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Development and evaluation of effervescent based gastroretentive floating tablets of nifedipine using natural gums

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ABSTRACT

The aim of the present work is to formulate and evaluate gastro retentive floating tablets of nifedipine to provide the drug action up to 12 h, using natural polymers like xanthan gum, guar gum and karaya gum by method direct compression. Sodium bicarbonate with citric acid was employed as effervescent gas generating agent which helps the formulation to float. The formulated gastro retentive floating tablets were evaluated for different parameters such as drug excipient compatability studies, weight variation, thickness, hardness, content uniformity, In vitrobuoyancy studies, *In-vitro* drug release studies performed in 0.1N HCl for 12 h. The results of the present study clearly indicates the promising potential of nifedipine floating system as an alternative to the conventional dosage and other sustained release formulations. The study also revealed the effectiveness of polymers in drug release.

Keywords: Buoyancy studies, Direct compression, Floating, Natural gums, Nifedipine

INTRODUCTION

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action [1]. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation [2]. A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that [1] are locally active in the stomach, [2] have narrow absorption window in gastrointestinal tract, [3] are primarily absorbed from stomach and upper part of GIT, [4] are unstable in the intestinal or colonic environment, [5] disturb normal colonic bacteria and [6] exhibit low solubility at high pH values [2, 3]. The controlled gastric retention of solid dosage forms may be achieved by floating systems which causes gastro retentive dosage form can remain in the gastric region for several h and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients [5]. Nifedipine is a selective calcium channel blocker used for the management of vasospastic angina, chronic stable angina, hypertension, and Raynaud's phenomenon. It is poorly soluble in water, and highly permeable (Class II drugs in accordance to biopharmaceutics classification system, BCS). The oral absorption is uniform, rapid, and complete; its bioavailability is nearly 45-50% and its elimination half-life is 2–4 h [7], thereby requiring two to three times daily dosing in large number of patients, which often leads to non-compliance. In the present study to

develop floating (based on effervescent technology) tablets of nifedipine were prepared by direct compression using natural polymers and the developed formulations were evaluated for various physico-chemical parameters. This delivery system used to retained drug in the stomach region and assist in improving its sustained delivery that have an absorption window in a particular region of gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. The formulation is also a cost effective process [8].

METHODOLOGY

PRECOMPRESSION PARAMETERS

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends were tested as per pharmacopoeia prior to the compression. The formulation powder blends were evaluated for their bulk and tapped density and from these values compressibility index and Hausner ratio were calculated [9]. While the flow properties of the powder bled were accessed from the angle of repose.

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. The bulk density was calculated using the formula, Bulk Density = M / V_o, Where, M = weight of sample; V_o = apparent volume of powder.

10 gm powder blend was sieved and introduced into a dry 20 mL cylinder, without compacting. The powder was carefully levelled without compacting and the unsettled apparent volume, V_o, was read [9].

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula, Tapped Density = M / V. Where, M = Weight of sample, V= Tapped volume of powder.

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the formula, Carr's Index = [(tap - b) / tap] × 100, Where, b = Bulk Density; Tap = Tapped Density.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. The fixed funnel method was employed. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured.

Angle of repose = Tan θ = h / r. where, h = Height of the cone, r = Radius of the cone base.

FORMULATION OF NIFEDIPINE FLOATING TABLETS

In presence of citric acid, sodium bicarbonate was employed as effervescent gas generating agent. At optimised concentration of sodium bicarbonate (15 mg concentration), floating granules of nifedipine using varying concentrations of different grades of polymers were prepared as shown in Table 1. The drug and all other ingredients were individually passed through sieve # 60 and they were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The powder was compressed by direct compression method using 7 mm tablet punch (Cadmach, India). Tablets of nine different formulations were prepared at various concentrations of different polymers. Based on following physicochemical and in vitro drug release studies, the best formulation was optimized [8, 10].

Table 1: Formulation composition for floating tablet

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nifedipine	30	30	30	30	30	30	30	30	30
Xanthan Gum	30	60	90	-	-	-	-	-	-
Guar Gum	-	-	-	30	60	90	-	-	-
Karaya Gum	-	-	-	-	-		30	60	90
PVP K30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
$NaHCO_3$	15	15	15	15	15	15	15	15	15
Citric Acid	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Mg. Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
MCC PH 102	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

POST EVALUATION OF PREPARED NIFEDIPINE FLOATING TABLETS

The prepared tablets were evaluated for quality control tests like weight variation tablet thickness, tablet hardness, friability, assay, *invitro* buoyancy and *in vitro* drugrelease studies.

Weight variation

Ten tablets were selected randomly from each batch and weighed individually, calculating the average weight and comparing the individual tablet weight to the average. From this; percentage weight difference was calculated and then checked as per USP specifications.

Hardness and friability

Hardness of tablet was determined by Monsanto hardness tester. Ten tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated. Friability test was conducted by Roche friabilator. Ten tablets were weighed and were subjected to the combined effect of attrition and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches height with each revolution. After operated for 100 revolutions, the tablets were de-dusted and reweighed. The percentage friability was calculated.

Tablet dimensions

Thickness and diameter of tablets were measured using a calibrated dial callipers. Three tablets of each formulation were picked randomly and dimensions were determined. It is expressed in mm and standard deviation was also calculated [11].

Determination of drug content

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of nifedipine were accurately weighed, transferred to a 100 mL volumetric flask containing 50 mL water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV-visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa et al. The tablets were placed in a 250 mL beaker, containing 200 mL of 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as Floating Lag Time (FLT) and the time period up to which the tablet remained buoyant is determined as Total Floating Time (TFT) [12, 13].

In vitro Dissolution Studies

The *In vitro* dissolution study was performed using a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 100 rpm. Exactly 900 mL of 0.1 N HCl was used as the dissolution medium and the temperature was maintained at 37±0.5^{o}C. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus at specified time interval for 12 h and the same volume was replaced with prewarmed fresh dissolution media. The samples were filtered through a Whatman filter paper (40μ) and diluted to a suitable

concentration with 0.1 N HCl. Absorbance of these solutions was measured at 238 nm using a UV spectrophotometer [14, 15].

Curve fitting analysis

The pattern of nifedipine release from the floating tablets was studied by fitting the dissolution data of optimized formulation (F6) in kinetic models like, zero order, first order, Higuchi model and Korsemeyer-Peppas equations. Based on the slope and the R^2 values obtained from the above models the mechanism of drug release was decided.

RESULTS AND DISCUSSION

In the present work, nifedipine a calcium channel blocker used in the treatment of angina, Reynaud's syndrome, has been utilized as an active drug and considered to be good candidate for reducing dose frequency, for solid oral controlled release formulation as well as more compliance in angina. Nifedipine is poorly soluble in water so an attempt has been made to improve the solubility of the drug by the incorporation of various concentrations of different natural gums and present it in the form of gastroretentive floating tablets to provide the desired controlled and complete release for prolonged period of time. Floating tablets of nifedipine were prepared by dry blending of solubility modifier to modulate solubility of the active drug and varying concentrations of different grades of polymers with sodium bicarbonate and citric acid by direct compression technique.

PRECOMPRESSION PARAMETERS

The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.48 to 0.59 (gm/mL) showing that the powder has good flow properties.

Table 2: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
F1	25.12	0.59	0.66	11.86	1.11
F2	26.8	0.48	0.54	12.5	1.12
F3	23.74	0.56	0.66	17.85	1.17
F4	26.33	0.44	0.55	18.18	1.18
F5	25.21	0.48	0.57	16.66	1.16
F6	27.18	0.51	0.59	15.68	1.15
F7	24.29	0.46	0.56	17.85	1.21
F8	26.01	0.50	0.59	15.25	1.18
F9	26.12	0.52	0.63	17.46	1.21

The tapped density of all the formulations was found to be in the range of 0.54 to 0.66 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which show that the powder has good flow properties.All the formulations has shown the hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.The results of precompression evaluation parameters are shown in (Table.2). All the precomression evaluation parameters were within the USP Pharmacopoeia limits.

QUALITY CONTROL PARAMETERS FOR TABLETS

Tablet quality control tests such as weight variation, hardness, and friability, thickness, content and drug release studies were performed for floating tablets.

Table 3: Evaluation of physical parameters of floating tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)	Total Floating Time (h)
F1	148.4	5.1	0.61	3.3	98.42	5.5	4
F2	149.2	5.2	0.58	3.2	99.65	4.2	6
F3	151.3	5.5	0.45	3.4	99.12	5.0	12
F4	146.3	5.1	0.61	3.3	98.42	5.1	6
F5	148.6	5.3	0.59	3.5	99.65	4.0	8
F6	152.4	5.5	0.65	3.4	99.12	3.2	12
F7	150.6	5.3	0.62	3.6	98.16	4.5	5
F8	151.2	5.2	0.59	3.4	98.11	3.6	12
F9	147.5	5.4	0.60	3.3	98.25	4.7	12

The results of physicochemical characterizations are shown in (Table 3). The thickness of tablets was measured by calibrated dial calliper. Tablet mean diameter and thickness were almost uniform in all the formulations and values for tablets ranged from 3.3±0.156 to 3.4±0.130 mm respectively. The standard deviation values indicated that all the formulations were within the range and show uniform thickness. The average weight of each formulation was recorded. The values were almost uniform and lie within the USP specifications. The values of tablets ranged from 145±0.147 to 147.9±0.178 mg. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of±2% of the weight. The hardness of all formulations was in the range of 5.25±0.165 to 5.5±0.196 kg/cm2. The values of standard deviation indicate that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness. The friability values of prepared tablets are given in (Table 3). The values ranged from 0.41 to 0.65%. All the values are below 1% indicating that the tablets of all formulations are having good compactness and showing enough resistance to the mechanical shock and abrasion. The content uniformity was performed for all seven formulations. The percent drug content of tablets was found to be in between 98.42% to 99.65% of nifedipine.

IN VITRO BUOYANCY STUDIES

All the intragastric floating tablet formulations were prepared by effervescent approach. On immersion in 0.1 N HCl, pH 1.2 solution at 37+0.5 °C all floating effervescent tablets float immediately and remain buoyant up to 24 h without disintegration. The *in vitro* buoyancy of nifedipine tablets was induced by sodium bicarbonate and anhydrous citric acid in optimized ratio (9:2) without compromising the matrix integrity with the possible shortest.

IN VITRO DRUG RELEASE STUDIES

From the dissolution data as shown in Fig. 1, it was evident that the formulations prepared with Karaya Gum as polymer were retarded the drug release more than 12 h. Whereas the formulations prepared with higher concentration of guar gum retarded the drug release up to 12 h in the concentration 90 mg. In lower concentrations the polymer was unable to retard the drug release. The formulations prepared with xanthan gum showed very less retardation capacity hence they were not considered.

Hence from the above dissolution data it was concluded that F6 formulation was considered as optimised formulation because good drug release (96.32%) in 12 h.

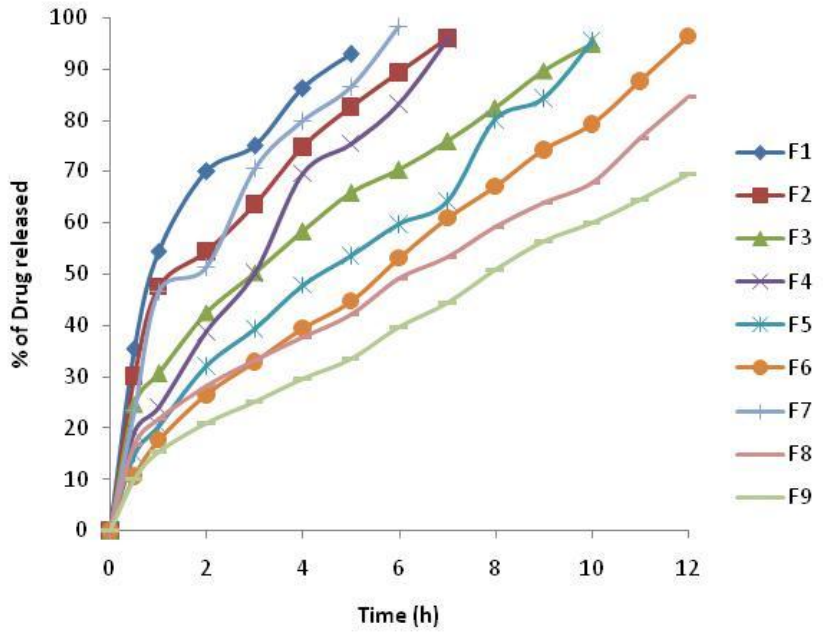


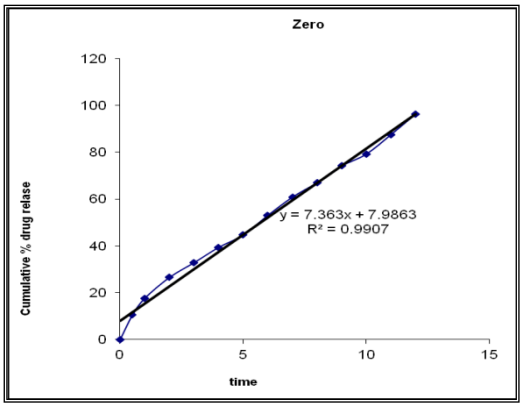
Fig. 1. *In vitro* drug release profile of formulations F1-F9

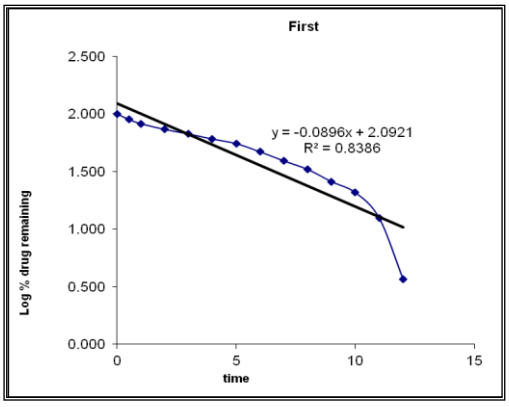
APPLICATION OF RELEASE RATE KINETICS FOR OPTIMISED FORMULATION (F6)

Optimised formulation F6 was kept for release kinetic studies. From the following Fig. 2, it was evident that the formulation F6 was followed zero order release mechanism. The drug release was diffusion controlled followed non-Fickian diffusion kinetics (n value > 0.5) where the drug from swollen polymer was assumed to move linearly with time (Table 4).

Table 4: Application of kinetics for optimised formulation F6

Kinetic model	R^2 value	Slope (m)
First order	0.8386	0.08386
Zero order	0.9907	7.363
Higuchi	0.9655	27.62
KorsmeyerPeppas	0.987	0.684





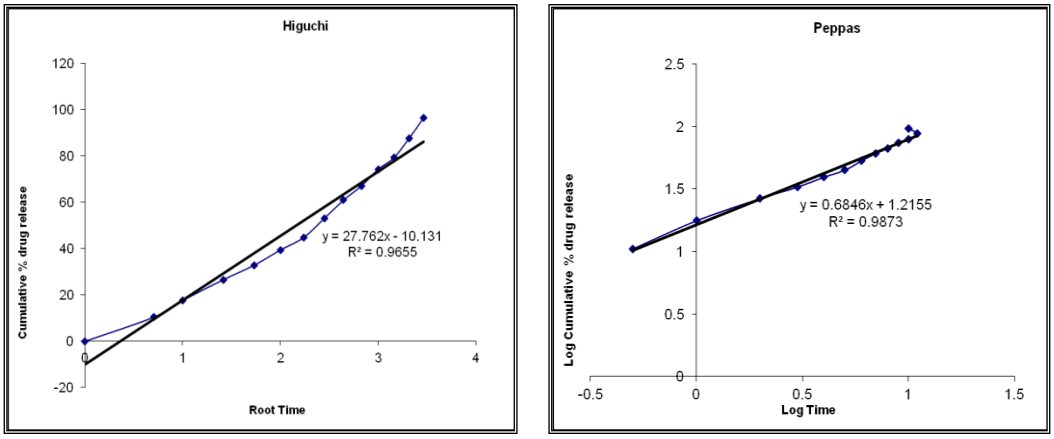


Fig. 2: Kinetic modeling of optimized formulation, F6 for (a) Zero order, (b) First order, (c) Higuchi and (d) KorsmeyerPeppas.

CONCLUSION

Development of gastro retentive floating drug delivery of nifedipine tablets is to provide the drug action up to 12 h. Gastro retentive floating tablets were prepared by direct compression method using various Natural polymers like xanthan gum, guar gum and karaya gum. The formulated gastro retentive floating tablets were evaluated for different parameters such as drug excipient compatability studies, weight variation, thickness, hardness, content uniformity, In vitroBuoyancy studies, *In-vitro* drug release studies performed in 0.1N HCl for 12 h and the data was subjected to zero order, first order, Higuchi release kinetics and Korsmayerpeppas curve fitting. Quality control parameters for tablets such as weight variation, hardness, friability, thickness, drug content and floating lag time were found to be within limits. *In-vitro* drug release studies were carried out for all prepared formulation and from that concluded F6 formulation has shown good results. Finally concluded release kinetics to optimised formulation (F6) has followed zero order kinetics. Present study concludes that gastro retentive floating system may be a suitable method for nifedipine administration.

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