Evaluation of swelling index

This test evaluates water absorption characteristics. The pre-weighed individually tablets (W_0) are placed separately in glass beaker containing 200 ml of 0.1 N HCl maintained at 37 ± 1 °C, without stirring, until 8 hours. At the end of each hour of the test, the swollen floating tablets are removed from beaker, and the excess water is gently removed with absorbent paper to remove the surface droplets and then re-weighed (W_t). The % swelling index (SI) is calculated by using the following equation:

$$\text{Swelling index } (\%) = \frac{Wt - Wo}{Wo} \times 100$$

Where, W_t = Weight of tablet at time t, W_0 = Initial weight of tablet. The results expressed as % of gain in mass as a function of time are the average of three measures.

2.8. *In vitro* dissolution study

The *in vitro* dissolution study was performed using the USP II paddle apparatus, Erweka DT 80, at a rotational speed of 75 rpm. The floating tablets are introduced inside a beaker containing 900 ml of 0.1 N HCl dissolution medium, maintained at 37 ± 0.5°C. This study is done for 8 hours. Samples (5 ml) of the solution are withdrawn at time intervals of 20,40,60,90 and 120 minutes, then every hour up to 8 hours. Each volume withdrawn is replaced with the same volume of pre-warmed fresh dissolution media. The samples are filtered through 0.45 μm porosity syringe filter and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 233 nm using UV-visible spectrophotometer (WPA Light II 7120 V 1.80). The percentage drug release was calculated by using calibration curve equation. The results of *in vitro* dissolution represent the average of six measures (Mean±CV).

2.9. Modeling of dissolution kinetics

We have determined the release mechanism by fitting the dissolution data to the various kinetic equations: Zero order, First order, Higuchi and model Korsmeyer-Peppas [23-27]. Linearization of dissolution data allows a more direct comparison by referring to classical parameters (Intersection-slopes) [28, 29].

Zero order: $Q_t = Q_0 + K_0 t$

First order: $\text{Log } Q_t = \text{Log } Q0 - \dfrac{Kt}{2,303}$

Higuchi model; $Q_t = K_H t^{1/2}$

Korsmeyer and Peppas model: $Log \left(\dfrac{Mt}{M\infty}\right) = \log k + n \log t$

The diffusion exponent, "n" was calculated for characterizing the different release mechanisms. If n = 0.45 the diffusion is Fickian, if 0.45 < n < 0.89 the release mechanism is anomalous transport or non-Fickian, if n = 0.89 the transport is of case II, if n > 0.89 the transport is of super case II.

The dissolution data was analyzed according to the different kinetic equations and the Correlation coefficient R^2 values were calculated of all batches and for each model.

2.10. Dissolution time of successive fractions

To best interpret release kinetics of metformin HCl from floating tablets, the times, $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ were calculated from dissolution data according to the best fit model with the highest correlation coefficient R^2 using the following formulas [30]:

$$T_{25\%} = (25/k)^{1/n}$$

$$T_{50\%} = (50/k)^{1/n}$$

$$T_{80\%} = (80/k)^{1/n}$$

Also, the mean dissolution time (MDT) was calculated from dissolution data using the following equation:

$$MDT = \frac{\sum_i ti\ \Delta Mi}{\sum_i \Delta Mi}$$

Where t_i is the average time during which the fraction ΔMi of the drug has been released from the pharmaceutical dosage form [31].

It should be noted that the times, $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ as well as the mean dissolution time (MDT) were used to evaluate the metformin HCl release and deduce the effectiveness of the matrix systems in slowing its dissolution. Indeed, the higher the dissolution time values of successive fractions, the more the floating system has the ability to retain the pharmaceutical ingredient. It should also be stressed that the value of MDT depends on the formulation factors (Nature, polymer concentration) and the physic-chemical properties of the molecule [30].

2.11. FTIR spectroscopy

Our study was completed by a FT-IR spectroscopy (Shimadzu IR Affinity 1S CE). This analysis was performed to investigate drug-excipient interactions. Samples of pure drug, stearic acid and floating matrices, F8 and F12, considered to promote MTH gastro-retention, were scanned in the spectral region of 4000 to 750 cm^{-1} with a resolution of 4 cm^{-1}.

2.12. Statistical analysis (ANOVA)

The results of *in vitro* release kinetics of metformin hydrochloride were statistically processed using GraphPadPrism 7 computer software to compare drug release profiles of MTH from floating systems prepared. Compare according to the nature, the concentration and the viscosity of the hydrophilic polymer. Statistical analyses were performed by one-factor analysis of variance (ANOVA). The differences were considered significant at $p < 0.05$ at a 95% confidence interval.

3. Results and discussion

3.1. Characterization of metformin hydrochloride

At $\lambda = 233$ nm, analytical wavelength [32] the calibration curve is a straight line obeying Beer Lambert's law (Figure 1). Linearity is between 5 and 60 mg/l metformin HCl dissolved in 0.1N HCl.
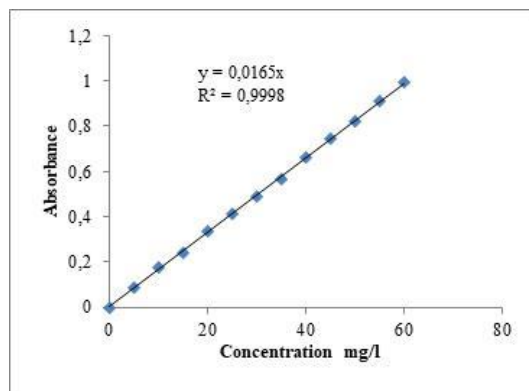

Figure 1 Calibration curve of metformin hydrochloride in 0.1 N HCl

3.2. Preliminary trials

According to the effervescent floating systems approach, preliminary trials were conducted to define the role of each ingredient of the formulation. Hydroxypropylmethylcellulose (HPMC) and acacia gum are used as hydrophilic polymer for extended metformin HCl release. Sodium bicarbonate is applied like an effervescent flotation agent, gas generating in contact the acid dissolving media. Stearic acid is used as a hydrophobic agent of melt granulation. Due to its low density and hydrophobic properties, stearic acid can improve floatation properties and slow the release of metformin HCl. Finally, talc and magnesium stearate are used as flow regulator and compression lubricant respectively. All formulas prepared F1 to F16 have shown in Table 1.

3.3. Pre-compression evaluation

Table 2 Pre-compression evaluation of metformin HCl floating tablets

Formulation Code	Angle of Repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	V_{10}–V_{500} (ml)	Carr's Index (%)	Hausner ratio
F1	34.79	0.515	0.606	16	14.94	1.17
F2	34.50	0.500	0.581	13	14.50	1.16
F3	34.99	0.495	0.581	13	14.85	1.17
F4	34.79	0.500	0.588	14	15.00	1.17
F5	34.68	0.495	0.581	16	14.85	1.17
F6	34.60	0.495	0.581	15	14.85	1.17
F7	33.50	0.492	0.546	12	10.34	1.11
F8	34.79	0.492	0.549	12	13.33	1.15
F9	34.16	0.500	0.549	11	12.50	1.13
F10	35.18	0.492	0.584	16	15.76	1.18
F11	34.91	0.470	0.529	13	11.26	1.12
F12	33.65	0.467	0.549	14	14.25	1.17
F13	31.29	0.594	0.687	12	13.53	1.15
F14	32.3	0.596	0.688	11	13.37	1.15
F15	32.61	0.595	0.689	11	13.69	1.15
F16	33.75	0.598	0.694	10	13.77	1.15

The granules of proposed formulations were evaluated for pre-compression parameters as shown in Table 2. Regardless of the nature and concentration of the hydrophilic polymer, all formulations have shown good flowability and good

compressibility proprieties. The values have indicated: angle of repose in the range 31.29° to 35.18°, $V_{10} - V_{500}$ between 10 and 16 ml, Carr's index between 10.34 and 15.76 % and Hausner's ratio between 1.11 and 1.18 (Table 2).

3.4. Post-compression evaluation

The floating tablets obtained by melt-granulation were evaluated for post-compression parameters as indicate in table 3. All tablets have shown satisfactory and reproducible physical parameters (Table 3): average level metformin HCl between 97.63 and 101.80%, weight uniformity within the prescribed limits; 500 ± 25 mg, sufficient hardness; in the range 4.99 ± 0.10 to 5.94 ± 0.54 kg/cm². Thickness and percentage friability ranged from 3.43 ± 0.03 to 3.82 ± 0.05 mm and 0.52 to 0.90 % respectively. All formulations have shown less than 1% (w/w) friability. Finally, the physical characteristics of floating tablets of the formulations proposed have shown no significant variation.

Table 3 Post-compression evaluation of metformin HCl floating tablets

Formulation Code	Average Drug content (%)	Weight variation (mg ± SD)[a]	Hardness (kg/cm² ± SD)[b]	Thickness (mm ± SD)[b]	Friability (%w/w)
F1	99.39	502.85±1.72	5.24±0.21	3.75±0.04	0.69
F2	101.21	502.55±1.60	5.39±0.28	3.78±0.07	0.78
F3	98.22	510.85±1.53	5.23±0.29	3.69±0.10	0.91
F4	100.60	509.15±1.39	5.06±0.26	3.69±0.07	0.83
F5	101.80	514±1.11	5.80±0.42	3.64±0.10	0.73
F6	98.23	505.1±1.62	4.99±0.10	3.82±0.05	0.89
F7	98.19	509.8±0.96	5.31±0.13	3.65±0.04	0.80
F8	99.39	486.70±0.67	5.67±0.45	3.50±0.05	0.73
F9	100.58	505.4±1.37	5.19±0.33	3.75±0.07	0.84
F10	101.20	498.4±0.83	5.05±0.20	3.73±0.02	0.52
F11	101.79	506.65±1.44	5.23±0.16	3.73±0.08	0.73
F12	101.18	508.95±1.44	5.94±0.54	3.63±0.10	0.82
F13	98.79	493.75±0.20	5.14±0.39	3.43±0.06	0.82
F14	100.58	500.35±1.30	5.10±0.26	3.45±0.06	0.81
F15	97.63	494.5±0.87	5.10±0.51	3.43±0.03	0.88
F16	98.81	498.2±0.82	5.01±0.20	3.44±0.17	0.90

a = (n = 20) and b = (n = 10)

3.5. *In vitro* buoyancy study

It should be recalled that metformin HCl floating tablets were prepared by melt-granulation according effervescent approach using sodium bicarbonate as a gas generating agent. $NaHCO_3$, in contact with dissolving medium 0.1 N HCl, generates CO_2. The carbon dioxide thus generated is trapped in the tablet and protected inside the gel formed by the hydration of polymer. The tablet density decreases below 1 g/ml and, as a result, the matrix becomes floating [33].

The results of *in vitro* buoyancy study; floating lag time (FLT), matrix integrity and total floating time (TFT) for all formulations were given in Table 4. These results have shown that buoyancy was dependent on formulation parameters. The buoyancy lags time of the formulations, F13, F14, F15 and F16 containing the acacia gum was more than 1 hour (no floating systems).

Table 4 *In vitro* buoyancy evaluation of metformin HCl tablets

Formulation Code	Floating lag time[a] FLT (sec)	Matrix integrity	Total floating time TFT (hrs)
F1	300±30	Disintegration	-
F2	240±40	Disintegration	-
F3	240±30	Disintegration	-
F4	240±20	Superficial erosion	< 12
F5	300±30	Superficial erosion	> 24
F6	240±30	+++	> 24
F7	360±20	+++	> 24
F8	360±30	+++	> 24
F9	300±30	+++	> 24
F10	300±25	+++	> 24
F11	300±30	+++	> 24
F12	360±30	+++	> 24
F13	No floating(>3600)	+++	> 24
F14	No floating (>3600)	+++	> 24
F15	No floating (>3600)	+++	> 24
F16	No floating (>3600)	+++	> 24

a = (n = 3)

With HPMC, the buoyancy lag time was short. It ranged from 240 ± 20 sec to 360 ± 30 sec. These might be due to rapid hydration of HPMC polymer, which results in a rapid flotation of the tablets compared to those tablets containing Acacia gum. All formulations with HPMC remained buoyant for more than 24 hours except for F1, F2, F3 and F4. The tablets of F1, F2 and F3, formulations with HPMC K4M have disintegrated rapidly after flotation. The tablets F4 have floated immediately but remained floating for less than 12 hours with a manifestation of surface erosion despite the maximum concentration of HPMC K4M (17.5%). These results could be attributed to the low viscosity grade of the HPMC K4M which has not allow the formation of a thick enough gelled layer resistant to the tensions generated by carbon dioxide release.

Except tablets obtained from F5, all the formulations with HPMC K15M and HPMC K100M corresponding respectively to F6-F7-F8 and F9-F10-F11-F12 were shown fast flotation time and total buoyancy time more than 24 hours with matrix integrity maintained. This could be explained by the high viscosity grade of HPMC K15M and K100M allowing sufficient hydration and gelling to retain the carbon dioxide bubbles generated by sodium bicarbonate in contact with dissolving media (H$^+$). F5 has shown short floating lag time (300 ± 30 sec), total floating time more than 24 hours but has manifested superficial erosion. This could be attributed to the low concentration of HPMC K15M (10%), which is insufficient to form a resistant gel barrier.

Finally, the results (Table 4) clearly showed that buoyancy properties of metformin hydrochloride tablets depended on the formulation parameters, mainly on the nature of the polymer. In general, concentration does not affect the buoyancy properties of the prepared matrixes. Also, it was concluded that at high viscosity of HPMC, we observed the best flotation properties which are in the following order: HPMC K15M>HPMC K4M and HPMC K100M>HPMC K4M.

3.6. Evaluation of swelling index

The swelling is an important factor for buoyancy and dissolution kinetic of floating matrixes. The swelling index was observed every hour up to 8 hours for all formulations and the percentage swelling was determined at the end of each hour of the test. Figure 2 clearly has shown that as the concentration of HPMC (K15M or K100M) increases the swelling index also increases. This observation is particularly marked at concentrations 15 and 17.5% for the K100M (Figure 2b) and 17.5% for the K15M (Figure 2a).
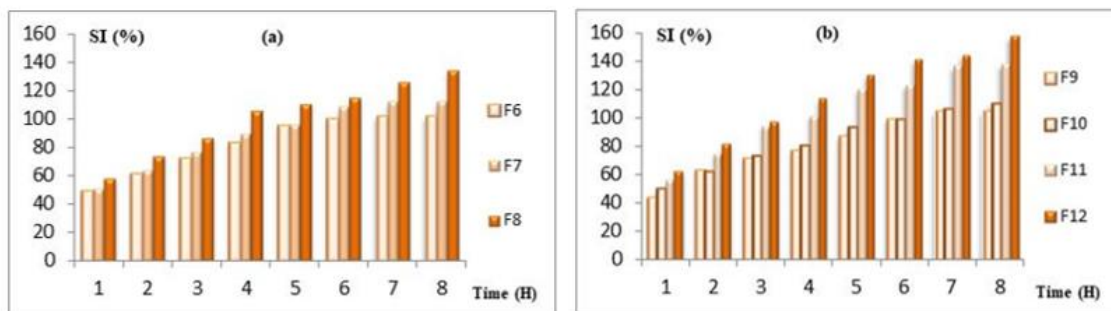
Figure 2 Swelling index. Effect of HPMC concentration (a) HPMC K15M, (b) HPMC K100M

In addition, we have observed that at concentrations, 15 and 17.5 % of HPMC, the swelling index increases with viscosity increasing [Figure 3(c, d)]. The F11 and F12, formulations containing HPMC K100M showed the highest swelling indexes during the test. This result may be explained by the fact that this polymer rapidly hydrates by absorption of the medium due to its hydrophilic nature and high concentration.
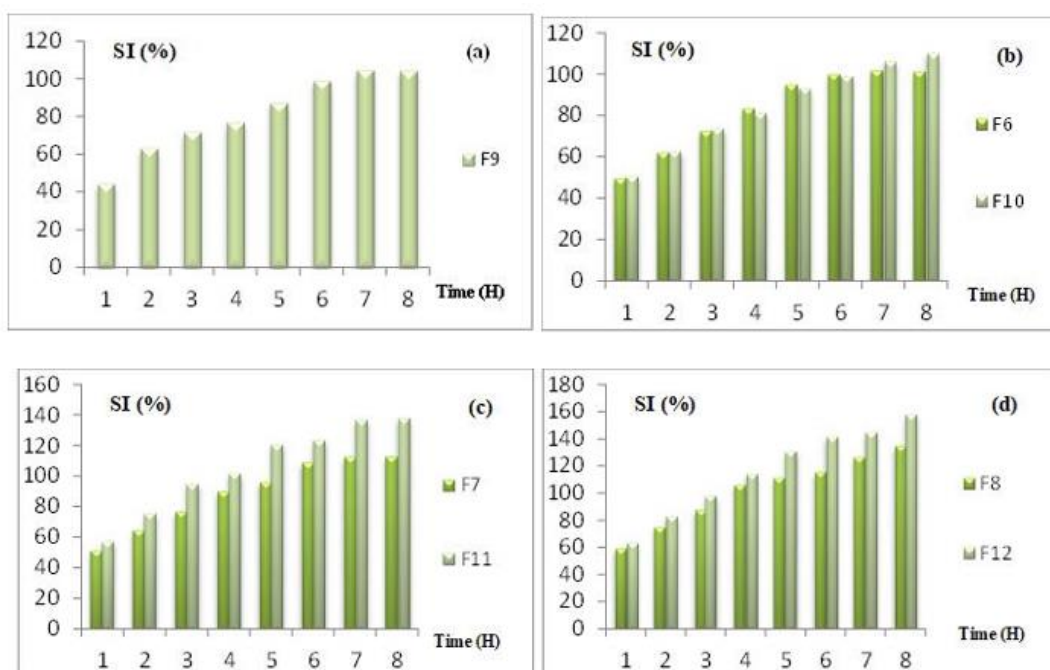

Figure 3 Swelling index. Effect of HPMC viscosity (a) 10% (b) 12.5% (c) 15% (d) 17.5%

It was concluded that the maximum swelling index increases with increasing HPMC concentration and viscosity. Observation particularly pronounced at 15 and 17.5% of HPMC. F11 and F12 (HPMC K100M) have shown the highest maximum swelling indexes, about 138 and 158 respectively.

3.7. *In vitro* dissolution studies

The dissolution data of metformin HCl floating tablets, F4 to F16, are shown in Table 5. In Table 6, we have mentioned the dissolution times $T_{25\%}$, $T_{50\%}$, $T_{80\%}$ and the mean dissolution time (MDT) of formulations for which we have observed a prolonged release and the following buoyancy properties: short FLT, TFT > 24 hours and matrix integrity (F6 to F12). Figure 4 illustrates the influence of concentration of hydrophilic polymer. Figure 5 shows the dissolution profiles of metformin hydrochloride associated with the effect of hypromellose viscosity.

Table 5 Dissolution data of metformin HCl floating tablets

Formulation code	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
F4	51.76±2.01	66.71±1.18	78.67±0.53	88.16±1.01	94.32±0.92	100.51±0.60		
F5	42.96±2.28	60.40±1.56	71.43±1.26	75.67±1.67	85.24±1.43	93.57±1.48	100.52±0.72	100.78±0.28
F6	42.51±1.90	59.17±0.76	69.98±1.71	74.83±1.33	84.51±1.17	90.99±1.04	95.29±1.10	100.26±0.62
F7	38.06±2.04	49.79±1.81	64.42±1.10	71.87±0.78	81.47±1.28	88.88±0.95	95.19±0.35	100±0.70
F8	28.71±3.58	43.78±2.20	56.18±1.65	66.40±0.94	72.89 ± 1.05	80.01 ± 1.59	86.53 ± 1.48	92.18±1.09
F9	37.83±3.05	51.87±2.31	64.32±1.06	74.48±1.75	81.51±0.74	92.98±1.30	100.08±0.57	100.10±0.58
F10	33.94±3.59	46.83±1.93	55.49±1.53	67.01±1.60	76.28±1.22	83.54±0.85	91.13±1.07	97.43±0.40
F11	32.55±4.63	45.82±2.04	54.16±4.20	63.07±2.13	71.05±1.86	80.34±1.16	84.28±0.78	93.64±1.16
F12	21.87 ± 2.19	34.95±2.43	45.17±2.07	52.34 ± 1.73	60.82 ± 1.10	65.21±1.12	73.58±1.14	80.00±1.14
F13	77.54±0.97	100.61±0.65	-	-	-	-	-	-
F14	61.70±0.34	100.12±0.47	-	-	-	-	-	-
F15	59.92±2.14	100.57±0.78	-	-	-	-	-	-
F16	59.19±1.91	93.62±1.54	100.61±0.37	-	-	-	-	-

3.7.1. Effect of hydrophilic polymer nature

The drug release kinetics was depended on the nature of the hydrophilic polymer. The results of *in vitro* dissolution studies mentioned in Table 5 clearly have indicated that, in the case of Acacia gum used as hydrophilic polymer, regardless of its concentration (10-12.5-15 and 17.5%), the *in vitro* release of metformin hydrochloride has not prolonged. Dissolution of drug was complete after 2 or 3 hours of testing (F13, F14, F15 and F16). This could be explained by the disintegration of the tablets after approximately 60-90 min of testing under the effect of stirring. Acacia gum therefore did not allow the formation of a thick enough gel layer able to retain the carbon dioxide generated by the effervescence of sodium bicarbonate in the 0.1 N HCl dissolution medium and to resist of the agitation speed. In contrast, with HPMC, we found that the drug release was significantly slowed and prolonged (6 H or $\geq$ 8 H) (Table 5). The kinetics of drug release therefore depends on the nature of the hydrophilic polymer. A very significant difference ($p < 0.05$) was noted between the release kinetics (HPMC, GA) and the extended release is in the following order; HPMC K100M>>>GA, HPMC K15M>>>GA and HPMC K4M>>>GA. Results in agreement with those of the flotation test.

3.8. Effect of HPMC concentration

The release profiles of floating tablets which related the effect of HPMC concentration were depicted in Figure 4. This figure was showed that the dissolution kinetics was slowed and extended for HPMC at both viscosity grades (K15M and K100M). In both cases. it is slower at concentration, 17.5%. Figure 4(a) indicated that in the case of the HPMC K15M, the kinetic was slowed down in the following order: F8>F7=F6=F5. A not negligible difference between the dissolution profiles of formulations F8 and F5 was found from 3 hours onwards of kinetic; *F8>F5*. Similarly, Figure 4(b) shows that in the case of the HPMC K100M the kinetics was slowed down in the following order: F12>F11=F10=F9. A significant difference between the release profiles of formulations F12 and F9 was found from 3 hours onwards of kinetics; *F12>F9* ($p < 0.05$). It was concluded that the formulations containing the HPMC with highest concentration (17.5%), F8 and F12 were exhibited extended release. Finally, the decrease in MTH release rate from the F8 (92.18%) (Figure 4a) and F12 (80%) (Figure 4b) formulations could be explained as follows: at high concentration (17.5%) of HPMC (K15M or K100M), the viscosity of the gelled matrix increases following rapid hydration of the polymer, resulting in a decrease in the drug diffusion coefficient, thus controlling and slowing down the release of metformin hydrochloride into the dissolution medium.
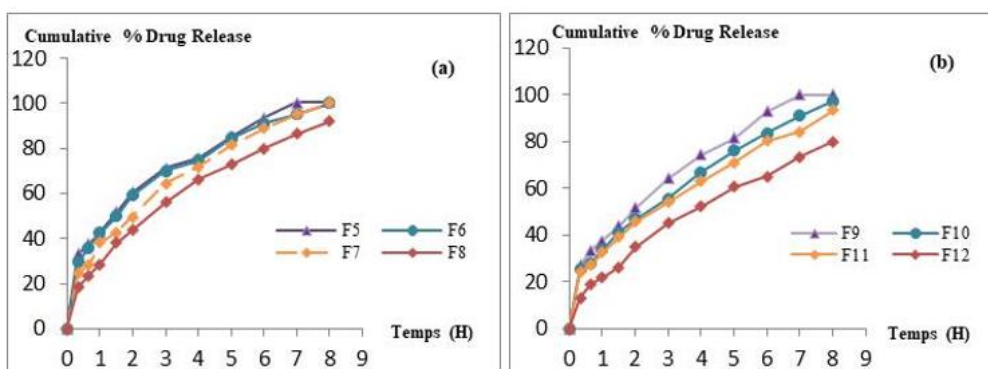

Figure 4 Dissolution profiles of metformin HCl floating tablets. Effect of HPMC concentration (a) HPMC K15M (b) HPMC K100M

3.8.1. Effect of viscosity grade of HPMC

We have evaluated the influence of HPMC viscosity on the dissolution kinetics of metformin HCl from effervescent floating systems prepared. Three viscosity grades of HPMC were studied: HPMC K4M (low), HPMC K15M (medium) and HPMC K100M (high). The dissolution profiles depicted in Figure 5 have shown that for HPMC concentrations of 10, 12.5 and 15%, the viscosity grade has no effect on the release of metformin hydrochloride. The *in vitro* dissolution profiles are similar [Figure 5(a, b, c)]. No significant difference was found ($p \geq 0.05$). While at 17.5% polymer, viscosity has an influence on the kinetics: A significant difference was found between the *in vitro* release profiles of MTH; F8≠F4 and F12≠F4 ($p < 0.05$). The extended drug release is in order; F8>F4 and F12>F4 (Figure 5d). A significant difference was noted between the kinetics of the formulations, F8 and F12 from the 3rd test hour ($p < 0.05$). The extended drug release is in this case; F12>F8 (Figure 5d). Generally speaking, at concentration 17.5% polymer, the drug release was slowed with the increase in viscosity grade in the following order: HPMC K100M>HPMC K15M>HPMC K4M. The floating tablets

containing the highest viscosity polymer, HPMC K100M, at 17.5% (F12) exhibited significantly slowed dissolution kinetics with a rate about 80.00 at 8 hours.

3.8.2. Dissolution time of successive fractions

For each viscosity grade of HPMC, no significant difference ($p \geq 0.05$) was noted between the dissolution times of the successive fractions for concentrations 10, 12.5 and 15%. However, at 17.5% of HPMC, particularly HPMC K100M, the times, $T_{25\%}$, $T_{50\%}$, $T_{80\%}$ were delayed and drug release was significantly extended. Indeed, the formulation, F12 (HPMC K100M 17.5%) has indicated respectively $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ of 1.1982-3.7160 and 8.0060 h compared to 0.7431-2.5670 and 5.9484 h, respectively, for the formulation, F8 (HPMC K15M 17.5%). In addition, the MDT values for these formulations are 3.0540 and 2.7863 h respectively (Table 6). It should also be noted that formulations F8 and F12 have indicated not complete dissolution with metformin hydrochloride release rates of 92.18 ± 1.09 and 80.00 ± 1.14% respectively at the end of 8 hours of testing (Table 5). Finally, it was concluded that at 17.5% of HPMC with highest viscosity (HPMC K100M), a slow and extended release of MTH was obtained from effervescent floating tablets prepared by melt granulation with stearic acid.
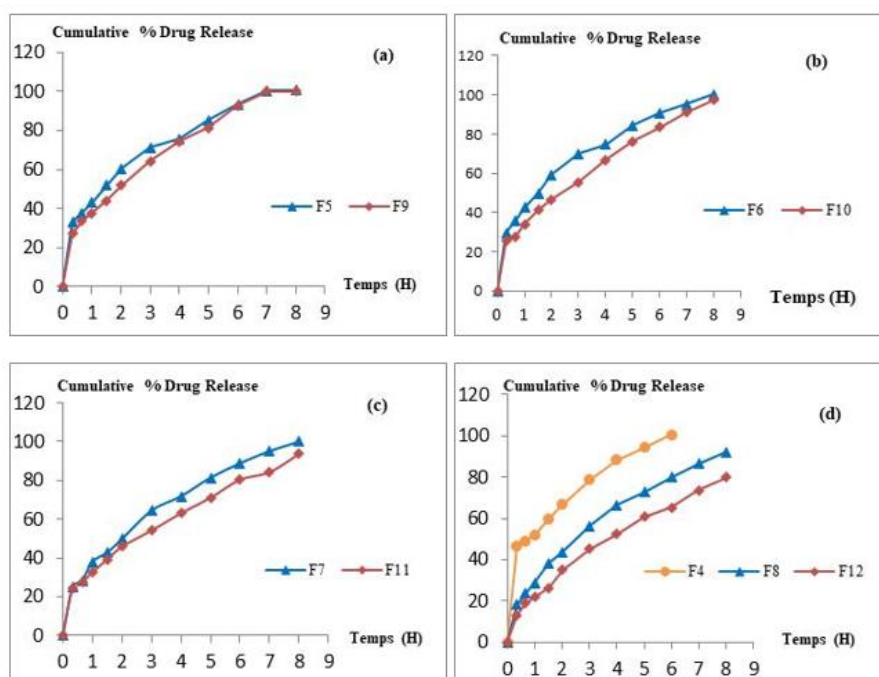

Figure 5 Dissolution profiles of metformin HCl floating tablets. Effect of HPMC viscosity grade (a) 10% (b) 12.5% (c) 15% (d) 17.5%

Table 6 The dissolution times ($T_{25\%}$, $T_{50\%}$, $T_{80\%}$) and the mean dissolution time (MDT) of metformin HCl floating tablets

Formulation Code	$T_{25\%}$ (h)	$T_{50\%}$ (h)	$T_{80\%}$ (h)	MDT (h)
F6	0.2571	1.4118	4.4805	2.3406
F7	0.4125	1.8463	4.9224	2.6032
F8	0.7431	2.5670	5.9484	2.7863
F9	0.4366	1.8019	4.7115	2.4733
F10	0.5820	2.2359	5.5693	2.8379
F11	0.6085	2.4275	6.2029	2.8943
F12	1.1982	3.7160	8.0060	3.0540

3.9. Data modeling of dissolution kinetics

In order to best interpret the kinetics and release mechanism of metformin HCl from floating tablets, *in vitro* release data from floating matrices F6 to F12 were integrated into different release kinetic models (Zero order, First order, Higuchi and Korsmeyer-Peppas) using the method described by Dash et al., and Deepak et al., [28-29]. Correlation coefficients R^2 are used to assess the fit accuracy of each model and to select the best model. The values of R^2, k and n obtained from the various kinetic models are given in Table 7. By comparing the values of R^2 and n of different models, we can choose the model best suited to the release profile and deduce the release mechanism of metformin HCl from formulations prepared. *In vitro* release profiles from all formulations, F6 to F12 could be best expressed by the Higuchi and Krosmeyer-Peppas models as plots showed highest linearity with R^2 values of 0.995 to 0.998 and of 0.995 to 0.997 respectively. The release kinetics of F12 expressed by Krosmeyer-Peppas/Higuchi equations showed R^2 values equal to 0.997. In Krosmeyer-Peppas, the linear plot was for F8 with R^2=0.996 and in Higuchi R^2=0.997. Also, the diffusion exponent "n" values, for all formulations except F6 are above 0.45 (0.478-0.612). It was concluded that for formulations F7 to F12, the metformin HCl release from floating tablets follows a Non-Fickian mechanism (anomalous transport) (n between 0.45 and 0.89). Finally, this indicates that for these formulations, the drug release mechanism is controlled by more than one process: a mixed mechanism of diffusion and erosion.

Table 7 Modeling dissolution kinetics' of MTH floating tablets

Formulation Code	Zero order		First order		Higuchi		Krosmeyer –Peppas		
	R^2	K	R^2	K	R^2	K	R^2	K	n
F6	0.957	7.828	0.976	0.400	0.998	31.07	0.995	43.45	0.407
F7	0.974	8.851	0.960	0.391	0.997	34.89	0.996	37.32	0.478
F8	0.968	8.762	0.986	0.294	0.997	34.67	0.996	29.51	0.559
F9	0.989	10.22	0.950	0.393	0.998	37.37	0.995	37.49	0.489
F10	0.989	9.039	0.907	0.393	0.996	35.37	0.996	33.03	0.515
F11	0.989	8.41	0.943	0.297	0.995	32.88	0.996	32.06	0.501
F12	0.983	7.960	0.990	0.186	0.997	31.26	0.997	22.32	0.612

3.10. FTIR spectroscopy

The FTIR spectroscopy results are shown in Figures 6 and 7. The IR spectra of the physical mixtures (M_{01}-M_{02}) (Figure 6) and the floating formulations (F8-F12) (Figure 7) clearly show the characteristic absorption peaks of MTH as mentioned below:

- N-H; 3 High intensity absorption peaks around 3173, 3302 and 3375 cm^{-1}.

- C=N; two intense absorption bands at 1632 cm^{-1} and 1576 cm^{-1}.

- Aliphatic CH_3; three absorption peaks around 1477, 1450 and 1410 cm^{-1}.

- C-N of aliphatic diamines; low intensity bands between 1250 and 1050 cm^{-1}.

These results confirm the identity of MTH in developed systems [34-36]. Also, no interaction between the active ingredient and the excipient was detected by the FTIR spectroscopy.
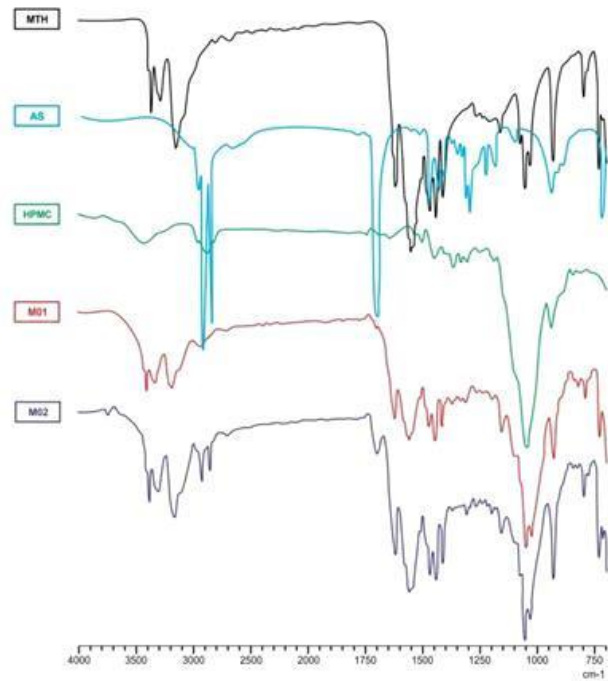
Figure 6 FT-IR spectra of MTH-HPMC-Stearic acid and physical mixtures (M_{01}, M_{02})
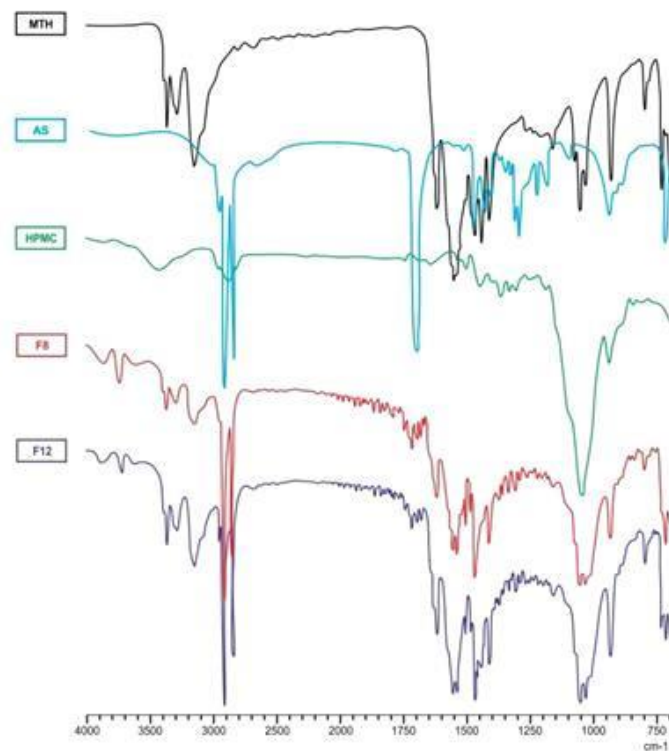

Figure 7 FT-IR spectra of MTH-HPMC-Stearic acid and floating matrixes (F8, F12)

4. Conclusion

In this first experimental part, the results have shown the effect of nature of hydrophilic polymer on the biopharmaceutical behavior of metformin HCl floating tablets prepared by melt granulation. Unlike Acacia gum which alone has not produced conclusive results, HPMC has produced floating matrices with good buoyancy properties and extended release of metformin hydrochloride. Also, the drug release kinetic was found to be dependent on HPMC viscosity, particularly at the concentration 17.5%. At this concentration, when the viscosity grade of HPMC increases, the dissolution kinetic of metformin HCl was more slowed and extended. Indeed, the floating tablets F8 (HPMC K15M) and F12 (HPMC K100M) have exhibited extended release kinetics (>8 hours) with release rates of 92.18±1.09 and 80±1.14% respectively. These formulations can constitute promoter systems for the development of extended-release metformin HCl floating tablets. Also, it should be noted that infrared spectroscopy did not reveal any PA-Excipient interaction despite the melt granulation manufacturing process with stearic acid. Finally, in a next experimental step; we propose to improve the biopharmaceutical properties of the natural polysaccharide, Acacia gum.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

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