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FORMULATION AND EVALUATION OF METFORMIN HCL EFFERVESCENT FLOATING TABLETS

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ABSTRACT

The aim of the present study involved the formulation and evaluation of metformin hydrochloride effervescent floating tablets. Two hydrophilic polymers are used at various concentrations (10, 12.5, 15 and 17.5%), xanthum gum and hydroxypropylmethylcellulose (HPMC) at three viscosity grades (K4M, K15M and K100M). The results have shown the effect of nature of hydrophilic polymer on the biopharmaceutical behavior of metformin HCl floating tablets. The prepared tablets were evaluated for number of parameters like Thickness, Hardness, Weight variation, Friability, Drug content uniformity, Floating lag time, Floating time and in vitro release studies. The drug release kinetic was found to be dependent on HPMC viscosity, particularly at the concentration 17.5%. 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.

KEYWORDS: Metformin HCL, HPMC, Xanthum Gum, Granulation.

1. INTRODUCTION

Oral controlled release drug delivery has recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing

administration, patient compliance and flexibility in formulation.[1,2] Drugs with short half-lives and drugs that easily absorbed from gastrointestinal tract development of oral sustained-controlled release formulations is an attempt to release (GIT) are eliminated quickly from the systemic circulation.

For these types of drugs, the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. Floating drug delivery system is an approach to prolong gastric residence time, there by targeting site-specific drug release in the upper gastro intestinal tract (GIT) for local or systemic effects. This drug delivery system not only prolongs GI residence time but does so in an area of the GI tract that could maximize drug reaching its absorption site in solution and hence ready for absorption.[3] Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach.

Normal gastric residence times usually range between 5 min and 2 h. In the fasted state the electrical activity in the stomach, the inter-digestive myoelectric cycle or migrating myoelectriccomplex (MMC) governs the activity and hence the transit of dosage forms. It is characterized by four phases: Phase I–period of no contraction (40–60 min), phase II–period of intermittent contractions (20–40 min), phase III–period of regular contractions at the maximal frequency that travel distally also known as house keeper wave (10–20 min), and phase IV–period of transition between phase III and phase I (0–5 min).[4]

2. MATERIALS AND METHODOLOGY

2.1 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. 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.

2.2 Preparation of metformin HCl floating tablets

The effervescent metformin hydrochloride floating tablets were prepared by melt granulation of stearic acid in the presence of hydrophilic polymers, xanthum gum Polymer 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 water bath. All the powders were accurately weighed 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 room temperature. Then, this solidified mass was calibrated (1000 µm sieve) and lubricated (addition of talc and magnesium stearate) then compressed using a alternative press equipped with a single flat punches and a 12 mm diameter die. The obtained tablets have the following characteristics: average weight, 500 mg, and diameter, 12 mm.[5-8]

Table no. 1: Formulation of Metformin hydrochloride's effervescent floating tablets.

Formulation Code			Composition of developed formulations (mg)							
	MTH	Stearic Acid	NaH CO3	HPMC K4M	HPMC K15M	HPMC K100M	Xanthum 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, NaHCO3: Sodium bicarbonate, HPMC: Hydroxypropylmethylcellulose, CMC: Microcrystalline cellulose.

2.3 Pre-compression parameters

a. Bulk density

BD=M/BV

Where, BD=Bulk density, M=Weight of sample in grams, BV=Final volume of blend.

b. Tapped Density(TD)

(TD)=M/TV

Where TD =Tapped density, M=Weight of powder in grams, TV=Tapped volume of powder.

c. Angle of Repose

It is defined as maximum angle possible between surface of pile of powder and the horizontal plane. It is an indicative of flow properties of powder.

Tan $^{\theta}$ = h/r,

Where, h=height in cms, r=radius in cms.

d. carr's index or compressibility index

CI=TD-BD/TDX100 Where,

TD=Tapped density of powder, BD=Bulk density of powder, It is expressed in "percentage

e. Hausner's ratio

It is defined as the ratio of tapped density to the bulk density. It is calculated by the formula as follow[9]

Hausner's ratio= TD/BD

Where, TD= Tapped density, BD=Bulk density.

2.4 Post Compression parameters[10-11]

a. Hardness test: The hardness of tablets was measured using Pfizer hardness tester. It is expressed in kg/cm2 Three tablets were randomly picked from each formulation and the mean and standard deviation values was calculated.

b. Thickness and Diameter: Thickness and diameter of the prepared tablets were evaluated with the help of Vernier callipers and screw gauge. It is expressed in mm.

c. Friability test

Friability (%) =Initial weight – final weight × 100 Initial weight

d. Weight variation: The weight variation test was performed as per procedure of IP. The weight of each of 20 individual tablets, selected randomly from each formulation was determined by using electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation¨

e. Determination of drug content uniformity: The test for uniformity of content of single dose preparations is based on the assay of the individual contents. To determine the drug content 10 tablets are selected randomly and assay is performed by using USP type 2 apparatus and UV-Visible spectrophotometer. The batch passes the test if all the tablets are within the limit of 85-115% of the average content, and the test fails if more than 1 tablet is out of limits.

Determination of disintegration time: Disintegration time is the time required for dosage form to break up into granules under a given set of conditions. The test is carried out by using the disintegration tester which consists of a basket rack holding 6 plastic tubes, The tube is opened at the top and bottom of the tube is covered by 10 mesh screen. The basket is immersed in a bath of suitable liquid held at 37^0 C, and the time taken for the tablet to disintegrate completely is recorded. The disintegration time for floating drug delivery system is usually more than 6 hours.

a. **Determination of floating lag time:** The In vitro buoyancy was determined by the lag time. The tablets were placed in the selected medium of 0.1 N HCL or stimulated gastric fluid and the time taken for the dosage from to emerge to surface after introducing it into the medium is recorded. The time for required for a tablet to rise to the surface for floating is called as floating lag time.

b. **Determination of floating time:** The time for which the tablet remains buoyant on the surface of the medium is called as floating time. Tablets were placed in a 10 ml beaker containing 0.1 N HCL and the time for which the tablet remained floating on the surface of the medium was determined.

2.5 *In vitro* buoyancy study

The *in vitro* buoyancy is carried out according.[12] 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.

2.6 Evaluation of swelling index

This test evaluates water absorption characteristics. The pre-weighed individually tablets (W0) 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 (Wt).[13-14]

2.7 *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.

2.8 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[56-60]. Linearization of dissolution data allows a more direct comparison by referring to classical parameters (Intersection-slopes).[15-16]

Zero order: $Qt = Q0 + K0t$

First order: $\text{Log } Qt = \overline{\text{Log}}\ Q0 - \frac{Kt}{2{,}303}$

Higuchi model; $Qt = KH\ t^{1/2}$

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

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.

3. RESULTS AND DISCUSSION

3.1 Characterization of metformin HCl

At 233 nm, analytical wavelength 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.[17-18]

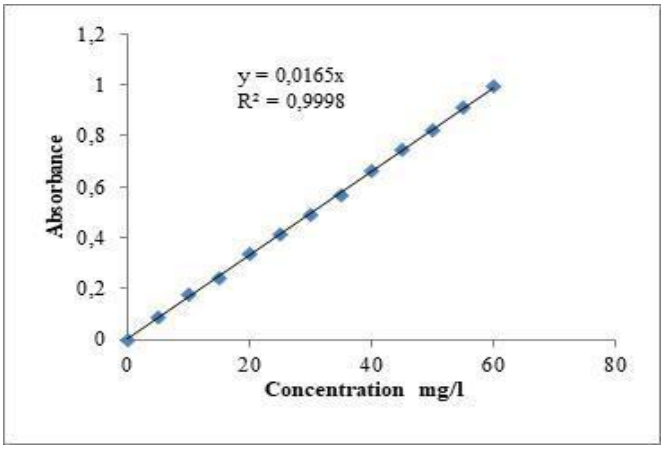

Figure 1: Calibration curve of metformin hydrochloride in 0.1 N HCl.

3.2 Formulation of Metformin HCL effervescent Floating Tablets

The effervescent metformin hydrochloride floating tablets were prepared by melt granulation of stearic acid in the presence of hydrophilic polymers, Xanthum gum Polymer 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 water bath. All the powders were accurately weighed 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 room temperature. Then, this solidified mass was calibrated (1000 µm sieve) and lubricated (addition of talc and magnesium stearate) then compressed using a alternative press equipped with a single flat punches and a 12 mm diameter die.

3.3 Pre-compression parameters

The granules of proposed formulations were evaluated for pre-compression parameters as shown in Table 2.

Table 2: Pre-compression evaluation of metformin HCl floating tablets.

Formulation Code	Angle of Repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Hausner ratio
F1	34.79	0.515	0.606	14.94	1.17
F2	34.50	0.500	0.581	14.50	1.16
F3	34.99	0.495	0.581	14.85	1.17
F4	34.79	0.500	0.588	15.00	1.17
F5	34.68	0.495	0.581	14.85	1.17
F6	34.60	0.495	0.581	14.85	1.17
F7	33.50	0.492	0.546	10.34	1.11

F8	34.79	0.492	0.549	13.33	1.15
F9	34.16	0.500	0.549	12.50	1.13
F10	35.18	0.492	0.584	15.76	1.18
F11	34.91	0.470	0.529	11.26	1.12
F12	33.65	0.467	0.549	14.25	1.17
F13	31.29	0.594	0.687	13.53	1.15
F14	32.3	0.596	0.688	13.37	1.15
F15	32.61	0.595	0.689	13.69	1.15
F16	33.75	0.598	0.694	13.77	1.15

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°, 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 parameters

The floating tablets obtained by melt-granulation were evaluated for post-compression parameters as indicate in table 3.

Table 3: Post-compression evaluation of metformin HCl floating tablets.

Formulation Code	Average Drug content (%)	Weight variation (mg ± SD)[a]	Hardness (kg/cm^2 ± 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

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/cm^2.

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.

3.5 *In vitro* buoyancy study

The results of *in vitro* buoyancy study; floating lag time (FLT), 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 Xanthum gum was more than 1 hour (no floating systems).

Table 4: In vitro buoyancy evaluation ofmetformin HCl tablets.

Formulation Code	Floating lag time[a] FLT (sec)	Total floating time TFT (hrs)
F1	300±30	-
F2	240±40	-
F3	240±30	-
F4	240±20	< 12
F5	300±30	> 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 Xanthum 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.

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).

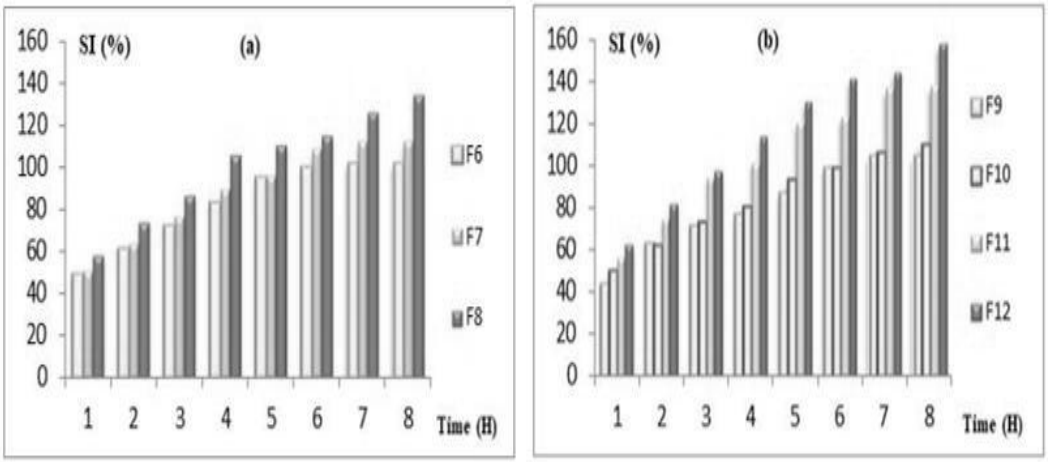

Figure 2: Swelling index. Effect of HPMC concentration (a) HPMC K15M, (b) HPMC K100M.

3.7 *In vitro* dissolution study

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 T25%, T50%, T80% 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 3 illustrates the influence of concentration of hydrophilic polymer. Figure 4 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 Xanthum 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. Xanthum 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 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.

3.7.2 Effect of HPMC concentration

The release profiles of floating tablets which related the effect of HPMC concentration were depicted in Figure 3. 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 3(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 3(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 11a) and F12 (80%) (Figure 3b) 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.

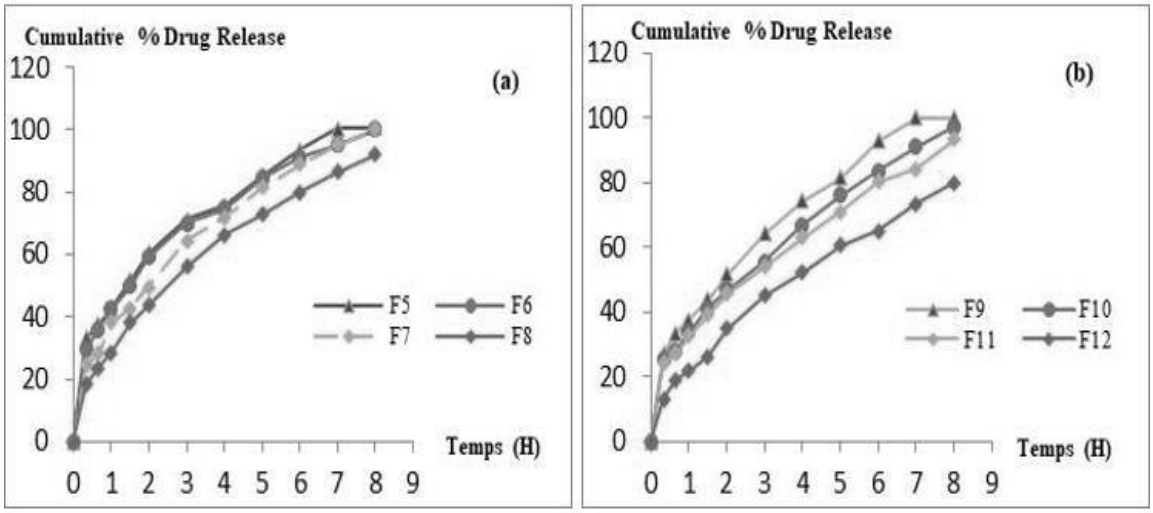

Figure 3: Dissolution profiles of metformin HCl floating tablets. Effect of HPM Cconcentration (a) HPMC K15M (b) HPMC K100M.

Dissolution time of successive fractions

For each viscosity grade of HPMC, no significant difference (p□0.05) was noted between the dissolution times of the successive fractions for concentrations 10, 12.5 and 15%.

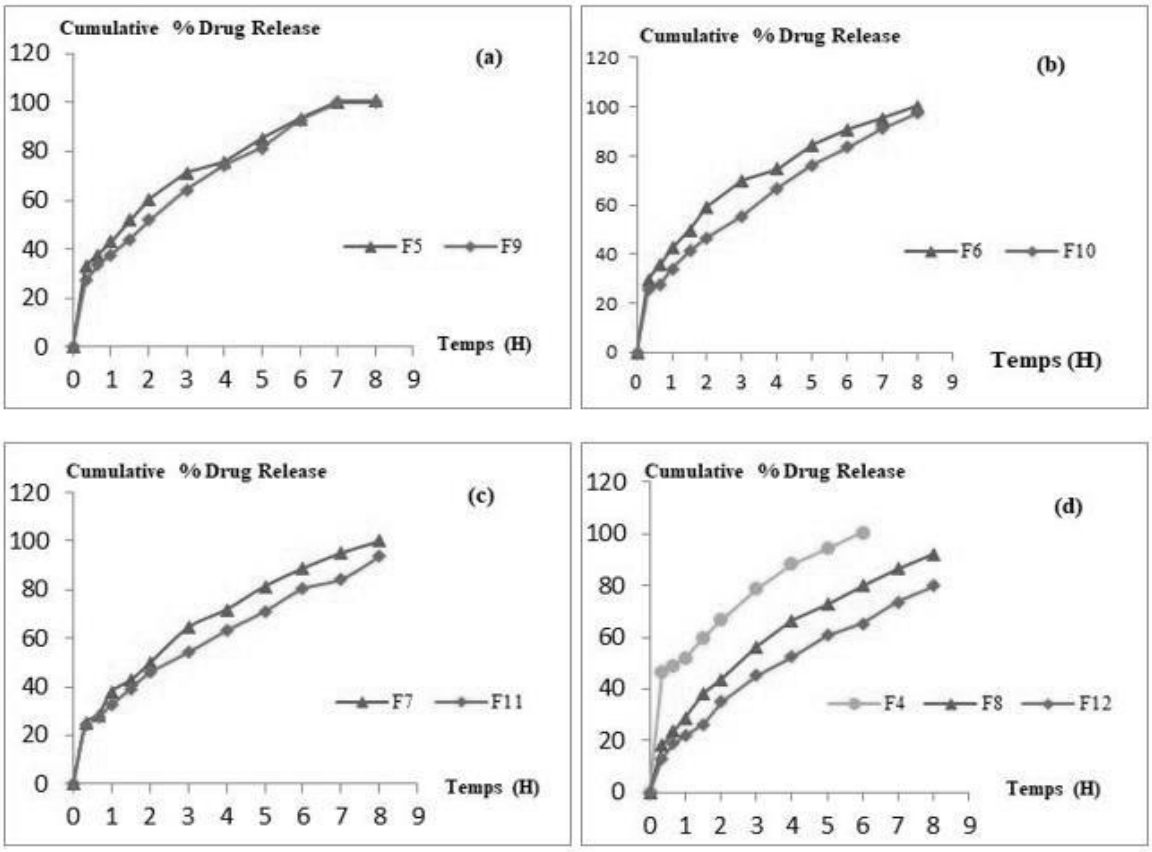

Figure 4: Dissolution profiles of metformin HCl floating tablets. Effect of HPMC viscosity grade (a) 10% (b) 12.5% (c) 15% (d) 17.5%.

However, at 17.5% of HPMC, particularly HPMC K100M, the times, T25%, T50%, T80% were delayed and drug release was significantly extended. Indeed, the formulation, F12 (HPMC K100M 17.5%) has indicated respectively T25%, T50% and T80% 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.

Table 6: The dissolution times (T25%, T50%, T80%) and the mean dissolution time (MDT) of metformin HCl floating tablets.

Formulation Code	T25% (h)	T50% (h)	T80% (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

3.8 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). 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.

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

3.9 FTIR spectroscopy

The FTIR spectroscopy results are shown in Figures 5-9. The IR spectra of the physical mixtures (M01-M02) (Figure 8) and the floating formulations (F8-F12) (Figure 9) clearly show the characteristic absorption peaks of MTH as mentioned below:

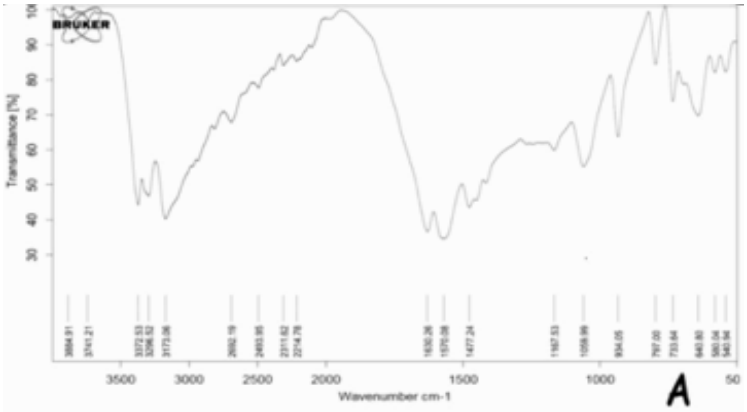

Fig. 5: FTIR Spectrum of Pure Drug Metformin Hydrochloride.

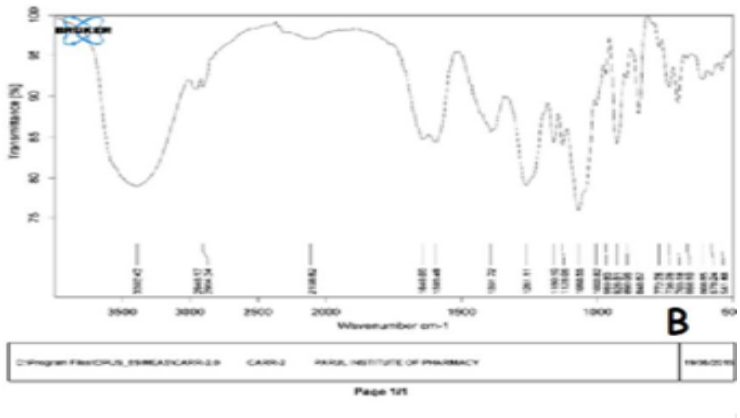

Fig. 6: FTIR Spectrum of polymer Xanthum gum.

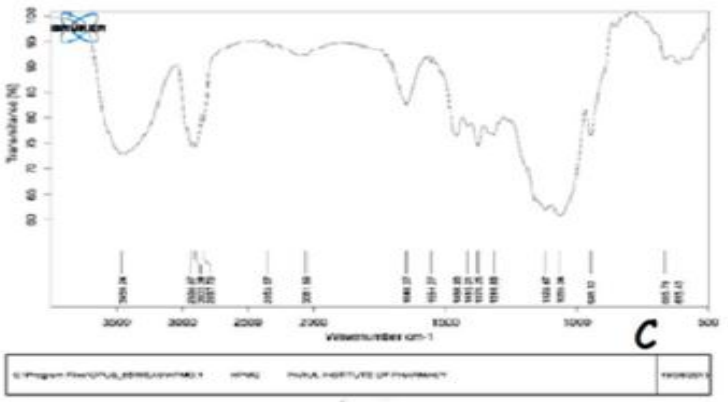

Fig. 7: FTIR Spectra of HPMC K15 Polymer.

- 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 CH3; three absorption peaks around 1477, 1450 and 1410 cm^{-1}.
- C-N of aliphatic diamines; low intensity bands between 1250 and 1050 cm^{-1}.

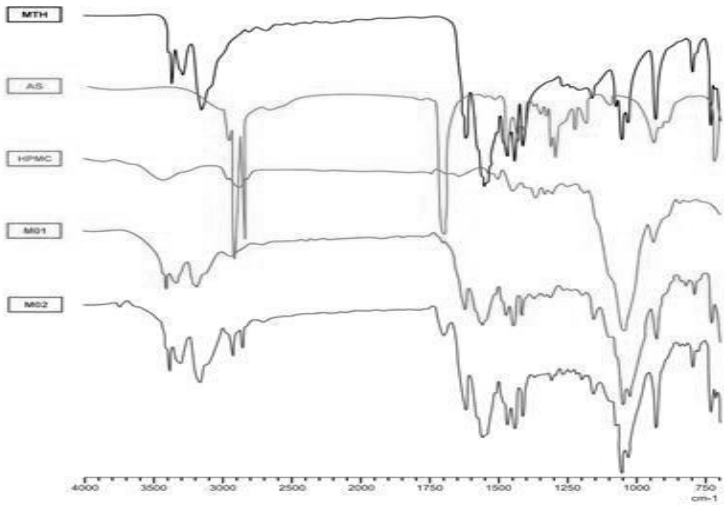

Figure 8: FT-IR spectra of MTH-HPMC-Stearic acid and physical mixtures (M01, M02).

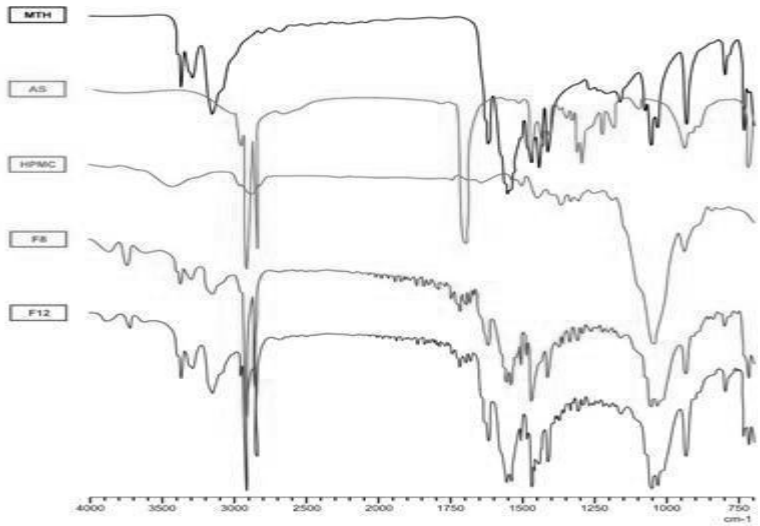

Figure 9: FT-IR spectra of MTH-HPMC-Stearic acid and floating matrixes (F8, F12).

These results confirm the identity of MTH in developed systemsAlso, no interaction between the active ingredient and the excipient was detected by the FTIR spectroscopy.

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