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Original Article

FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING TABLET OF AMLODIPINE BESYLATE USING NATURAL ORGANIC POLYMERS

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ABSTRACT

Objective: This study was designed to formulate and evaluate the gastro retentive floating tablets of Amlodipine besylate by using different proportions of four polymers, namely xanthan gum, gum acacia, carbopol 940, and HPMC K 100 M.

Methods: Nine different batches of the floating tablets were formulated by direct compression technique. The constant amount of gas generating agents, namely, sodium bicarbonate and citric acid, were used for the floating character. The powder blend was subjected to pre-compression parameters analysis and the prepared tablets were evaluated for post-compression parameters such as hardness, friability, drug content, weight variation, floating lag time, total floating time, and swelling index. *In vitro* dissolution study was carried out for 12 h as per the specification of Indian Pharmacopeia 2018.

Results: For the optimized batch (4th batch), all the physicochemical parameters like angle of repose (33.47), Carr's index (17.46%), Hausner's ratio (1.21), weight variation (221 mg), hardness (5.2 Kg/cm^2), friability (0.1%), thickness (3.92 mm), dissolution (94.65% at 12 h), and drug content (92.5%) were within the acceptable limit. Furthermore, swelling index, floating lag time, and total floating time was reported to be 203.0%, 7.5 seconds,>12 h, respectively. Fourier Transform Infrared Spectroscopy analysis suggested that there is no drug excipients interaction.

Conclusion: Hence, this study suggested that gastro retentive floating tablets of Amlodipine besylate can be formulated to enhance gastric residence time and thereby improve its drug release characteristics.

Keywords: Amlodipine besylate, Acacia gum, Xanthan gum, Floating tablets, Gastro-retentive tablets

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INTRODUCTION

Among the different routes for drug administration, the oral route is the most common and preferential, as it ensures ease of ingestion, precise dosing, self-medication, accurate, flexible dosing regimen, and desirable patient compliance with a low probability of administration difficulty [1, 2]. However, it also has some major disadvantages, such as the first-pass effect, unpredictable onset of action and gastric residence time, incomplete absorption, etc. To overcome these demerits, the development of gastro-retentive formulations could be a better option. The enhanced gastric retention time of the drug can improve its bioavailability, curtail the waste of the drug, and mitigate the solubility of drugs that are less soluble in an elevated pH environment [3].

Gastro-retentive floating drug delivery systems (GFDDS) are designed to remain the drugs in the stomach for several hours. This prolonged gastric retention can improve the solubility of drugs that are less soluble in gastric fluid [4, 5]. Nowadays, a considerable number of gastro-retentive drug delivery systems have been manufactured by using several techniques such as floating drug delivery systems, low-density systems, raft systems incorporating alginate gel, bio-adhesive or mucoadhesive systems, high-density systems, super-porous hydrogel, and magnetic systems [6, 7]. Among them, the floating drug delivery systems are on the frontline [8]. Floating drug delivery systems (FDDS) or hydrodynamically balanced systems (HBS) have a bulk density lower than the gastric fluids and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period, thus releasing the drug in a sustained manner [9]. More specifically, the effervescent types of floating drug delivery systems generate CO_2 gas, hence reducing the density of the system and remaining buoyant in the stomach for a prolonged-time period and slowly releasing the drug at a sustained and constant rate [9, 10]. These drug delivery systems are formulated for sustained and prolonged release of drugs to the upper part of the gastrointestinal tract [11, 12]. Such a modified drug delivery system is advantageous for drugs acting locally in the stomach, especially for those absorbed in the stomach or the upper part of the small intestine or those unstable in the intestinal or colonic environment, or those having low solubility at high pH values [9, 12].

Amlodipine is a dihydropyridine type of long-acting calcium channel blocker (fig. 1) that prevents the movement of calcium ions into smooth vascular cells and cardiac muscles. Thus, at present days, it is the most commonly prescribed medicine for the treatment of hypertension and chronic stable angina. In both vascular disorders, an initial dose of 5 mg *p. o.* once per day is prescribed, which could be adjusted to a maximum daily dose of 10 mg *p. o.* [13]. It is categorized as a biopharmaceutical classification system (BCS), class I drug [3].

Most often, Amlodipine is available as an immediate-release tablet which possesses some limitations, such as immediate drug release after oral administration, leading to incomplete absorption of drug molecules, nausea, first-pass metabolism, abdominal pain [3, 14]. Moreover, Amlodipine is highly soluble in stomach pH compared to that of the small intestine, which makes it a suitable candidate for floating gastro-retentive dosage form [3, 6]. This study was aimed to formulate and evaluate the gastro retentive floating tablets of Amlodipine besylate by using different proportions of natural polymers, namely, acacia, xanthan gum, and carbopol (synthetic polymer) at different concentrations; thus, retain in the stomach for a desirable time for the improvement of its bioavailability, solubility, lessen drug damping, and diminish undesirable effects such as nausea and gastric mucosal irritation.

MATERIALS AND METHODS

Chemical Ingredients

The active ingredient, Amlodipine besylate (100.01% pure with the loss on drying 0.31%)) used in the study was gifted by Lomus Pharmaceuticals Pvt. Ltd., Kathmandu, Nepal. Hydroxypropyl methylcellulose K 100 M (HPMC K 100M), aerosil were purchased from

Loba Chemie Pvt. Ltd, Mumbai. Acacia, xanthan gum, citric acid, and carbopol 940 (CP) were obtained from Himedia Laboratories India. Sodium bicarbonate ($NaHCO_3$) was purchased from Fischer Scientific. Magnesium stearate, microcrystalline cellulose powder 200 (MCCP 200), and talc were purchased from Sigma-Aldrich, Inc. (St Louis, MO, USA). All the chemicals and reagents used in this project were of analytical grade.

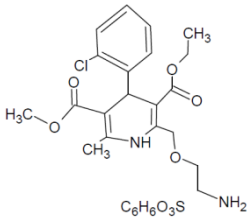

Fig. 1: Chemical structure of amlodipine besylate [14]

Instruments

UV spectrophotometer and Vernier caliper (Shimadzu, Japan). FTIR Spectrophotometer (Perkin-Elmer FTIR, Perkin-Elmer, USA), Friability tester (Toshiba, India), dissolution apparatus and digital hardness tester (Electrolab India), Tablet compression machine (punch) 16 station (Shiva Pharma Enginering India), laboratory water purification system (HiTech Instruments Co. Ltd, China).

Preparation of floating tablets

Nine different formulations of Amlodipine besylate floating tablets (table 1) were prepared by adopting a previously established method with slight modification [3]. For this, a direct compression method was applied using 16 station rotary compression tableting machine at Lomus Pharmaceuticals Pvt. Ltd., Kathmandu, Nepal. $NaHCO_3$ was used as a gas-generating agent. At first, the active ingredient and half of the sodium bicarbonate were mixed properly by passing through a sieve (sieve number 50). Then, the remaining amount of $NaHCO_3$, acacia, CP, and xanthan gum were also mixed homogenously with the previous blend by passing through the same sieve (sieve number 50). Similarly, microcrystalline cellulose and HPMC K 100M were mixed into the powder mixture after passing through the sieves 30 and 50, respectively. All the ingredients, aerosil, talc, and magnesium stearate, were also passed through the sieve number 50 and mixed with the initial mixture. The powder blend was tested for the different pre-compression parameters and compressed by the direct compression method.

Table 1: Composition of various batches of tablets

Ingredients	Functions	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Amlodipine besylate	Active ingredient	6.9	6.9	6.9	6.9	6.9	6.9	6.9	6.9	6.9
Acacia	Polymer	50	40	30	-	-	-	-	-	-
Carbopol 940	Polymer	-	-	-	50	40	30	-	-	-
Xanthan gum	Polymer	-	-	-	-	-	-	50	40	30
HPMC K 100 M	Polymer	20	30	40	20	30	40	20	30	40
Sodium bicarbonate	Gas generating agent	50	50	50	50	50	50	50	50	50
Citric acid	Gas generating agent	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose	Anticaking agent	69.1	69.1	69.1	69.1	69.1	69.1	69.1	69.1	69.1
Magnesium stearate	Lubricant	4	4	4	4	4	4	4	4	4
Talc	Glidant	8	8	8	8	8	8	8	8	8
Aerosil	Glidant	2	2	2	2	2	2	2	2	2
Total		220	220	220	220	220	220	220	220	220

Evaluation of different quality control parameters

Evaluation of pre-compression parameters

Various quality control parameters of all the batches of Amlodipine besylate floating tablets were analyzed by following the method described in Indian Pharmacopeia 2018 [15] and other literature. Before the compression, the formulation powder blends were evaluated for their bulk density, tapped density, compressibility index and Hausner's ratio. The flow properties of the powder blend were accessed by measuring the angle of repose.

Bulk and tapped density

Bulk density and tapped density were determined by pouring 5 mg of powder into a 25 ml graduated cylinder and the bulk volume was noted. Then the cylinder was subjected to 50 tappings and the tapped volume was also noted. The bulk and tapped density were calculated by using Equations 1 and 2 [16, 17]. All the measurements were performed in triplicates for each batch.

$$\text{Bulk density} = \frac{\text{Mass of powder (g)}}{\text{Bulk volume of powder in measuring cylinder (ml)}} \ldots (1)$$

$$\text{Tapped density} = \frac{\text{Mass of powder (g)}}{\text{Tapped volume of powder in measuring cylinder (ml)}} \ldots (2)$$

Carr's index/Compressibility index

Compressibility is the simplest way of measuring the flow property of powders. It is an indication of the ease with which materials can be induced to flow and is given by Carr's index (CI), which can be calculated from Equation 3 [18]. The relationship between CI and flow character is given in table 2.

$$\text{Carr}^{'}\text{s index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \ldots \ldots (3)$$

Table 2: Effect of carr's index, Hausner's ratio, and angle of repose on flow character

Carr's index (%)	Flow character	Hausner's ratio	Flow character	Angle of repose	Flow character
<10	Excellent	1.00-1.11	Excellent	<25 °	Excellent
11–15	Good	1.12-1.18	Good	25-30 °	Good
16–20	Fair	1.19-1.25	Fair	30-40 °	Passable
21–25	Passable	1.26-1.34	Passable	>40 °	Very poor
26–31	Poor	1.35-1.45	Poor		
32–37	Very poor	1.46-1.59	Very poor		
>37	Very very poor	>1.600	Very-very poor		

Hausner's ratio

It is an index of flow properties of powders that is related to the inter-particle friction and is calculated as shown in Equation 4 [19]. The relationship between Hausner's ratio and flow character is given in table 2 [20].

$$\text{Hausner}' \text{s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \ldots . . (4)$$

Angle of repose

A widely accepted funnel method was utilized to determine the angle of repose. A funnel was adjusted with the help of a stand so that its lower tip lies at the height of about 2 cm from the horizontal surface. The lower tip was closed by using cotton. Five grams of accurately weighed powder were loaded on the funnel and the cotton was removed slowly and the powder was allowed to flow. The height and diameter of the powder pile were noted and the angle of repose was calculated as in Equations 5 and 6. For every measurement, data were investigated thrice. The relationship between flowability and angle of repose is given in table 2 [15].

$$\text{Tan } \theta = \frac{\text{Height of the pile}}{\text{Radius of the pile}} \ldots \ldots (5)$$

$$\theta = \tan - 1\left(\frac{\text{h}}{\text{r}}\right) \ldots \ldots (6)$$

Evaluation of post-compression parameters

The compressed tablets were evaluated for quality control tests like weight variation, thickness, hardness, buoyancy study, content uniformity and dissolution test by using IP and literatures [15].

Weight variation

Twenty tablets from each formulation were evaluated for weight variation to check for the variation limits as shown in table 3 [15]. The average weight was calculated.

Table 3: Weight variation limit

Average weight (mg)	Maximum difference (%)
84 or less	10
84–250	7.5
>250	5

Friability test

The friability test is the most effective way to access the resistance of tablets towards breakage while shipping, storage, transportation, and handling before use. It was measured for twenty tablets from each formulation taken randomly, weighed, and subjected to 100 revolutions at a speed of 25 revolutions per minute (rpm) in a Roche friabilator. The final weight of the tablets was measured after dedusting. The friability was calculated by using Equation 7 [15].

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets (g)}}{\text{Initial weight of tablets (g)}} \times 100. (7)$$

Tablet hardness test

Monsanto hardness tester was used to measure the hardness of the tablet. Ten tablets from each formulation were taken randomly and the average hardness was calculated and expressed in kg/cm^2.

Tablet thickness test

The thickness and diameter of ten tablets from each formulation were determined using the digital Vernier caliper and expressed in millimeter (mm).

Drug content

Twenty tablets from each formulation were taken and crushed in a mortar and pestle. Powder equivalent to 6.9 mg Amlodipine besylate was weighed and dissolved in 100 ml of 0.1 N HCl. Similarly, the standard solution was also prepared by taking 6.9 mg of Amlodipine besylate standard and diluted with 0.1 N HCl. One ml of the standard was pipetted out and further diluted with 100 ml of 0.1N HCl. Thus, prepared final solutions were analyzed at 239 nm using the UV-Visible spectrophotometer. The drug content was determined by using Equation 8 [15, 21, 22].

$$\frac{\text{Absorbance of sp}}{\text{Absorbance of std}} \text{ x } \frac{\text{Wstd}}{100} \text{ x } \frac{5}{50} \text{ x } \frac{100}{\text{Wsp}} \text{ x } \frac{50}{5} \text{ x Potency of std \% x } (100 - \text{LOD})\% \text{ x Avg wt } \ldots \ldots (8)$$

(Abbreviations-sp: sample, std: standard, Wsp: weight of sample powder, Wstd: weight of standard drug, LOD: loss on drying for standard, Avg wt: average weight of 20 tablets.)

Swelling index

Swelling index was studied using 0.1 N HCl. The swelling time for all formulations was measured for 8 h. All the experiments were conducted in triplicate [23].

***In vitro* buoyancy studies**

For the study of *in vitro* buoyancy properties, five tablets from each formulation were studied. One tablet each was placed in a 100 ml beaker, each containing 0.1 N HCl. The time required for the tablet to float up to the top of the medium was noted as buoyancy lag time and the total time up to which the tablet floats over the medium was noted as total floating time [24]. For every measurement, data were investigated thrice.

***In vitro* dissolution test**

In vitro dissolution profile of each batch was observed by applying the method, described in the Indian Pharmacopoeia 2018 and some literature [15, 25]. The rotating paddle method was chosen to study drug release from the tablets. Six tablets from each batch (n=3) were taken for the dissolution study. The test was carried out in 900 ml of simulated gastric fluid for 12 h at 37±0.5 °C. The samples were withdrawn at regular intervals i.e. one, two, three, four, six, eight, ten, and twelve hours. After making the required dilutions; the filtered samples were analyzed at 239 nm using a UV-Visible spectrophotometer. The percentage of drug release was also calculated by using equation 8.

Drug release kinetics

Data obtained from the dissolution study were fitted to different kinetic models, namely zero order, first order, Higuchi, Korsmeyer-Peppas, and Hixon-Crowell models to determine the release kinetics of the different batches. The zero-order release rate depicts the concentration-independent drug release rate, which gives information about the cumulative percent drug remaining versus time. For a formulation that follows Higuchi's model, the release of the drug from an insoluble matrix takes place as a square root of a time-dependent process based on Fickian diffusion. Moreover, Higuchi's root kinetics is used to indicate the cumulative percentage of drug release versus the square root of time. The correlation coefficient (R^2) was determined according to the plot of different release model kinetics using Microsoft excel. A value close to 1 was considered the most preferred one [26, 27].

Compatibility study

To investigate drug excipient compatibility, infrared (IR) spectroscopy was adopted using a FTIR spectrophotometer and the spectrum was recorded in the wavelength region of 1950 to 400 cm^{-1}. In this technique, the uniform mixture of drug excipients or drug alone is dispersed in potassium bromide and compressed into discs with the help of a pressure of 5 tons up to 5 min by using a hydraulic press. The pellet was placed in the light path and the spectrum was obtained [23, 27].

Statistical analysis

All the experiments were analyzed three times and the data were presented as mean±SD. Statistical significance of differences was calculated by two-way analysis of variance (two-way ANOVA) with Tukey posthoc test using Graphpad Prism 6.0 software. A *p*-value<0.05 indicates data are statistical significant.

RESULTS AND DISCUSSION

Evaluation of pre-compression parameters

The evaluations of pre-compression parameters are given table 4.

Bulk and tapped density

The bulk density and tapped density ranged from 0.51-0.56 gmL^{-1} and 0.63-0.60 gmL^{-1}, respectively (table 4), which showed that the densities are not affected by the choice of polymer.

Carr's Index/Compressibility index

Carr's index of all formulations ranged from 17.46 to 20.89 % (table 6). All the formulations were found to have fair or passable flow character according to table 2.

Table 4: Evaluation of pre-compression parameters of granules

Polymers	Formulations	Bulk density (g. ml^{-1})	Tapped density (g. ml^{-1})	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
Acacia	F1	0.51±0.04	0.64±0.028	20.31±0.13	1.25±0.17	34.97±0.11
	F2	0.53±0.06	0.67±0.027	20.89±0.16	1.26±0.18	33.02±0.16
	F3	0.51±0.011	0.64±0.027	20.31±0.13	1.25±0.15	32.76±0.14
Carbopol 940	F4	0.52±0.013	0.63±0.021	17.46±0.18	1.21±0.15	33.47±0.12
	F5	0.54±0.05	0.68±0.020	20.58±0.17	1.26±0.18	33.96±0.11
	F6	0.53±0.02	0.66±0.024	19.69±0.18	1.25±0.20	31.68±0.15
Xanthan gum	F7	0.52±0.017	0.67±0.023	22.38±0.12	1.28±0.12	33.69±0.17
	F8	0.56±0.016	0.69±0.028	18.84±0.11	1.23±0.16	33.86±0.14
	F9	0.53±0.013	0.67±0.027	20.89±0.16	1.26±0.16	31.22±0.16

Data expressed as mean±SD, n=3.

Table 5: Evaluation of post-compression parameters of tablets

Polymer	Formulations	Weight variation (mg±SD)	Friability (%)	Hardness (kg/cm^2±SD)	Thickness (mm±SD)	Drug content (%±SD)	Swelling index
Acacia	F1	220±0.002	0.24	5±0.55	3.97±0.088	88.24±0.98	0±0
	F2	218±0.002	0.27	5.5±0.34	3.86±0.048	91±1.03	0±0
	F3	218±0.002	0.30	5.1±0.46	3.54±0.198	95.58±1.26	0±0
Carbopol	F4	221±0.002	0.10	5.2±0.39	3.92±0.021	92.15±0.87	203±3.4
940	F5	220±0.029	0.35	4.9±1.10	3.69±0.039	93.76±2.07	190±2.09
	F6	218±0.002	0.22	4.8±1.05	3.72±0.044	92.91±0.90	178±1.70
Xanthan	F7	220±0.003	0.56	5.2±0.35	3.63±0.032	95.46±0.75	154±4.12
gum	F8	217±0.002	0.25	5±0.72	3.52±0.073	96±2.13	166±3.77
	F9	220±0.003	0.36	5.1±0.84	3.59±0.054	94.31±0.88	176±1.78

Data expressed as mean±SD, n=3.

Hausner's ratio

It was determined by the ratio of tapped to bulk density. Formulations that used acacia and carbopol (F1, F3, F4, and F6) showed fair or passable flow properties (table 4) which are also similar to the results of other studies [28].

Angle of repos

Briefly, the angle of repose ranged from 31.22°-34.97° (table 4), which showed the passable flow property of the powder blend according to Indian Pharmacopoeial specifications.

Evaluation of post-compression parameters [29]

Weight variation

From each batch, twenty tablets were randomly selected and were accurately weighed on the analytical balance. The average weight of the tablet was found to be between 217 and 221 mg, which were similar to a study conducted by previous research [29]. As shown in table 5, the results of the weight variation were observed to be within the limit as indicated in the IP 2018 as in table 3.

Friability

The friability of tablets is within the limit according to IP and the slight variation in friability might be due to the variation in compression force applied and its total weight. A maximum weight loss was not more than 1% of the weight of the tablet being tested. F7 was found to have maximum friability (0.56%) and the minimum was observed in F4 (0.10%) as seen in table 5.

Tablet hardness

By using the Monsanto hardness tester, the hardness of the tablets was tested and the results are tabulated in table 5. F2 and F6 were found to have a maximum and minimum hardness of 5.5 kg/cm^2 and 4.8 $kg/cm^{2,}$ respectively. The hardness of the tablets of all formulations was found to be in the range of 4.8 to 5.5 $kg/cm^{2,}$ which falls within the limit according to a study [30].

Tablet thickness

According to table 5, the thickness of all the formulations was in the range of 3.52 to 3.97 mm. As the tablet thickness of each formulation is comparable, it can be predicted that the powder blend was consistent due to uniform particle size [31].

Drug content

An assay is an investigative procedure for qualitatively assessing or quantitatively measuring the presence or amount or the functional activity of an analyte. The percentage of drug content was determined spectrophotometrically by measuring absorbance at 239 nm. The percentage drug content of the formulation was found to be between 88.24% and 96% (table 5). The maximum percentage content was found to be 96% of formulation F8.

Swelling index

The swelling index was calculated by measuring the swelling behavior of all the batches for 8 h. The results achieved are depicted in table 5. There was no significant change in their morphological shape and form, all over the study. The batches (F1-F3) containing the polymers acacia and HPMC K 100 M, did not exhibit swelling behavior. Significant swelling behaviors were exhibited by other batches containing the combination of CP and HPMC K 100 M (F4-F6) as well as xanthan gum and HPMC K 100 M (F7-F9). The maximum swelling was exhibited by the batch F4 containing HPMC K 100 M and CP i.e. 200% whereas the minimum swelling behavior was shown by the batch F7 (154%) containing HPMC K 100 M and xanthan gum.

Swelling ensures buoyancy and drug dissolution, especially in floating tablets as the polymers form a gel layer when they come in contact with water and influence the drug release. The swelling index varies with the type and amount of polymers (molecular weight, hydrophilicity, functional groups) used as well as the swelling duration [4, 32]. In this study, the swelling tendency of the different batches was improved by increasing the proportion of CP. A similar result was shown in the previous studies [27, 33, 34]. In the case of batches F4-F6, the swelling index was decreased gradually when the amount of HPMC K 100 M was gradually increased and the CP amount was gradually decreased. Thus, while comparing the effect of CP and HPMC on the basis of their concentration, CP increases swelling behavior to great extent in comparison to HPMC. According to Perioli *et al.*, because of the slow hydrating nature, the swelling index of the tablet decreases with an increase in HPMC proportion [35]. However, many other studies claimed that if the effect of HPMC only at different concentrations is observed, the extent of swelling increases proportionally with increased concentration of HPMC [36, 37]. In our study, the combination of both of these polymers has a substantial role to achieve the swelling behavior of floating tablets.

In vitro buoyancy studies

Floating lag time and total floating time

The *in vitro* buoyancy study was performed using 0.1N HCl as a medium. As shown in fig. 2, all of the batches exhibited excellent buoyance properties as they floated instantly after immersion into the media and remained floated for more than 12 h. Results showed that the floating lag time changed with the type and amount of polymer used (fig. 2). The lowest floating lag time of 1 second (s) was observed for F1 where 50 mg acacia was used as the polymer. On the other hand, the longest floating lag time of 43 s was observed when the acacia was decreased to 30 mg. The floating lag time for formulations containing xanthan gum was about 20 s. The gas generating agents, $NaHCO_3$, and citric acids were used as gas generating agents at a constant concentration for all the batches to achieve the desirable floating character of tablets. $NaHCO_3$ is necessary to induce prompt floating. Moreover, to balance the elevated pH condition of the stomach after the fed condition, citric acid was incorporated, which ensures sufficient acidic condition for $NaHCO_3$ to react. According to previous studies, if the concentration of $NaHCO_3$ increased in the formulation, it results in increased drug release, whereas the swelling index and floating lag time get decreased. A decrease in floating lag time is because of the generation of greater quantity effervescence [16, 35]. Thus, major factors affecting the floating lag time are the type and amount of gas generating agent $NaHCO_3$ [38]. In this study, the amount of $NaHCO_3$ was constant for all the batches. However, despite the use of the constant proportion of gas generating agents, the onset of floating was different for different formulations. This could be due to the type and amount of polymers used. The total floating time for all formulations (F1-F3) containing acacia was less than 2 h (table 6). Interestingly, other batches containing the combination of CP and HPMC K 100 M (F4-F6) as well as xanthan gum and HPMC K 100 M (F7-F9) exhibited a floating time of more than 12 h. This large variation in total floating time could be due to the different swelling properties of polymers as observed in table 6. The total floating time of the tablet is directly related to its swelling index. The tablet that has a high swelling index can uptake a higher amount of water, which makes the matrix swell completely and decreases the bulk density, which ultimately increases the buoyancy [38]. Overall, the batches F4-F6 were reported to be more satisfactory in terms of floating lag time. According to a previous study, the combination of CP and HPMC K 100 M always results in the tablet having improved swelling behaviors, floating characters, and sustained-release properties. In this combination, the floating behaviors of the tablets are controlled by both the availability of internal spaces (porosity) in the center of the tablets and the swelling tendency of the hydrocolloid particles on the tablet surface when they came into contact with the gastric fluids. Finally, this results in the prolonged release of the drug [38].

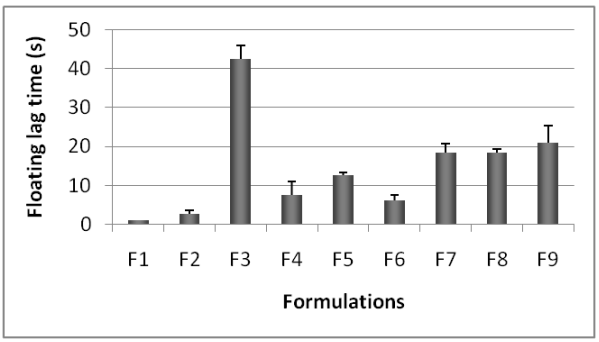

Fig. 2: Bar diagram representing the floating lag time of all the evaluated batches, Data expressed as mean±SD, n=3

Table 6: Total floating time of all the evaluated batches

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9
Total floating time (h)	1	1.2	1.5	>12	>12	>12	>12	>12	>12

In vitro dissolution test

To investigate the effect of polymer composition and amount on drug release pattern, the *in vitro* dissolution of newly formulated batches of Amlodipine besylate floating tablets was conducted and the results are depicted in table 7. As shown in table 7, about 50% drug release in all formulations was observed within 3 h. After 12 h, the maximum and minimum drug release was shown by F1 and F9 respectively. It was observed that the drug release varied with the type of polymers suggesting that the use of polymers (acacia, carbopol, xanthan gum) helps to modify drug release patterns. However, at 12 h, variation in drug release profile of formulations containing different concentrations of the same polymers as well as different polymers was reported to be statistically insignificant (p>0.05). This could be because the variation in the amount of polymer was not sufficient to vary the drug release pattern. In the case of batches with acacia and HPMC K 100 M (F1-F3), the drug release was relatively fast as compared to other batches. Poor floating nature and swelling index might be responsible for this. For other batches (F4-F9) the drug release pattern was sustained and almost similar. To release more than 90% of the drug, about 12 h were needed in all formulations. This result was consistent with the results of the total floating time and swelling index (Tables 5 and 6) where the formulations were found to float for longer than 12 h, which showed that the drug release is related to its total floating time.

Drug release kinetics

The highest correlation coefficients (R^2) obtained from *in vitro* dissolution studies were fitted to zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models, and the results are presented in table 8. It was observed that all of the formulations showed the best fit with the Higuchi model indicating drug release by diffusion mechanism. The release pattern of Amlodipine besylate from all the batches did not fit into the Hixson-Crowell cube root model signifying that dissolution was not the predominant mechanism for drug release [35]. Similarly, the results were also fitted to the Korsmeyer-Peppas model to analyze the release pattern of drugs from the polymeric system. The values of n were calculated by plotting a linear regression of log (Mt/M versus log (t), and R^2 values in this model signified that the releases of the formulations (F1-F9) were followed by the Korsmeyer-Peppas model also. Since the slope 'n' value ranged from 0.379 to 1.254, these values signified that the release pattern of Amlodipine besylate was found to be a Fickian diffusion (F4), non-Fickian diffusion (F3, F7, and F9), and super case II transport (F1, F2, F5, F6,

and F8). None of the formulations followed the Hixson-Crowell model which showed that highest linearity for Higuchi's equation, zero-order and first-order equations and this could also be the reason for the slow release of drug from the formulation. Surface area and diameter are not the key parameters to determine the release pattern of the drug in this study [27, 39, 40].

Overall, the formulations F4 and F7 were found to be optimized formulations as they satisfied all the criteria of quality control limit, swelling index, floating time, as well as prolonged and effective drug release. Among them, F4 was found to be the most satisfactory batch in terms of both pre-compression and post-compression parameters.

Table 7: Dissolution profile of tablets

F Formulations	Percentage of drug release							
	1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h
F1	34.05±0.78	54.84±1.82	63.94±0.73	76.48±1.99	83.73±2.35	91.39±1.73	93.85±1.98	96.50±1.44
F2	29.41±1.98	49.74±0.77	64.27±1.81	73.52±0.59	79.04±2.19	86.63±2.47	90.32±0.66	96.03±0.85
F3	24.83±0.67	39.84±2.87	51.59±0.95	69.55±1.12	76.31±1.33	82.59±0.74	89.74±1.87	95.53±0.30
F4	33.27±0.87	45.06±1.58	52.3±2.18	55.78±3.28	64.23±±3.21	70.06±1.32	83.12±0.90	94.65±1.88
F5	20.24±1.45	31.58±0.24	48.66±0.74	63.89±0.96	73.23±1.88	88.24±1.45	90.34±2.39	93.12±1.20
F6	11.03±2.01	23.72±2.29	39.23±2.65	48.66±1.32	56.8±1.29	63.21±1.68	79.34±0.29	92.12±0.93
F7	20.55±0.89	28.9±1.21	42.07±1.74	51.6±0.25	64.98±0.50	69.3±2.30	78.23±1.30	94.76±1.15
F8	16.41±2.11	29.3±0.75	51.22±1.22	65.54±2.09	71.47±2.31	81.76±0.87	88.73±0.45	94.24±0.55
F9	22.48±1.53	30.82±2.41	42.83±0.69	50.09±1.32	64.14±1.87	68.37±0.98	76.94±2.02	89.48±1.32

Data expressed as mean±SD, n=3

Table 8: Drug release kinetics data of tablets

Formulations	Zero order (R^2)	First order (R^2)	Higuchi model (R^2)	Hixson crowell (R^2)	Korsemeyer-Peppas (R^2)	Korsemeyer-Peppas (n)
F1	0.825	0.834	0.9228	0.7547	0.9427	1.21
F2	0.8292	0.813	0.923	0.7442	0.9261	1.13
F3	0.8803	0.8764	0.9546	0.8055	0.961	0.667
F4	0.9776	0.9241	0.9744	0.945	0.9839	0.379
F5	0.9565	0.8607	0.9546	0.8072	0.9575	1.254
F6	0.825	0.8801	0.9815	0.8551	0.9609	1.169
F7	0.961	0.9457	0.984	0.9020	0.9873	0.671
F8	0.8702	0.7026	0.9472	0.7709	0.9296	1.014
F9	0.963	0.8709	0.9891	0.9048	0.9905	0.588

Compatibility studies

The study of the drug excipient compatibility studies was accomplished by an IR spectrophotometer. The IR spectra of pure Amlodipine besylate and the drug with polymers are shown in fig. 3.

The major characteristic bands on the spectra of both pure compound and formulated tablets at 1686.82 cm^{-1}, 1619.31 cm^{-1}, 1595.86 cm^{-1}, 1303.94 cm^{-1}, 1266.32 cm^{-1}, 1120.46 cm^{-1}, 1098.51 cm^{-1}, and 745.52 cm^{-1} were found to be similar. Besides, the absence of other peaks in the tablet spectra justified that there is no interaction [3].

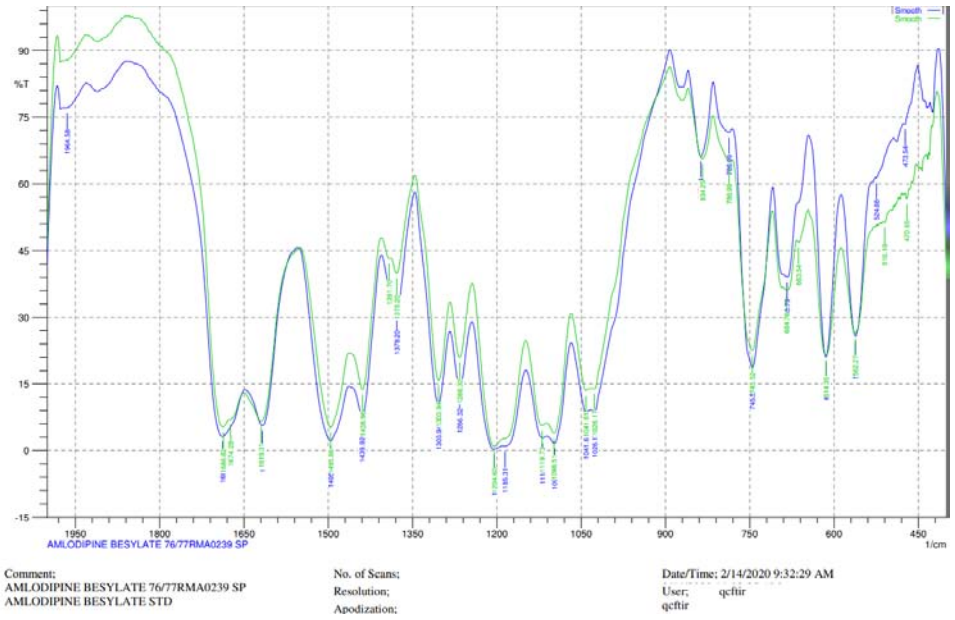

Fig. 3: FTIR spectrum for amlodipine besylate, blue color: FTIR chromatogram of standard drug, green color: FTIR chromatogram of the Amlodipine besylate floating tablet containing xanthan gum, acacia gum, HPMC K 100 M, and carbopol

CONCLUSION

This study assured that floating tablets of Amlodipine Besylate can be successfully formulated to retain the tablet in the gastric region so that it increases gastric residence time and thereby enhance its bioavailability. Also, drug administration frequency can be minimized. It also foretells that Amlodipine besylate floating tablets prepared by using hydrophilic controlled release polymer HPMC K 100M and carbopol can ensure floating of tablets for the maximum period and fascinate the release of the active ingredient in a controlled and steady manner. The optimized formulation (F4) followed Korsmeyer-Peppas kinetics while the drug release mechanism was found to be Fickian diffusion, a zero-order release type, governed by both drug diffusion and relaxation of polymer. However, evaluation of pharmacokinetic parameters in human subjects is recommended complementing the findings of the study. Moreover, drug excipients compatibility study by using differential scanning calorimetry and investigation of real time and accelerated stability is mandatory to ensure commercial acceptability.

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AUTHORS CONTRIBUTIONS

Shila Gurung conceived and designed the project. Susma Acharya, Hari Prasad Joshi, Gyanu Parajuli, Narayani Poudel, Srijana Poudel, and Jitendra Pandey performed the experiment. Hari Prasad Joshi, Jitendra Pandey, and Shila Gurung analyzed the data. Hari Prasad Joshi and Jitendra Pandey wrote the manuscript. Jitendra Pandey and Shila Gurung revised the manuscript. Sushma Acharya, Jitendra Pandey, and Hari Prasad Joshi act as co-first authors.

CONFLICT OF INTERESTS

We declare no conflicts of interest.

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