



Behavior of polymers and *in-vitro* evaluation on gastroretentive nifedipine sustained release floating tablets

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ABSTRACT

Nifedipine is one of the calcium channel blockers widely employed in indications such as high blood pressure and angina pectoris. In the present study, a prompt attempt is done in the formulation of gastro retentive sustained-release tablets. The effect of polymers and their combination on release pattern, initial burst release, and floating behavior were studied. Out of four polymers, two polymers such as cellulose derivatives like highly viscous polymer Hydroxypropyl methylcellulose (HPMC) K100, low viscous HPMC K4M and their combinations, and other two polymers used were from natural sources like xantham gum, guar gum and their combinations were studied. The percentage of drug release was compared with the theoretical model. Formulated gastro retentive Nifedipine floating tablets were evaluated with various parameters such as wetting time, floating behavior, hardness test, swelling studies, and drug release. The combinations of natural polymers had shown the best result on drug release and initial burst release such as 98.28 and 22%, respectively, with floating lag time of 90 s. Dissolution data were fitted into various mathematical equations like zero-order, First order, Hixon Crowell, and Higuchi model to understand the concept of drug release. Based on result, it was found that optimized formulation follows the Hixon Crowell equation ($r^2 > 0.966$) and zero-order drug release ($r^2 > 0.968$). The conclusion is that gastroretentive Nifedipine floating tablets followed dissolution controlled mechanism of drug release. The similarity factor f_2 and dissimilarity factor f_1 were found to be 76.02 and 4.32, respectively, for Nifedipine release from the optimized batch in comparison with the theoretical drug release profile. Short term accelerated stability studies were conducted as per ICH guidelines and evaluated.

Keywords: Nifedipine, gastro-retentive floating tablets, floating tablets, *in-vitro* evaluation

INTRODUCTION

The prolonged retention of the floating tablets in gastric medium promises sustained release of certain drugs having short half-life, narrow absorption window, less stability in the intestinal tract, or low solubility.^[1] Such drugs lead to poor patient compliance when formulated in conventional dosage forms.^[2,3] Out of many novel dosage forms, floating tablets are considered a promising tool which will not interfere with the normal physiological function of the body. Floating tablets can be prepared by different methods^[4,5] as shown in Figure 1.

The present study is based on the formulation of effervescent floating tablets of Nifedipine. Sodium bicarbonate^[6] was used as a gas generating agent; the gas generated is entrapped in a matrix-forming component of the floating system.

Nifedipine has an oral dose up to 30 mg/day in divided doses^[7] and the biological half-life^[8] of 2–6 h, favors the development of a sustained release dosage form. Nifedipine rapidly lowers blood pressure and patients are commonly warned about the feeling of dizziness or faintness after taking

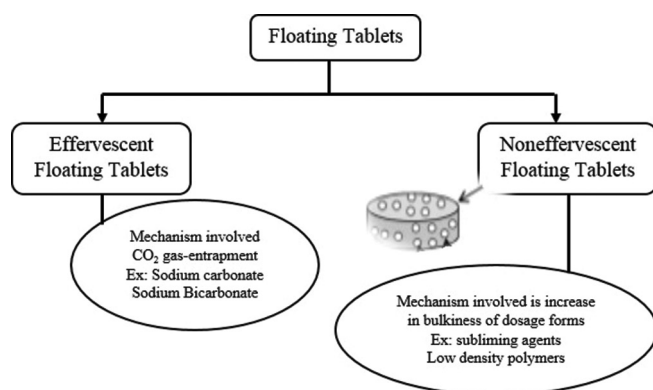


Figure 1: Different methods of preparation of floating tablets

the first few doses and even tachycardia may occur.^[9] These problems are much less frequent in the sustained-release preparations of nifedipine. A more novel system like sustained release floating tablet provides a 24-h release of nifedipine in the stomach.

MATERIALS

A gift sample of nifedipine was obtained from Cadila Pharmaceuticals Ltd., Ahmedabad, India. Two grades of hydroxypropyl methylcellulose (HPMC), K4M and K100M, were received as gift samples from Medreich Pharmaceuticals Ltd., Bangalore, India. Natural polymers such as xanthan gum and guar gum were purchased from S.D. Fine Chem. Ltd., Mumbai.

Excipients used for the formulations such as sodium bicarbonate, citric acid, and dibasic calcium phosphate were used as such as purchased from S. D. Fine Chem. Ltd., Mumbai. Distilled water was prepared in the laboratory throughout the study.

METHODS

Development of Analytical Method

For estimation of the drug, the ultraviolet spectrophotometric method was employed using 0.1N hydrochloric acid solution. Ten µg/ml solution of nifedipine was scanned to get a peak at i.e. $\lambda_{\max}$ 238 nm.^[8] The calibration curve was plotted accordingly with 3 runs having a regression value of 0.999.

Melting Point

The open capillary method was employed to determine the melting point of the nifedipine. The drug was filled into the capillary tube whose one end was sealed by fusion and kept in melting point apparatus for the rise in the temperature slowly. The temperature at which the solid drug starts melting was recorded 3 times and the average was taken.

Fourier Transform Infra-Red (FT-IR) Spectroscopy

The pure drug was mixed with 100 mg of potassium bromide (KBR pellet method) and analyzed by FT-IR (Jasco FT-IR 4100).

Assay

The percent purity of the drug was determined as per the procedure mentioned in IP 1996.

Loss on drying (LOD)

This was determined using a hot air oven as per the method mentioned in BP 2008. One gram of the sample taken in a petri plate was kept in a hot air oven at 100°C for 2 h and the percent LOD was calculated.

Saturation solubility

The saturation solubility of nifedipine in 0.1 N hydrochloric acid solution was determined. Excess of nifedipine was added into a volumetric flask having 10 ml of 0.1 N hydrochloric acid solution and shaken in cryostatic water shaker bath at a constant temperature for 24 h, filtered, and analyzed for drug content at 238 nm.

Preformulation studies

Preformulation studies were carried out on the tablet blend of each batch by testing each parameter thrice.

Angle of repose

The funnel method (Reposogram) was employed for the determination of angle of repose.^[10] Angle of repose was calculated using the formula $\tan \theta = h/r$, where h and r are the height and radius of the powder cone, respectively. An average of 3 trials was recorded.

Bulk density

Using automated bulk density apparatus ETD-1020 of Electrolab, Mumbai, India, loose bulk density and tapped bulk density of powder blend were calculated after passing through sieve no 16 to break any clumps if present. Tapping was set initially for 500 times, further it was continued for 750 times. The average was recorded. The LBD and TBD were calculated in g per ml using the following formulae, LBD = weight of the powder/volume of the packing, TBD = weight of the powder/tapped volume of the packing.

Compressibility index

Carr's index was determined using formula Carr's index (%) = $([TBD - LBD] \times 100)/TBD$. Average was recorded after three runs.

Interference of excipients

The pure drug, a drug with polymers, and optimized formulation were mixed with 100 mg of potassium bromide and analyzed by FT-IR (Jasco FT-IR 4100) to eliminate the interference of the excipients with the estimation of the drug.

DEVELOPMENT OF THEORETICAL DRUG RELEASE PROFILE

The total dose (DT) of nifedipine for a once-daily sustained-release formulation was calculated as $D_T = D_{IR} (1 + 0.693 \times t/t_{1/2})$ using pharmacokinetic data available in the literature^[11,12] where t = time during which the sustained release is desired (24 h); $t_{1/2}$ = half-life of the drug (4 h). The dose of the

immediate release part (D_{IR}) was calculated as $D_{IR} = (C_{ss} \times V_d)/F$, where, V_d = volume of distribution (1), F = fraction of drug available (0.45). The steady-state concentration (C_{ss}) of the drug was calculated as $C_{ss} = (F \times \text{Maximum dose})/Cl_p \times \tau$, where, Cl_p = Plasma clearance, (10); τ = frequency of dosing (3). Hence an oral sustained-release formulation of nifedipine should contain a DT of 10.316 mg (10 mg) and should release 2 mg in the first 1 h like conventional tablets, and 0.347 mg/h up to 24 h thereafter.

Preparation of Gastroretentive Sustained Release Tablets of Nifedipine

Floating tablets of nifedipine were manufactured using the ingredients shown in Table 1 by direct compression technique. Formulated method schematically represented and shown in Figure 2. The drug was used as such for the formulations

whereas sodium bicarbonate (# 36), citric acid (# 36), and magnesium stearate (# 60) were passed through the sieves. Weighed amounts of drug and excipients were manually mixed in a polythene bag for 10 min. The powder mixture as per the formula was compressed on a 10-station rotary press (Rimek, Ahmedabad) using round-shaped punches measuring 12.6 mm in diameter. As the drug was sensitive to light, all the processes were carried out in the darkroom. Several batches were sequentially developed to release the drug which matches with that of the theoretical drug release profile. Similarity (f_2) and dissimilarity (f_1) factors were calculated and compared to support the results obtained.

Weight variation

The twenty tablets were picked randomly from each formulation and subjected to the test as per the official method.

Table 1: Various formulations of floating nifedipine tablets

Sl. No.	Ingredients (mg)	FB 1	FB 2	FB 3	FB 4	FB 5	FB 6	FB 7	FB 8
1	Nifedipine	10	10	10	10	10	10	10	10
2	Xanthan gum	-	-	-	45	45	75	45	45
3	Guar gum	-	-	-	-	-	175	105	105
4	HPMC K100M	150	-	105	105	-	-	-	-
5	HPMC K4M	-	150	45	-	105	-	-	-
6	Sodium bicarbonate	120	120	120	120	120	100	100	120
7	PVP K 30	10	10	10	10	10	10	10	10
8	DCP, mg	150	150	150	150	150	120	170	150
9	Magnesium stearate	10	10	10	10	10	10	10	10
	Total weight	450	450	450	450	450	450	450	450

Evaluation of post-compression parameters of floating tablets

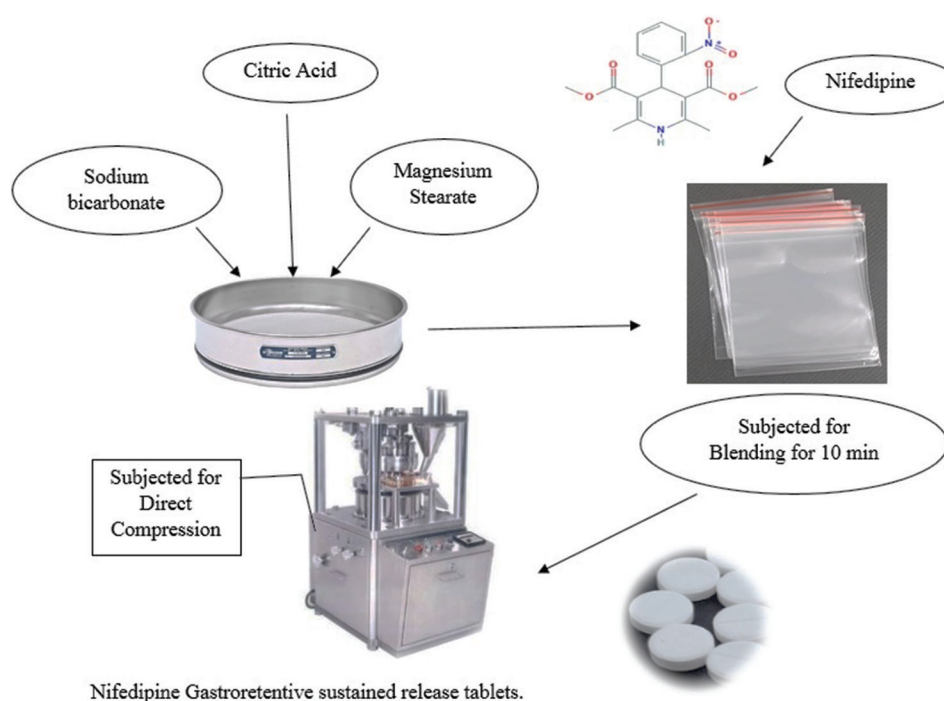


Figure 2: Formulation method of Nifedipine floating tablets

Diameter and thickness

Randomly ten tablets were chosen from each formulation and were measured through a digital micrometer screw gauge (Mitutoyo, New Delhi, India). The average was recorded from three trials.

Hardness test

Monsanto hardness tester (Shital Scientific Industries, Ahmedabad, India) was used to study the hardness of tablets which were chosen by random sampling.

Friability^[13]

A friability tester (Electrolab, Mumbai, India) was used for testing the friability of randomly picked tablets for each formulation and ran for 25 rpm for 4 min of duration. A friability was calculated using a formula, $\text{Friability} = [(W_1 - W_2)/W_1]/100$, where W_1 and W_2 represent the weight of floating tablets before and after the test, respectively.

Content uniformity

Content uniformity was estimated by adopting the procedure as given in Indian Pharmacopoeia 1996 using 0.1N Hydrochloric acid solution and estimated at λ_{max} 238 nm against 0.1 N HCl solution as a blank.

In vitro floating behavior

Floating lag time and total floating duration were determined for all formulations. The time taken by the tablet to float is considered as lag time, and the total duration of the float was noted. 100 ml of 0.1N hydrochloric acid solution was used as a medium for the study. The floating behavior of the tablet is as shown in Figure 3.

In vitro release of nifedipine from floating tablets^[14,15]

USP – type II tablet dissolution tester TDT-08L (Electrolab, Mumbai, India) was used to study the Nifedipine release from the floating tablets. The gastric environment was created using 900 ml of 0.1 N HCl solution as dissolution medium at $37 \pm 0.5^\circ\text{C}$ and rpm of 100 for 24 h. Aliquots measuring 10 ml were withdrawn after 1, 2, 4, 8, 12, 16, 20, and 24 h using pipette replacing with an equal volume of fresh dissolution medium. The collected samples were analyzed at 238 nm against 0.1 N hydrochloric acid as blank.

Kinetics

For better understanding the release pattern of Nifedipine floating tablets, the results were fitted into various

mathematical models such as zero-order, first order, Higuchi, and Hixson-Crowell model. Determination of coefficient (r^2) calculated through regression analysis.

Swelling Behavior and Water Uptake Studies of Floating Tablets

The percentage of weight gained by each tablet determines its swelling and water uptake capacity. The swelling and water uptake behavior of optimized formulation (FB 8) was carried out. A tablet was randomly selected and kept on #20 at the bottom of the dissolution flask containing distilled water. At the end of 1, 2, and 4 h, the floating tablet was withdrawn, soaked with tissue paper, and weighed. Then for every 4h, weights of the tablet were noted, and the process was continued for 24 h, % swelling was calculated as $\% \text{ swelling} = (100 [\text{swollen thickness} - \text{original thickness}]) / \text{original thickness}$. At the same time, % water uptake was calculated as $\% \text{ water uptake} = (100 [\text{wet weight} - \text{dry weight}]) / \text{dry weight}$.

Accelerated Stability Studies

Short term stability studies were carried out for 6 months for optimized formulation as per ICH guidelines. Floating tablets were packed in the aluminum foil which was laminated with PVC and placed in a humidity chamber maintained at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\% \text{ RH}$ for 6 months. Further drug content, buoyancy, and *in vitro* release were carried out.

RESULTS AND DISCUSSION

Pre-formulations studies revealed that powder mixture was suitable for direct compression.

Melting Point

The melting point of nifedipine was 173.33°C ($\text{SD} = 1.154$), which was nearer to the literature value of 173°C .^[16]

Interference of Excipients

The prominent peaks observed in the pure drug were 3106.76 cm^{-1} (CH in methyl ester), 1684.03 (C=O in ester), 1225.54 (C-O in ester), 2839.67 (C-H in methyl), 3336.25 (N-H in pyridine), and 1535.54 (N=O in *p*-nitrophenyl). Perusal to Figure 4 indicated that these peaks remain unaffected, with which it can be concluded that the excipients may not interfere with nifedipine estimation. The spectrum is shown in Figure 4a, which matched with the literature values confirming the drug as nifedipine.^[5]

LOD

LOD was calculated and results were shown that the value within the limits of 0.4%.

Assay

The percent purity determined was 101.2 ($\text{SD}=0.735$), which was within the limits specified.

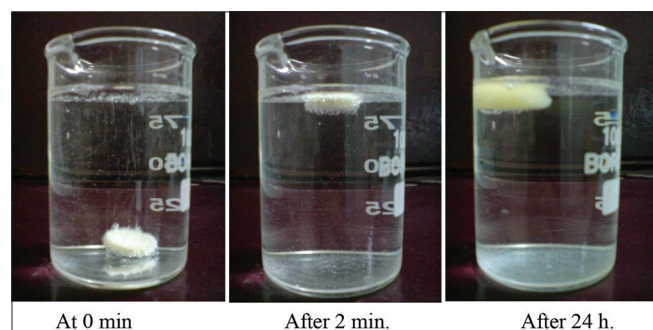


Figure 3: The floating position of nifedipine floating tablets (FB 8) in 0.1 N HCl solution at different time intervals

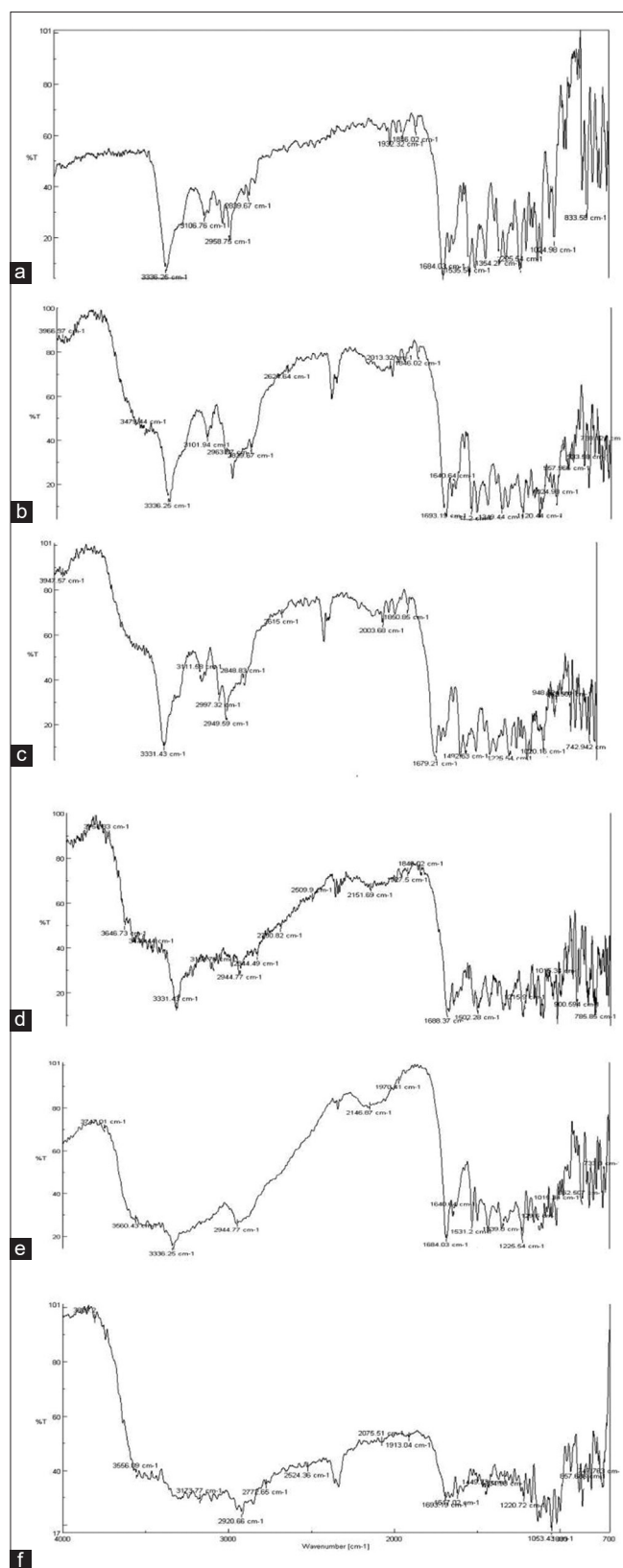


Figure 4: FT-IR spectra of (a) Nifedipine (pure) and nifedipine with (b) HPMC K100M (c) HPMC K 4 M (d) Xanthan Gum (e) Guar Gum and (f) Powder blend (FB 8)

Table 2: Dissolution profile of nifedipine according to theoretical calculations

Sampling time (h)	Percent drug release
0	0
1	22.75
2	26.11
4	32.82
8	46.26
12	59.69
16	73.13
20	86.56
24	100.00

Saturation solubility

The saturation solubility determined was 0.122 mg/ml (SD=0.001). It is an average mean of three runs. This value helped to verify the quantity of the dissolution medium.

Development of theoretical drug release data

Data were calculated as per the method discussed in the methodology. The data are tabulated in Table 2. These data were used to compare the drug release pattern of floating tablets of nifedipine.

Evaluation of Floating Tablets

The tablets of all the batches exhibited the quality control parameters within the permissible limits as shown in Table 3. The hardness of the tablets fell in the range of 4–6 kg/cm² with the maximum standard deviation of 0.25%. Tablets have shown the friability in the range of 0.399–0.907. The maximum percentage difference in the weight variation was less than $\pm 5\%$. Diameter values were found uniform with the maximum standard deviation of 0.63%. The drug content in the tablets was within the pharmacopoeial limits. All the properties revealed that the formulations can be studied further.

Floating Behavior

The effervescent method was employed in the formulation of floating tablets. Various gas generating agents can be used like sodium carbonate, sodium bicarbonate, potassium carbonate, and so on. In this study, sodium bicarbonate was used as a gas generating agent. Carbon dioxide was generated in presence of a gastric medium (0.1N HCl solution). The density of the tablets was decreased by less than 1, by trapping of carbon dioxide gas in the form of a gel, which was achieved by hydration of the polymers. Hence, the tablet becomes buoyant. Formulated tablets showed good persistence and sufficient strength when they are used in combinations except for alone, that is, xanthan gum. Gas generating agent (sodium bicarbonate) is essential to achieve optimum *in vitro* buoyancy. The data of floating behavior are as shown in Table 4.

Table 3: Preformulation and quality control data of formulated batches from FB 1 to FB 8

Sl. No	Parameters	FB 1	FB 2	FB 3	FB 4	FB 5	FB 6	FB 7	FB 8
1	Hardness (kg/cm ²)*	5.9±0.2	6±0.0	5.9±0.2	4.83±0.25	5±0.0	4±0.0	4±0.0	4±0.0
2	Friability (%)**	0.508	0.399	0.591	0.907	0.724	0.557	0.758	0.584
3	Uniformity of weight (mg)*	450±3.06	450±3.24	450±1.296	450±2.52	450±2.55	450±3.06	450±1.1	450±3.9
4	Drug content (%)**	100.82	101.17	90.71	94.55	102.21	80.61	96.46	96.64
5	Diameter (mm)*	12.700±0.005	12.710±0.002	12.700±0.005	12.771±0.003	12.768±0.011	12.753±0.036	12.756±0.036	12.771±0.007
6	Loose bulk density (gm/cc)	0.698	0.714	0.592	0.645	0.697	0.648	0.643	0.730
7	Tapped bulk density (gm/cc)	1.099	1.224	0.869	0.772	1.046	0.772	0.771	1.096
8	Angle of repose (θ)	25.64	24.70	26.56	23	20.37	24.02	23.37	22.831
9	Compressibility index (%)	36.48	41.66	31.87	14.89	33.37	16.06	16.60	33.39

Similarity Factor and Dissimilarity Factor^[17-19]

The formulated optimized batch of floating tablets have shown acceptable results when applied with mathematical approach such as similarity factor (f_2) = 76.02 (standard range = 50–100), and dissimilarity factor (f_1) = 4.32 (standard range = 0–10). Hence, the manufacturing procedure is consistent in formulation of the floating tablets with reproducible results. Data are as shown in Table 5.

In-vitro Drug Release

The drug release pattern from each formulation varies as different polymers and the combination has its effect on the release of the drug. This is one of the major aspects, we considered in optimization of the formulated floating tablets.

In the present study, we used combination of natural gums/polymers such as xanthan and guar gum followed by the combination of HPMC derivative having low viscosity and high viscosity HPMC 4KM and HPMC K100M, respectively.

The formulations with xanthan gum and guar gum were used in the ratio of 3:7. When the matrix tablets of nifedipine come in contact with the dissolution medium, they take up water and swell, forming a gel layer around the matrix. Then, the dissolved drug diffuses out of the swollen gum matrix depending on the amount and viscosity of the gum.

In FB 1, HPMC K100M, the high viscosity polymer alone was used. Batch 1 showed 72.96% of drug release in 24 h. This was a lesser value. It could be because of the high viscosity of the polymer. Therefore, in FB 2, a relatively low viscosity polymer, HPMC K4M was used. FB 2 showed 83.58% of drug release in 24 h. There is a slight improvement in controlling the drug release. Still, the drug release profile of these two formulations did not appear to be closer to the theoretical drug release profile. Hence, it was decided to use the combination of the two polymers in the next batch to improve the results. FB 3 had shown 84.38% drug release. There was a slight improvement when compared to the earlier two batches. The values of similarity (f_2 value) and dissimilarity (f_1 value) factors of the batches from FB 1 to 3 are shown in Table 5. A perusal of Table 5 indicates that the values are not within the acceptable range. Although HPMC is a hydrophilic type of polymer, 100% drug was not released in three formulations because of the relatively high viscosity of the matrix formed in the dissolution medium. Initial burst drug release was also very less, which indicates that HPMC polymers of the selected grades were not suitable for the formulation of floating tablets of nifedipine either alone or in combination and hence the aim was not achieved. Hence, further attempts were made to improve the formulation using alternate polymers.

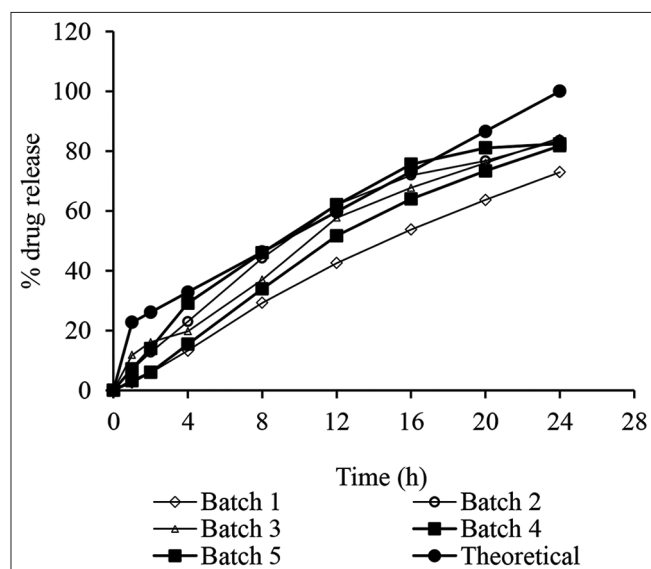
Jaleh *et al.*, used xanthan gum to prepare sustained-release matrix tablets of tramadol hydrochloride.^[10] The moment HPMC polymers failed to give the desired results, xanthan gum appeared as an alternate. HPMC K100M (high viscosity polymer) and HPMC K4M (low viscosity polymer) were used along with xanthan gum in batches FB 4 and 5, respectively. The similarity and dissimilarity factors of these batches are shown in Table 5. FB 4 showed 81.78% of drug release whereas batch

Table 4: Floating behavior of all formulated formulations

	FB 1	FB 2	FB 3	FB 4	FB 5	FB 6	FB 7	FB 8
Floating Lag time, s	60	60	60	60	60	900	150	120
Floating duration, h	24	24	24	24	24	24	24	24
Cumulative drug release	72.96	83.58	84.38	81.78	82.45	96.64	95	98.28

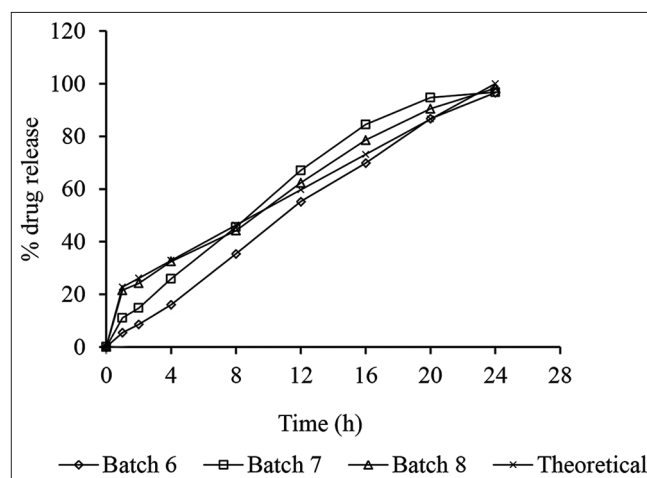
Table 5: Comparison of f_1 and f_2 Values for the Tablets of the FB 1–8

Batch	f_2 value (Similarity factor)	Acceptable range	f_1 value (Dissimilarity factor)	Acceptable Range
1	34.231		36.520	
2	48.6		15.854	
3	49.049		17.178	
4	40.579	50-100	26.385	0-15
5	50.556		13.283	
6	46.96		16.49	
7	53.42		13.60	
8	76.02		4.32	

**Figure 5:** Comparison of *in vitro* release of the tablets of nifedipine from the FB 1 to 5 with theoretical drug release profile

5 showed 82.45% of drug release in 24 h, not an encouraging result. We compared the theoretical release of drug from actual formulated batches as shown in Figure 5. From this, it was concluded that HPMC combination with xanthan gum is not a successful one. Hence, further attempts were made to improve the formulation using guar gum replacing HPMC.

In FB 6, xanthan gum and guar gum were used in 3:7 ratio. FB 6 showed 96.64% of drug release in 24 h. This is a considerably good release trend. However, because the formulation did not show the required amount of initial burst release, similarity and dissimilarity factors have gone far away from the acceptable range. The floating lag time was also very high, that is, 18–20 min. There is a need to decrease floating lag time and improve initial burst release. Therefore, the batch was rejected and decided to

**Figure 6:** Comparison of *in vitro* release of the tablets of nifedipine from the FB 1 to 5 with theoretical drug release profile

improve the formulation further. The problems with FB 6 were overcome by taking reduced polymer concentrations. Therefore in FB 7, the polymer combination was reduced to 1/3rd the total weight of the tablet. There is an improvement in the results obtained as the floating lag time decreased from 18–20 min to 1–5 min. Similarity and dissimilarity factors have come within the range. Even though the initial burst release was improved by 5% in FB 7 compared to FB 6, the result is not significant. Hence, there was a need to improve the formulation concerning initial burst release [Figure 6].

Based on the experience with the earlier batches, it was thought to improve the performance of the floating tablets by increasing the sodium bicarbonate proportion. In FB 8, keeping all other ingredients of the FB 7 same, the proportion of sodium bicarbonate was increased by 20 mg per tablet at the expense of dibasic calcium phosphate. Results were interesting. An increase in sodium bicarbonate concentration

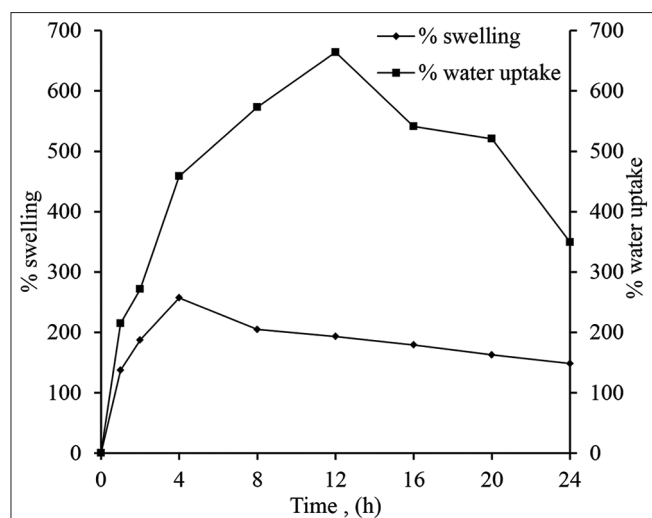


Figure 7: The percentage swelling and water uptake of tablets of FB 8

increased the effervescence formation decreasing floating lag time. The same could be the reason to increase the initial burst release. FB 8 showed 98.28% of drug release in 24 h, an improvement in controlling the drug release. Floating lag time was decreased to 1–2 min. Initial burst release (after 1 h) was increased to 21.52% against the requirement of 22%. Similarity and dissimilarity factors have reached the extremes of the acceptable limits [Table 4]. Since FB 8 gave the required dissolution profile, it was selected as an optimized formulation.

Tablets of FB 8 showed best fit with Hixon Crowell equation ($r^2 > 0.966$) and followed zero-order kinetics ($r^2 > 0.968$). Hence, nifedipine release from the tablet followed dissolution controlled mechanism.

Swelling Studies

The percent swelling index and percent water uptake were calculated for the tablets of FB 8 and are given in Figure 7. As time increases, the swelling index was increased, because weight gain by tablet was proportional to the rate of hydration up to 4 h. Similar is the case with water uptake, which increased up to 12 h. Later on, it decreases gradually due to the dissolution of the outermost - gelled layer of the tablet into the dissolution medium. The observation of the polymer concentration of the tablets of batches 6 and 7 indicates that the cumulative percent drug release increases with the decrease in the concentration of gum. The reason attributed to this fact could be due to lesser swelling index and fast erosion of the gelled layer from the surface of the tablets containing a lesser amount of gum. Apart from the effect of the concentration of the gum, increased cumulative percent drug release rates were observed with an increase in the concentration of effervescing agent (sodium bicarbonate in FB 8 compared to FB 7), which could be due to more effervescence formation.

CONCLUSION

This study had shown that there is a potential to develop a tablet dosage form which remains in the stomach for a long time. This tablet will release the drug in the desired time and

then either disintegrate into small fragments or will lose its integrity so that it can be expelled from the stomach. This study had also shown that such a tablet can be used for poorly soluble drugs. This tablet provides ideal attributes of gastric retention system and overcomes some of the drawbacks associated with presently available systems.

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