Original Article

FORMULATION AND *IN VITRO* EVALUATION OF AMLODIPINE GASTRORETENTIVE FLOATING TABLETS USING A COMBINATION OF HYDROPHILIC AND HYDROPHOBIC POLYMERS

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ABSTRACT

Objective: The aim of this study was to formulate a developed floating tablet of amlodipine using different concentrations and types of hydrophilic and hydrophobic polymers to be conserved in the stomach for modulating solubility and bioavailability, diminishes drug waste and decline side effects.

Methods: Through this study, eleven innovative formulations of amlodipine floating tablets were prepared [mixture of amlodipine, sodium bicarbonate ($NaHCO_3$), hydroxypropyl methylcellulose (HPMC) E50, HPMC K100M, ethylcellulose (EC) 5 mp. a. s.] by direct compression method. The pre-compressed mixtures were then evaluated for numerous parameters such as angle of repose, bulk density, tapped density, Carr's compressibility index and Hausner's ratio. After compression, tablets were subjected to several tests like; floating behavior of tablets, tablet thickness, hardness test, friability test, weight variation, *in vitro* dissolution test. In addition, the optimum formulation was evaluated for Fourier transform-infrared (FT-IR) and differential scanning calorimetry (DSC) tests.

Results: From *in vitro* dissolution tests and kinetic assessments; F8 was selected as an optimum formula, depending on the R^2 value of zero order kinetics (0.9915) and (n) value of Korsmeyer-Peppas (0.9635) which indicate purely relaxation zero order kinetic with good delaying in drug release that was reached to 14 h.

Conclusion: It can be concluded that the developed formulation of a certain combination of low viscosity grades of HPMC and EC was considered an efficient floating tablet.

Keywords: Floating tablet, Gastroretentive, Amlodipine, EC 5 mp. a. s., HPMC E50, HPMC K100M

INTRODUCTION

Over 90% of the formulations manufactured today are ingested orally. This show that this class of formulation is the most popular worldwide and major attention of the researcher is towards this direction [1]. Furthermore, oral delivery of drugs is the utmost chosen route of drug delivery due to the ease of administration; low cost of therapy, patient compliance, and flexibility in formulation [2]. In addition, this drug delivery system gives place for a therapeutic amount of drug to the desired site in the body to attain promptly and then preserve desired drug concentration [3].

Gastric emptying is an intricate process with high inconstant and alteration *in vivo* execution of drug delivery system [4]. Prolonged gastric retention enhances bioavailability, minimize drug waste, and ameliorate solubility of drugs with less solubility in an elevated pH environment [5]. Numerous trials have been made to conserve the dosage form in the stomach as a method of increment in the retention time. These trials involve presenting floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Between these, the furthermost ordinarily used system is the floating dosage forms [6, 7].

The idea of floating tablets is primarily constructed on the drug delivery system of matrix type, so the drug exists embedded in the matrix which after approaching in contact with the gastric fluid swells up, and the slow erosion of the drug without disintegration of the tablet takes place [8]. In these sorts of drug delivery system, the gel-forming hydrocolloid and the drug are mixed carefully. Afterward oral administration, this dosage form upon imping with gastric fluids it swells and achieves a bulk density of <1. The entrapped air inside the swollen matrix pickup flotation to the dosage form. Therefore, the designed gel-like structure is swollen and turns as a barrage and permits the release of the drug in a sustained form over the gelatinous mass. Drug release from hydrophilic matrix tablets is taking control by the creation of a hydrated viscous layer around the tablet which turns as a barrier to drug release by opposing penetration of water into tablet and movement of dissolved solutes out of the matrix tablets [9-11].

Amlodipine (AD) can be classified into the group of calcium channel blockers. Thus, it is frequently used to treat different heart diseases like angina and hypertension [12, 13]. Moreover, it has an ultimate solubility in acidic pH [14]. Based on this, an attempt was made through this investigation to formulate floating tablet of amlodipine besylate using different hydrophilic and hydrophobic polymers and their combinations; thus, conserve in the stomach to modulate solubility, bioavailability, diminishes drug waste and decline side effects such as gastric irritation and nausea.

MATERIALS AND METHODS

Materials

Amlodipine Besylate (Samara drug industry, Iraq), Avicel (Samara drug industry, Iraq), Talc (Samara drug industry, Iraq), Magnesium Stearate (Samara drug industry, Iraq), Hydroxypropyl methylcellulose (HPMC) E50 and HPMC K100 (Aladdin, China), Ethylcellulose (EC) 5 mp. a. s. (Aladdin, China), Sodium bicarbonate ($NaHCO_3$) (Samara drug industry, Iraq).

Method

Preparation of floating amlodipine tablets

The preparation of amlodipine floating tablets was done by direct compression method according to formulas given in (table 1). Floating tablets contained a mixture of amlodipine, sodium bicarbonate (as a generating agent of gas). Hydroxypropyl methylcellulose (HPMC) E50, HPMC K100M, ethylcellulose (EC) 5 mp. a. s act as rate controlling polymers. Altogether ingredients were precisely weighed then passed over sieve no.70. After sieving these ingredients were mixed uniformly for 10 min. The powder blend was then mixed with the required

amount of magnesium stearate and talc powders. After this addition, the mixture was further mixed for two minutes. The mixture result is compressed into tablets by a single punch tablet machine (Riva MII-UK) using 8 mm set of punch and die.

Table 1: Formulation of amlodipine floating tablets

Formulas ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Amlodipine	5	5	5	5	5	5	5	5	5	5	5
HPMC E50	50	60	70	80	90	80	80	80	80	80	-
HPMC K100M	-	-	-	-	-	-	-	-	-	-	80
EC 5 mp. a. s	5	5	5	5	5	10	20	30	40	30	30
Avicel	133.5	123.5	113.5	103.5	93.5	98.5	88.5	78.5	68.5	73.5	78.5
NaHCO$_3$	5	5	5	5	5	5	5	5	5	10	5
Mg Stearate	1	1	1	1	1	1	1	1	1	1	1
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total amount	200	200	200	200	200	200	200	200	200	200	200

Characterization of floating amlodipine tablets

Pre-compression parameters

The flow properties of powders before compression were qualified in terms of different tests that are according to US Pharmacopeia standards.

Angle of repose

The angle of repose utilized as indirect methods of determining powder flow ability due to their connection with interparticle cohesion. A static pile will slide when the inclination angle is vast enough to conquer frictional forces and stopover when gravitational forces balance the forces. The sides of the pile will produce an angle with horizontal which is termed as the angle of repose [15].

$$\text{Tan } \theta = \frac{h}{r}$$

Where h is the height of pile and r is the radius of the pile.

Bulk density

Bulk density (Pb) of floating tablets can be expressed in grams per cc (g/cc), and it was defined as the mass "M" of the powder picking a known volume 'V_0' according to the relevance [16].

$$\text{Bulk density (Pb)} = \frac{\text{Mass (M)}}{\text{Bulk volume (V}_0)}$$

It leans on particle size, shape, the tendency of the particle to adhere.

Tapped density

A weighed quantity of powder was introduced into a graduated cylinder and was tapped from a height of 2 cm for a fixed number of taps (100). It is the proportion of the weight of the sample to tapped volume [17].

$$\text{Tapped density} = \frac{\text{Mass (M)}}{\text{Tapped volume (Vt)}}$$

Carr's compressibility index

Carr's compressibility index constructed on the obvious bulk density and the tapped density, the percentage compressibility was determined as the following formula [18].

$$\% \text{ Compressibility} = \frac{\text{Tapped density-bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio

Hausner's ratio can be determined as the ratio of tapped density to the bulk density of the powders and as the resulting equation [19].

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Post-compression parameters

Content uniformity

Assessment of drug content, 10 tablets were haphazardly selected and powdered. A measured amount of powder equivalent to the mass of one tablet (200 mg) was precisely weighed and transferred into a volumetric flask and dissolved in 100 ml of 0.1 N HCl. The flask was shaken until complete dissolving, and the solution was filtered. 1 ml of the above solution was diluted suitably with 0.1 N HCl. The absorbance of the resulting solution was measured at 366 nm using UV-visible spectrophotometer (Shimadzu 1650 pc-Japan) [20].

Floating behavior of tablets

These studies can be applicated by taking tablets (*n* = 3) and place in 1000 ml of 0.01 N HCl in USP type II dissolution apparatus (Copley–USA) (37±0.5 °C, 50 rpm). The time desired for tablets to be a float at the topmost of the medium was considered as floating lag time. The interval of time the tablet continuously keep on the surface was considered as the total floating time [21].

Tablet thickness

The thickness of the tablet was set using a vernier caliper (Copley-UK). Twenty floated tablets were used from each formula, and the average values were decided.

Hardness test

The hardness test was implemented in which 10 tablets from each formula were examined haphazardly, and the average reading±SD was recorded as kg/cm^2 [22].

Friability test

The friability test was achieved by placing 20 pre-weighed tablets in the friabilator (Vanguard-USA) which was then run for one hundred revolutions; the tablets were then dusted and reweighed. Tablets that lose a maximum of not more than 1% of their weight are generally considered acceptable [23]. Percentage friability was calculated from the following equation:

$$\% \text{ Friability} = \frac{(W_0) - (W)}{(W_0)} \times 100$$

W_0 = weight of tablets before the test

W = weight of tablets after the test

Weight variation

This test was achieved by weighing 20 floating tablets separately and the average weight calculated. The demands are encountered if the weights of not more than 2 of the floating tablets differ from the average weight by more than the percentage recorded in the USP and no tablet varies in weight by more than double that percentage [24].

In vitro dissolution studies

The release of amlodipine from floating tablets was executed by USP Dissolution Test Apparatus Type-II (Paddle method; Copley-USA). The temperature of the dissolution medium (0.1 N HCl, 900 ml) was maintained at 37±1 °C with a stirring rate of 50 rpm. The floating tablets were dropped inside the dissolution apparatus vessels. A 5 ml sample of the solution was withdrawn hourly, and the same amount of samples were replaced with fresh dissolution medium.

The obtained samples were filtered and analyzed in a triplicate using UV-visible spectrophotometer at 366 nm and the % drug release was calculated using an equation obtained from a standard calibration curve [25].

Kinetic assessment of dissolution data

The dissolution rate data obtained were evaluated for compatibility with the kinetics of zero order, first-order, Higuchi, and Korsmeyer-Peppas and verdict the R^2 values of the dissolution profile incongruent to each model. The time required for 80% ($T_{80\%}$) drug release was calculated according to the best fit model with the highest determination R^2 [26].

Drug-excipients interaction study and identification

Fourier transform infrared spectroscopy (FT-IR)

Compatibility studies were implemented to distinguish the conceivable interactions between Amlodipine and polymers used in the formulation. Physical mixtures of drug and polymers were all set to study the compatibility. These compatibility studies were achieved utilizing FT-IR spectrophotometer (SPECTROLAB MB3000, UK). The IR spectra's scanning range were recorded in between 450–4000 cm^{-1} [27].

Differential scanning calorimetry (DSC)

The possibility of drug-excipient interaction was further investigated by differential scanning calorimetry. DSC curve for each of pure powders of amlodipine, hydroxypropyl methylcellulose (HPMC) E50, ethylcellulose (EC) 5 mp. a. s., in addition to the physical mixture of the optimum formula of amlodipine in the presence of polymers (Precompression) and compressed tablet (post compression) analysis, was implemented using DSC instrument (DSC-60, Shimadzu–Japan). The samples were accurately weighed and heated in a sealed aluminum pan at a rate of 10 °C/min. within a 10 and 250 °C temperature range under a nitrogen flow of 40 ml/min. Alumina was utilized as a reference [15].

RESULTS AND DISCUSSION

Characterization of floating amlodipine tablets

Pre-compression parameters

Pre-compression parameters play a vital role in improving the flow properties of pharmaceuticals, particularly in tablet formulation. These contain an angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio.

Angle of repose

Flow properties of the powder, the resistance of particle to particle movement could be arbitrated by using the angle of repose. This mensuration gives a qualitative and quantitative estimation of internal cohesive and frictional force under low levels of the external load as might be utilized in mixing and tablet compression [18]. Values for the angle of repose were showed in (table 2) and found to be in the range of 21.15 °±0.25 to 31.23 °±0.22 indicating excellent flow properties.

Tablet 2: Pre-compression parameters of the prepared amlodipine tablets

Formula code	Angle of repose	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility index (%)	Hausner's ratio
F1	28.67±0.34	0.431±0.06	0.591±0.09	22.1±0.05	0.065±0.11
F2	21.30±0.27	0.583±0.11	0.496±0.12	24.05±0.09	1.81±0.05
F3	28.15±0.39	0.561±0.01	0.632±0.08	21.78±0.12	0.141±0.03
F4	26.19±0.31	0.571±0.02	0.519±0.06	21.07±0.06	1.15±0.09
F5	24.34±0.28	0.521±0.07	0.632±0.14	17.32±0.14	0.146±0.03
F6	31.23±0.22	0.437±0.04	0.623±0.11	28.78±0.03	0.121±0.07
F7	21.15±0.25	0.541±0.16	0.512±0.06	24.24±0.12	1.1±0.04
F8	24.58±0.21	0.510±0.02	0.610±0.03	21.32±0.02	0.112±0.01
F9	25.67±0.31	0.467±0.12	0.455±0.11	22.52±0.08	1.39±0.02
F10	30.90±0.25	0.458±0.03	0.581±0.07	25.9±0.13	0.078±0.27
F11	28.13±0.37	0.486±0.14	0.614±0.02	18.12±0.15	0.154±0.07

All formulas represent (Number of experiments n=3, mean±SD)

Carr's compressibility index

Carr's Index is considered as a mensuration of powder bridge strength and stability. Thus, the values of compressibility index range between 17.32±0.14% to 28.78±0.03% as showed in (table 2) and this point outs good flowability of the powder blend and represented low cohesiveness; that is adequate for the essential tableting technological parameters [28].

Hausner's ratio

Hausner's ratio was measured to determine the inter-particulate friction and consolidation. The powder blend of most formulas has Hausner ratio below 1.25 as showed in (table 2) and thus indicate good flow properties so these values displayed that the powder blend had acceptable flow properties [29].

Post-compression parameters

Content uniformity

For content uniformity test, table 3, results are in the acceptable range, indicating that all tablets fit (BP) criteria; in which each tablet drug content was between 98.4% and 99.7% of related average content [16].

Tablet thickness

The thickness of the tablets was showed in (table 3); that was between (4.2±0.01-4.8±0.03) mm. From these results, it can be detected that those batches with a low concentration of polymer showed less thickness of the tablets obtained due to lower concentrations of polymer. Moreover, a higher concentration of polymers produces more thickness for tablets and less dense [30].

Table 3: Post-compression parameters of the prepared amlodipine floating tablets

Formula code	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm²)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	4.2±0.01	8.04±0.03	7.2±0.02	199.2±1.63	0.48±0.05	99.3±0.61
F2	4.2±0.02	8.04±0.01	7.2±0.01	199.1±2.51	0.51±0.12	98.9±0.57
F3	4.3±0.05	8.01±0.02	7.3±0.01	199.5±2.82	0.52±0.01	99.3±0.77
F4	4.5±0.10	8.03±0.02	7.3±0.03	199.2±2.71	0.45±0.11	98.8±0.96
F5	4.5±0.15	8.02±0.01	7.4±0.02	198.8±1.92	0.43±0.03	99.7±0.45
F6	4.4±0.02	8.03±0.05	7.3±0.02	199.3±2.25	0.52±0.07	98.6±0.91
F7	4.3±0.01	8.02±0.03	7.4±0.02	198.9±1.15	0.41±0.04	99.4±0.81
F8	4.6±0.01	8.01±0.01	7.4±0.03	199.2±2.11	0.40±0.01	99.2±0.62
F9	4.8±0.03	8.01±0.01	7.5±0.01	199.1±2.32	0.53±0.02	99.3±0.73
F10	4.5±0.02	8.02±0.02	7.4±0.02	199.2±1.85	0.43±0.14	98.4±0.94
F11	4.4±0.05	8.01±0.01	7.3±0.02	199.2±1.91	0.51±0.06	98.4±0.88

All formulas represent (Number of experiments n=3, mean±SD)

Hardness test

In table 3 the hardness of the tablets was between (7.2±0.01-7.5±0.01) kg/cm² and this confirms best characteristics of handling for all the batches. The study shows a slight increase in the hardness of tablet containing the largest quantity of ethylcellulose (EC) as shown in (F9), this may be due to the increase in density of powders blend and a reasonable increase in the number of interaction points or the bonding surface area that governs the tablet more hardness which is confirmed by the increase in thickness of tablet as shown in F9 [5].

Friability test

The friability of the tablets normally performed and quite expectedly as showed in (table 3). The results of all formulas were in the range (0.41±0.04-0.53±0.02) %. This fact appears to specify that the plasticity of ethylcellulose (EC) ameliorate the cohesion strength of the tablet. According to this, the recorded friability values for the specified formulas were under 1% which can generally be regarded as a desirable mechanical resistance of the tablet [31, 32].

Weight variation

Weight is compendial standard to assess the quality of tablets, and thus the weight variation test must indicate that all the tablets were uniform with low standard deviation values. In case of amlodipine floating tablets; (tablet 3) demonstrate that weight variation of all formulas was in the range of (198.8±1.92-199.5±2.82). The formulated matrix tablets met the acceptable pharmacopeial range (>0.5%) which indicate good uniformity requirement of weight [33].

Floating behavior of tablets

Floating behavior of amlodipine tablets including floating lag time and total floating time was investigated and showed in (table 4). These floating tablets were all set with different grades of hydrophilic polymers in addition to hydrophobic polymer and then evaluated for the entrapment of CO_2 bubble efficiency and the ability to maintain matrix integrity.

Floating tablets prepared with hydroxypropyl methylcellulose (HPMC) E50 [hydrocolloid gelling agent] (F1-F5) absorbs water and swell upon contact with an aqueous medium (0.1 N HCl, pH 1.2), which retarded the drug release. In addition, the floating property of these prepared tablets was evaluated to determine the effect of increasing hydroxypropyl methylcellulose (HPMC) E50 concentration. This polymer was found capable of retaining the matrix integrity for a desired time span and a decrease in floating lag time was achieved, moreover, that total floatation time was maintained for more than 24 h. This may be assigned to the fact that as the raised in volume was greater in comparison to the increase in mass during swelling, the density decreases, and the systems started to float [34].

Ethylcellulose (EC) 5 mp. a. s. was added to the formulation (F6-F9) release retardant polymer being insoluble in gastric pH. It was observed that floating lag time and total floatation time is elevated for these formulations by increasing concentration of ethylcellulose. This is due to ethylcellulose (EC) hydrophobic nature, so it can retard the diffusion of the dissolution medium to the matrix, and this will delay the reaction between the dissolution medium and $NaHCO_3$ (Sodium bicarbonate); thus, the generation of CO_2 will be affected, and hence floatation time will be prolonged [35].

Sodium bicarbonate stimulates carbon dioxide generation in the incidence of dissolution medium (0.1 N HCl). The gas produced is trapped and protected within the gel, formed by hydration of polymer, thus diminishing the density of the tablet. As the density of the tablet falls below 1 g/ml, the tablet turns out buoyant [36]. The effect of sodium bicarbonate on the buoyancy of the tablets was evaluated in formulas (F9 and F10) by using it at two diverse levels 5, 10 mg per tablet. Table 4 illustrates the outcomes of the *in vitro* buoyancy, such that; all formulations kept their matrix integrity for more than 24 h. The result of the total floating time for the formulations was more than 24 h irrespective to the amount of sodium bicarbonate ($NaHCO_3$) whereas floating lag time decreases with increasing amount of sodium bicarbonate [37]. The carbon dioxide generated is widely relative to the quantity of sodium bicarbonate ($NaHCO_3$) in the tablet. The decrease in floating lag time of the formulations can be referred to the availability of an increased amount of CO_2 as the concentration of sodium bicarbonate ($NaHCO_3$) was increased, being captured in the formed gel to give buoyancy [38].

In Formula 11, the floating tablets that prepared with a higher viscosity grade of hydroxypropyl methylcellulose (HPMC) K100M were observed to have increased in floating lag time and total floatation time for more than 24 h in comparison with F10 that prepared with a lower grade of hydroxypropyl methylcellulose (HPMC). This was probably owing to more polymer entanglement and more gel strength also, to the smaller efficacious molecular diffusion area within a high viscosity as compared with a low-viscosity grade of hydroxypropyl methylcellulose (HPMC) [39].

Table 4: Floating lag time and total floating time of formulations

Formulas tests	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Floating Lag Time (min)	4	3	2.5	1.75	0.5	3.5	3.75	4	8	3	4.5
Total Floating Time (h)	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24

***In vitro* dissolution studies**

It was evident from fig. 1 that formulations (F1-F3) showed rapid release within 7 h, while in (F4 and F5) they showed a delay in drug release for 8 h and 11 h respectively. This clearly elucidates that release rate influenced by hydroxypropyl methylcellulose (HPMC) E50 concentration significantly ($p < 0.05$), as the concentration of hydroxypropyl methylcellulose (HPMC), E50 increased; the release rate decreased [40]. Accordingly, it may be imputed to the increment in the molecular weight of the polymer, resulting in an increased entanglement of the macromolecules. Thus, the mobility of the polymer concatenations decreased, minimizing the free volume accessible for diffusion. Hence, the possibility for a drug molecule to jump from one cavity to another is diminished, leading to a diminished mass transfer rate [34].

In addition, formulations (F6-F9) were used to inspect the effect of ethylcellulose (EC) 5 mp. a. s. concentration on drug release as showed in fig. 2. The results pointed out that as the concentration of EC raised; the drug release rate decrease significantly ($p < 0.05$). This is owing to the hydrophobic polymer characteristics that are essentially insoluble in this media which retards the drug release to a greater extent [41]. A more plausible explanation for this phenomenon would be the higher molecular weight ethylcellulose (EC) 5 mp. a. s. the polymer was less soluble in water and thus with lower aqueous viscosity. Moreover, formula 8 showed an optimum drug release as there was a combination effect between hydroxypropyl methylcellulose (HPMC) E50 with hydrophilic effect and ethylcellulose (EC) 5 mp. a. s. with hydrophobic effect [42].

Formulations (F8 and F10) were chosen to determine the effect of sodium bicarbonate ($NaHCO_3$) concentration on drug release. The results showed that a non-significant effect ($p > 0.05$) for increasing the concentration of sodium bicarbonate on drug release rate as showed in fig. 3.

The release of amlodipine from formulations (F8 and F11) was studied to determine the effect of various hydroxypropyl methylcellulose (HPMC) grades on dissolution profile and as showed in fig. 4. The cumulative drug release rate from hydroxypropyl methylcellulose (HPMC) K100M was significantly ($p < 0.05$) lesser than hydroxypropyl methylcellulose (HPMC) E50. This is owing to decreases in the primary burst release which could be due to increase swelling of the high viscosity polymer with increasing

amount; forming greater matrix integrity and longer diffusional path length; thus, less permeability of water. As perspective, the drug release rate was relying on the viscosity grade, and concentration of the polymers utilized [43].
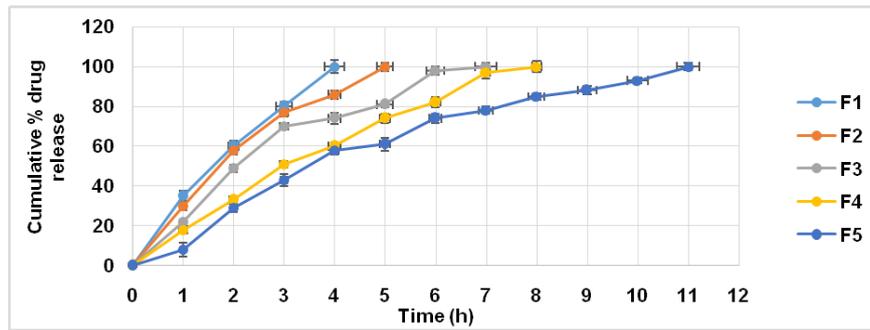

Fig. 1: Dissolution profile of amlodipine from floating tablets containing different concentrations of HPMC E50 (F1-F5), data given in mean±SD, n=3
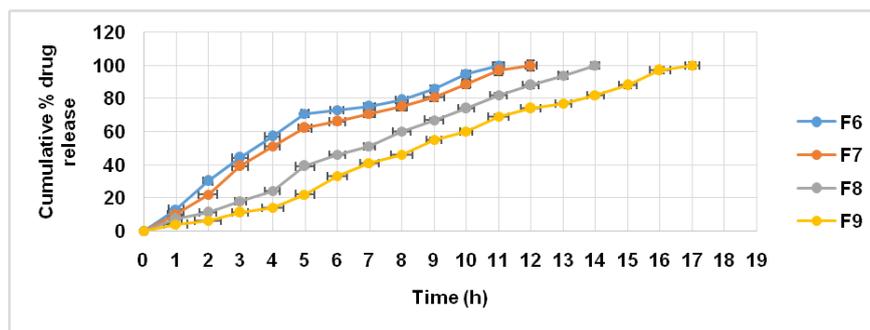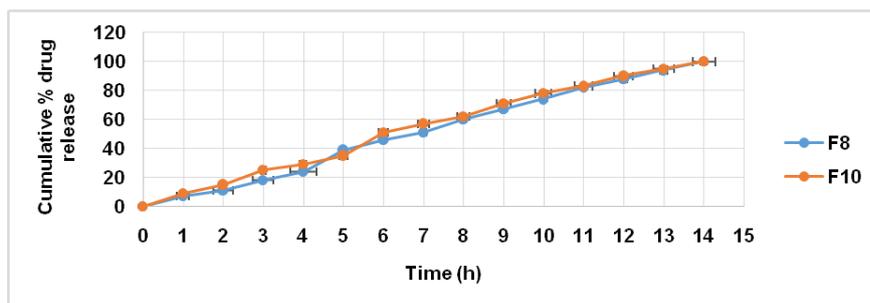

Fig. 2: Dissolution profile of amlodipine from floating tablets containing different concentrations of EC 5 mp. a. s. (F6-F9), data given in mean±SD, n=3

Fig. 3: Dissolution profile of amlodipine from floating tablets containing different concentrations of $NaHCO_3$ (F8 and F10), data given in mean±SD, n=3
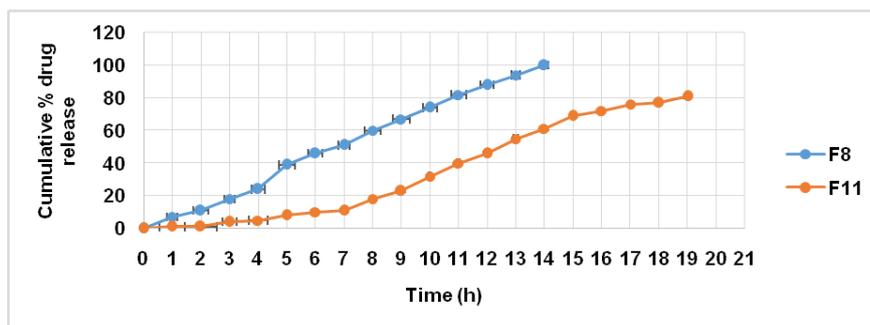

Fig. 4: Dissolution profile of amlodipine from floating tablets containing different grades of HPMC (F8 and F11), data given in mean±SD, n=3

Kinetic assessment of dissolution data

The drug release date acquired were extrapolated by zero order, first order, Higuchi, and Korsmeyer-Peppas equations to distinguish the mechanism of drug release.

The data from table 5 shows that F1-F4 have n value ranging from 0.45 to 0.89 that could indicate coupled diffusion and relaxation (non-Fickian) release mechanism [44]. While F4 was used to study the influence of ethylcellulose (EC) concentration on drug release kinetics as it provides the longest time for drug release and higher regression (R^2) for zero order kinetic. In addition, F6-F9 were used to study the effect of ethylcellulose (EC) 5 mp. a. s. concentration on drug release kinetics. Thus, F8 was selected as an optimum formula, this is due to the (R^2) and (n) value indicate purely relaxation zero order drug release with good delayed in drug release, and this will maximize the efficacy while minimizing dose frequency and toxicity [45].

Table 5: *In vitro* release kinetic data for the prepared formulations

| Formulation	Zero-order		First-order		Higuchi-order		Korsmeyer-Peppas		
	K_0 (mg h^{-1})	R^2	K_1 (h^{-1})	R^2	K_H (h$^{-1/2}$)	R^2	n	K_{kp} (h$^{-1/3}$)	R^2
F1	22.5	0.9959	-0.2559	0.9898	61.416	0.9999	0.7552	1.5459	0.9994
F2	18.7	0.9509	-0.2358	0.9986	57.054	0.9841	0.7776	1.4971	0.9784
F3	14.3	0.8896	-0.1519	0.9662	47.955	0.9476	0.8180	1.3909	0.9427
F4	12.914	0.9860	-0.1318	0.9841	45.143	0.9950	0.8589	1.2647	0.9948
F5	10.476	0.9481	-0.1085	0.9889	41.696	0.9885	1.0776	1.0345	0.9375
F6	8.6167	0.9073	-0.0941	0.9747	36.378	0.9666	0.8369	1.1955	0.9553
F7	8.7	0.9360	-0.0832	0.9923	36.450	0.9821	0.9506	1.0670	0.9653
F8	7.709	0.9915	-0.0723	0.9585	33.934	0.9707	0.9635	0.9208	0.9912
F9	6.611	0.9892	-0.0574	0.9606	32.108	0.9577	1.2735	0.4856	0.9811
F10	7.8	0.9931	-0.0686	0.9530	34.259	0.9680	1.0936	0.7780	0.9861
F11	5.1719	0.9638	-0.0423	0.9181	28.136	0.8924	1.7381	-0.2718	0.97
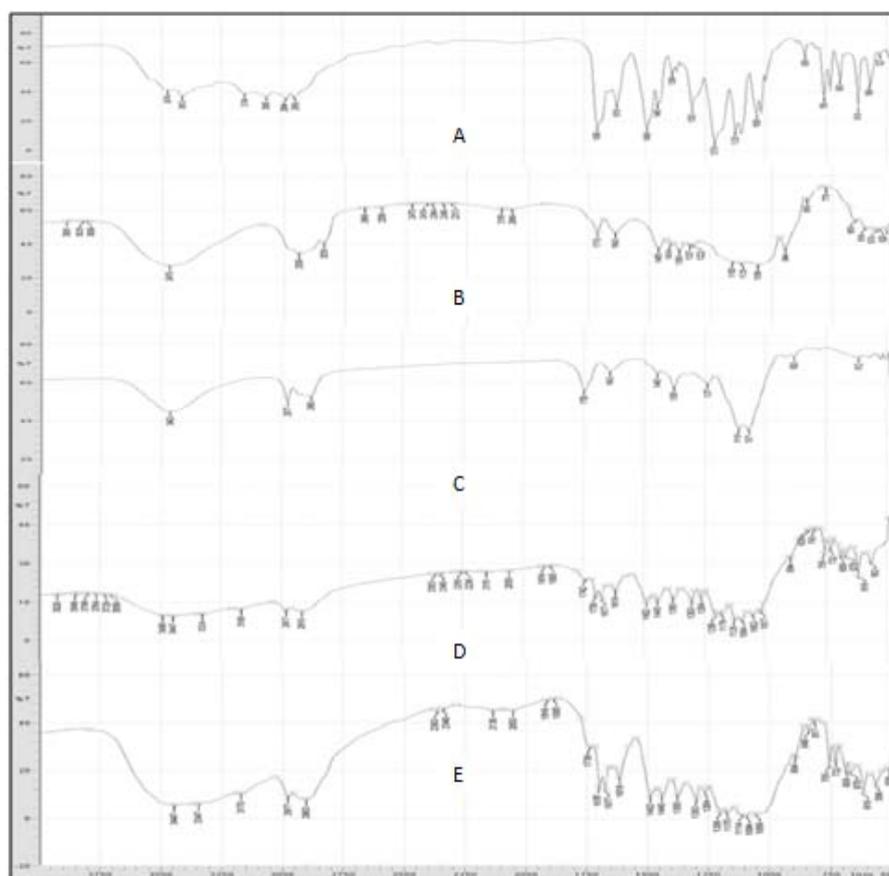
Fig. 5: The FT-IR spectra for (A) pure amlodipine; (B) HPMC E50; (C) EC 5 mp. a.s; (D) Physical mixture; (E) Amlodipine floating tablet [F8]

Drug-excipients interaction study and identification

Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectroscopy was used to establish the compatibility of amlodipine besylate with polymers. The pure drug powder (fig. 5A), polymers [HPMC E50, EC 5 mp. a. s] as showed in (fig. 5B and 5C) respectively, a physical mixture of the drug with polymers (fig. 5D); in addition to amlodipine floating tablet (F8) as showed in (fig. 5E) were individually scanned.

The FT-IR spectrum for pure drug was characterized by the principal absorption bands at 3415/cm and 3154/cm due to N‑H (stretching), 3065/cm due to =C‑H (aromatic stretching), 2984 and 2950/cm due to C‑H (stretching), 1 696/cm due to C=O (stretching vibration), 1615/cm and 1488/cm due to C=C (ring stretching),

1445/cm due to CH$_3$ (stretching),1303 and 1125/cm due to C-N (stretching),1210/cm due to C-O-C (stretching), 836/cm,755/cm and 693/cm due to C-H (out of plane bending of aromatic ring) [46]. The IR spectra patterns for physical mixture and amlodipine floating tablet [F8] were compared with the IR spectrum of the pure drug for confirmation of common peaks. All the spectra amlodipine besylate with polymers showed no significant variation in height, intensity and position of peaks, suggesting that drug and excipients were compatible. This indicates no interaction between pure amlodipine powder and the used polymers. Subsequently, it can be decided that the drug is in a free state and can release with ease from the formulation.
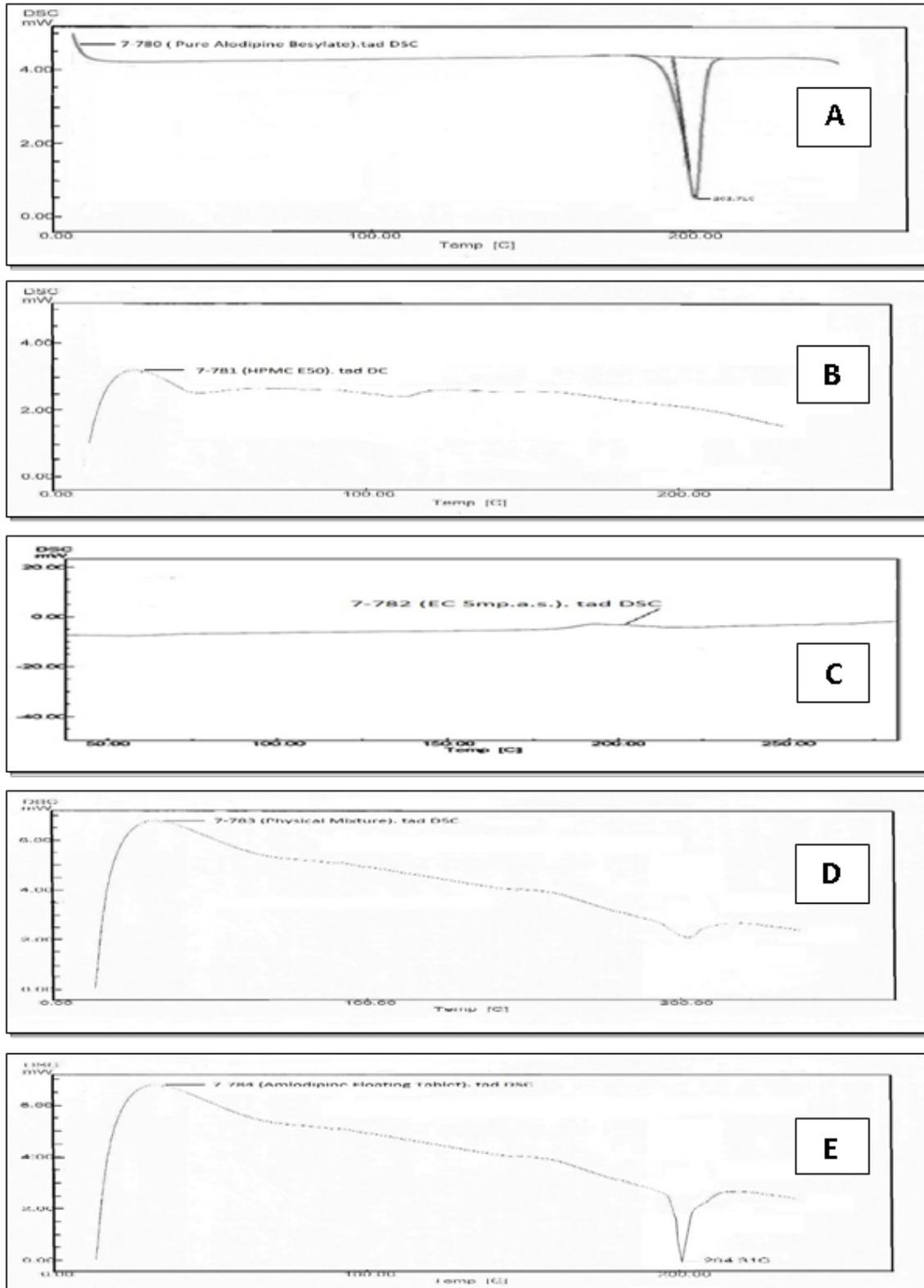

Fig. 6: Differential scanning calorimetry thermograms of (A) Pure amlodipine; (B) HPMC E50; (C) EC 5 mp. a. s.; (D) Physical mixture; (E) Amlodipine floating tablet (F8)

Differential scanning calorimetry (DSC)

DSC thermogram of pure amlodipine besylate power showed in (fig. 6A) which represents a sharp endothermic peak at 202.71 °C corresponding to the drug melting point indicating its crystalline nature [47]. While the DSC thermogram of hydroxypropyl methylcellulose (HPMC) E50 showed in (fig. 6B) has broad endotherm due to residual moisture; thus, the absence of any peak beside that of residual water revealing its amorphous nature [48]. In addition, the DSC thermogram curve of ethylcellulose (EC) 5 mp. a. s also showed no peaks (fig. 6C), signifying the complete amorphous nature of ethyl cellulose [49].

The physical mixture in (fig. 6D) showed no shift in the melting endotherm for amlodipine besylate but giving broad endotherm indicating that there is no chemical interaction between the amlodipine besylate and mixture of polymers (HPMC E50 and EC 5 mp. a. s.); nonetheless depicted some miscibility of the drug with polymers [50]. The DSC thermogram of the optimized formula (F8) depicted the similar melting point as observed with the pure amlodipine besylate powder. DSC thermogram of optimized formulation also shows some step changes in heat curve. These step changes are glass transition temperature which indicates the amorphous nature of other components of formulation like hydroxypropyl methylcellulose (HPMC) E50, ethylcellulose (EC) 5 mp. a. s. as showed in (fig. 6E) [51].

CONCLUSION

This study established a unique optimal formula of amlodipine floating tablet (F8) that led to the possibility of preparing successful tablets containing a combination of hydrophilic and lipophilic polymers. A suggesting zero order mechanism for drug dissolution profile was approved via combining both hydroxypropyl methylcellulose (HPMC) E50 and ethylcellulose (EC) 5 mp. a. s. and as increasing the concentration of both as the release rate was noticed to be decreased which is the most challenging aspect of the floating drug delivery system. Also, the effect for sodium bicarbonate ($NaHCO_3$) on the drug release rate was non-significant. In addition, the cumulative drug release rate from high viscosity grade hydroxypropyl methylcellulose (HPMC K100M) was significantly lesser as compared with the low viscosity grade hydroxypropyl methylcellulose (HPMC E50). Thus, it can be concluded that a combination of hydroxypropyl methyl-cellulose (HPMC) E50 and ethylcellulose (EC) 5 mp. a. s. in the formulation was considered a promising approach for preparing efficient amlodipine floating tablet that has an ultimate solubility in acidic pH.

AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

No conflict of interests between authors

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