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Development and Evaluation of Gastroretentive Floating Tablets of Neem Leaf Extract Using Psyllium Husk

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ABSTRACT

Gastro retentive systems can remain in the gastric region for several hours and hence prolongs the gastric residence time of drugs and improve the bioavailability. The aim of this project was to develop sustained release floating matrix tablet for hydroalcoholic extract of neem leaves using psyllium husk as release controlling polymer along with synthetic polymer HPMC K100 M and sodium bicarbonate as gas generating agent. The tablets were prepared by direct compression method. Seven different formulations A1 to A7 were prepared by varying the concentration of psyllium husk, HPMC K100 M and sodium bicarbonate. Tablets were evaluated for pre and post compression parameters like tablet thickness, hardness, weight variation, drug content, friability, floating lag time and *in vitro* drug release. Results for angle repose, swelling index, weight variation, drug content, thickness, hardness, % friability for all the formulations were found to be in acceptable limit. *In vitro* drug release was observed for 12 hours and all the tablet formulations followed zero-order kinetics and/ or Korsemeyer-Peppas model in drug release. The formulations were optimized on the basis of buoyancy time and *in vitro* drug release. The optimized formulation was found to be A4 with 98.77% *in vitro* drug release in 12 h and 212 seconds buoyancy time. The $BaSO_4$ tagged formulation, similar to formulation A4 was tested in *in vivo* gastric retention study in rabbits. It was observed that formulation kept floating in the stomach region till 10 hours. Formulations containing combination of psyllium husk and HPMC K100M with sodium bicarbonate as gas generating agent can be a promising way for formulating gastroretentive drug delivery systems.

Keywords: Neem extract, psyllium husk, floating drug delivery, buoyancy.

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INTRODUCTION

The increase in prevalence of multidrug resistance dramatically illustrates the continuous need for new antimalarial agents. One possible approach is the identification of new antimalarial drug candidates in plants, empirically used to treat malaria. Combination therapies preferably using "novel" antimalarial drugs are the way forward for improving therapeutic efficacy and delaying development of resistance. Artemisinin (qinghaosu) derivatives have all been used in combination with other antimalarial drugs for the treatment of malaria. Artemisinin derivatives are eliminated rapidly and has a short half life. When given in combination with a longer half-life "partner" antimalarial drug allows a reduction in the duration of treatment, while at the same time enhancing efficacy and reducing the likelihood of resistance development[1,2]. Azadirachta indica (A. indica), is one of the most promising medicinal plants, having a wide spectrum of biological activity. Every part of the neem tree has been known to possess a wide range of pharmacological properties. Neem has been extensively used in Ayurveda, Unani and Homeopathic medicine. The Sanskrit name of the neem tree is 'Arishtha' meaning 'reliever of sickness'. The importance of the Neem tree has been recognized by the US National Academy of Sciences, which published a report in 1992 entitled 'Neem-a tree for solving global problems'. Neem has found to contain a vast array of biologically active compounds, which are chemically diverse and have got an enormous therapeutic potential[3,4,5]. Nimbidin, azadirachtin and gedunin are reported to possess antimalarial activity. An active ingredient irodin A isolated from Neem leaves is toxic to causative strains of malaria. Components of the alcoholic extracts of leaves and seeds are effective against both chloroquine-resistant and sensitive strains of malarial parasite[6]. The antimalarial potential of neem can be explored in combination with artimisinin derivative provided that its plasma concentration in the blood is maintained for a longer time and its release from formulation is controlled. This can be achieved by designing a floating drug delivery system for neem extract that will control the rate of release for longer duration thus maintaining plasma concentration. The objective of this study was to prepare a sustained release floating matrix tablet of neem leaf extract using psyllium husk as a rate controlling polymer and HPMC k 100 M. Psyllium husk possesses good swelling and gelling properties. Therefore, recently been used as a matrix forming agent in the modified release formulation. Adjutants of natural sources like Psyllium husk are preferred over synthetic material due to their nontoxicity, low cost and availability. Psyllium husk has high affinity for water (swelling index is about 20 times in volume), regulatory acceptance and is chemically inert and assimilable[7].

MATERIALS AND METHOD

The HPMC K100M sample was gifted by US Vitamin Pharmaceutical Ltd., Mumbai. Sodium bicarbonate (Sigma Chemicals, UK), magnesium stearate, talc (S.D. Fine Chemicals, Mumbai), HCl (E. Merck India Ltd.), and Psyllium husk was procured from local market.

Animals

Inbred rabbits of either sex were obtained from the animal house of Pravara Medical College, Pravaranagar. The research was conducted in accordance with standard institutional guidance given by the Institutional Animal Ethics Committee (IAEC). The Labs used for the purpose was approved by the Committee for the purpose of control and supervision of experiments on animals, Ministry of social justice and empowerment, Govt. Of India (Registration No.-448/01/c/CPCSEA).

Extraction of crude drugs

The leaves of *A. indica* was collected from Ahmednagar district and shade dried. The dried parts were coarsely powdered in grinder and powder material was passed through 120 mesh to remove fine powders and coarse powder was used for extraction. About 100gm of powdered leaves was utilized for extraction using continuous hot extraction method. The powdered neem leaves were extracted with petroleum ether for removal of coloring matter by defattation process. The completion of extraction was indicated by taking sample out of siphon tube on TLC plate and placing it in iodine chamber. Absence of colored spot on the plate indicates complete extraction. The defatted leaves were refluxed with water and alcohol (1:1) for 3hr to get hydroalcoholic extract. The extraction temperature was maintained at 50 ^{0}C with constant shaking. The extract was filtered and concentrated to get thick paste and after it freeze dried to get the powder. The extract was stored in air tight container[8].

a) Determination of λ max

The extract was dissolved in 0.1 N HCL and the solution was scanned on UV spectrophotometer between 200 to 400 nm for determination of λ max and it was found at 280nm.

b) Preparation of standard curve

Serial dilutions of concentration 5, 10, 15, 20, 25 and 30 µg/ml were prepared in 0.1 N HCl and analyzed on a UV spectrophotometer at 280 nm for absorbance.

Preformulation study

Fourier Transform Infrared Spectroscopy (FTIR) analysis[9]

FTIR spectroscopy of neem extract and excipients was performed on FTIR (Jasco FT/IR-4100) spectrophotometer. About 5mg of sample is mixed with 100 mg of KBr and compressed to form

pellets. The spectra of sample were scanned from a wave number range of 450 to 4000 cm^{-1}.

Preparation of floating tablet containing neem extract[10]

In the present study, all the tablets were formulated by direct compression technique using HPMC K100M and other ingredients like psyllium husk, magnesium stearate, talc and sodium bicarbonate. All ingredients were passed through sieve no # 80 and weighed accurately. The extract, HPMC K100M, sodium bicarbonate and psyllium husk were mixed properly in a mortar and pestle to get a uniform tablet blend. Finally talc and magnesium stearate were mixed with the blend. The tablet blend was then weighed individually according to the formula and compressed into tablets using 10 station tabletting machine. The different formulations were labeled A1-A7 as per composition given in Table 1.

Table 1: Composition of floating tablet formulation

Ingredients mg	A1	A2	A3	A4	A5	A6	A7
Neem extract	250	250	250	250	250	250	250
Psyllium husk	75	100	125	100	100	100	100
HPMC K100M	50	50	50	40	60	50	50
Sodium bicarbonate	100	100	100	100	100	90	110
Talc	20	20	20	20	20	20	20
Magnesium stearate	5	5	5	5	5	5	5

EVALUATION OF FORMULATION[11,12,13,14]

A) Evaluation of powder blend

Angle of repose

10 gm of powder was passed through funnel and the pile was formed. The height and weight of the pile were measured and the angle of repose was calculated by using the formula:

Angle of repose (θ) = $\tan^{-1}$ height /radius

Bulk density

Both loose bulk density and tapped bulk density were determined for powder blend. A quantity of 2 gm powder of each formula, previously shaken to break agglomerates was taken into a 10 ml measuring cylinder. Initial volume was observed and cylinder was tapped for a fixed time till 100 tapings. LBD (loose bulk density) and TBD (tapped bulk density) were calculated using following formula:

LBD= weight of powder/volume of packing.

TBD=weight of powder/tapped volume of packing.

Carr's compressibility index

The Carr's compressibility index was calculated by calculating the tapped and bulk density using

the 100 ml measuring cylinder. Compressibility is calculated by the formula.

Carr's compressibility index = (TBD- LBD)/TBD X100)

B) EVALUATION OF FLOATING TABLETS

Tablet hardness

The hardness of tablets from all the batches was determined using the Monsanto hardness tester.

Friability

For each formulation, the friability of 20 tablets was determined using the Roche friabilator. In this test tablets were subject to the combined effect of shock and abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre weighted 20 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 min. The tablets were then dusted and rewieghed. Percent friability (%F) was calculated as follows,

% F= (loss in weight / initial weight) x 100

Thickness

Thickness of all tablets was measured using the Vernier caliper.

Tablet weight variation

Twenty tablets were randomly selected and accurately weighed. Results are expressed as mean values ± SD.

Drug content uniformity

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of 10 mg was dissolved in 10 ml of 0.1N HCI. The solution was filtered through a membrane filter (0.45 um). The drug content was determined by UV spectroscopy at a wavelength of 280 nm after a suitable dilution with 0.1 N HCI. Each sample was analyzed in triplicate. The standard curve of neem leaf extract was taken using different concentrations and the slope and intercept was calculated from the standard curve. Then concentration of the sample solution was calculated by using the formula X= Y-CM

Where, X= concentration in µg/ml.

Y=absorbance of solution at 280 nm.

C= intercept of standard curve.

M= slope of standard curve.

Further, the % drug content was calculated from the concentration using the equation as follows

% drug content = Concentration of sample solution X 100 Equivalent concentration of drug taken.

The equivalent concentration of drug taken in this case was 10 mg.

Swelling index

For calculating the swelling index, the previously weighed tablets were placed in the 100 ml beaker containing 0.1 N HCI. The tablets were removed at the time interval of 1 hr for 8 hours, the excess quantity of solution was removed and tablets were weighed. The swelling index (SI) was calculated using the formula:

Swelling index= (Wt-Wo) X 100/Wo

Where, Wt= Final weight of tablets at time t.

Wo= Initial Weight of tablets.

Buoyancy lag time (BLT) and total buoyancy time

BLT is the time required for the formulation to float in the medium and the total buoyancy period is the time for which the formulation remains afloat in the medium. The BLT and total buoyancy time of all the formulations was calculated by placing the tablets in 100 ml of 0.1 N HCI for 18 hours.

***In vitro* drug release studies**

Drug release studies of the prepared floating tablets were performed, in triplicate, in a USP Dissolution Tester Apparatus, type-II (Paddle method) (Dissolution tester, Electrolab) at 37 ± 0.5°C. The paddles rotated at a speed of 50 rpm. The tablets were placed into 900 ml of 0.1 N HCl solution (pH 1.2). Aliquots of 5 ml were withdrawn from the dissolution apparatus at different time intervals and filtered through a cellulose acetate membrane (0.45 um). The drug content was determined spectrophotometrically at a wavelength of 280 nm. At each time of withdrawal, 5 ml of fresh medium was replaced into the dissolution flask. Cumulative percent drug release for formulations from A1-A7 was calculated.

***In vivo* gastro retention study[15]**

The digital X-ray obtained for radio-opaque placebo tablet in rabbits provides the evidence of floating nature of formulation in rabbit's stomach. The $BaSO_4$ tagged formulation, similar to formulation A4 was observed in stomach region till 10 hours. The protocol for *in vivo* study was approved by the Institutional Animal Ethics Committee of Pravara Rural College of Pharmacy, Pravaranagar. *In vivo* study of the final formulation (A4) was performed using the Albino rabbit by an X-ray imaging method. Three albino rabbits were selected for the study. The animals were fasted overnight with free access to water and a radiograph was made just before the administration of the floating tablet to ensure the absence of any radio-opaque material in the stomach. The formulation was administered by the natural swallowing by the rabbit followed by 50 ml of water. The radiographic imaging was taken in a supine position and the distance between

the sources of X-rays and the animal was kept constant for all imaging; thus, the observation of the floating tablet movement could be easily noticed. Gastric radiography was carried out at the 2 h time intervals for a period of 10 h using an X-ray machine (WiproGEDX-300 with the horizontal X-ray system, model SI-0146-3128).

RESULTS AND DISCUSSION

Preparation of standard curve

Various concentrations of neem extract in 0.1 N HCL were scanned on UV spectrophotometer and absorbance values for various concentrations were noted. A standard curve was developed. It followed the linear relationship between concentration and absorbance as shown in figure 1.

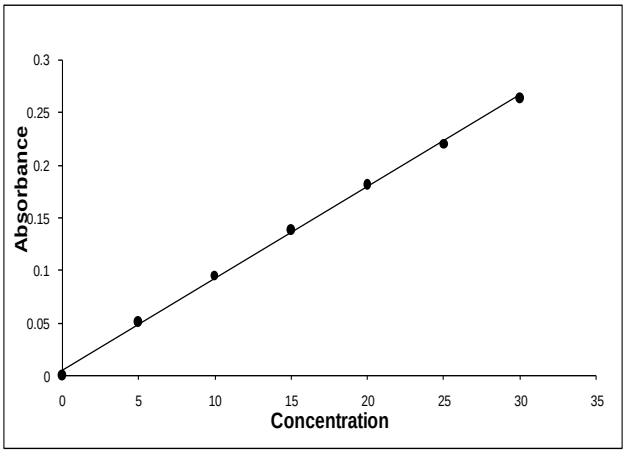

Figure 1: Calibration of curve of neem extract

Tablet 2: Analytical Parameter

Parameters	Value
Wavelength of detection	280 nm
Beer's law limit	1-50 mcg/ ml
Regression equation	Conc. = 114.43 Abs. + -0.579
Correlation coefficient	0.9994

Preformulation study

FTIR analysis

Neem extract, excipients and physical mixture into powdered form was scanned between 4000cm^{-1} to 450 cm^{-1}. The resultant spectrum obtained shown in figure 2 to 5. Presence of peaks for aldehydic C-H stretching (around 2940 cm^{-1}), C=C group (around 1625 cm^{-1}) and Germinal methyl group (around 1350 cm^{-1}) were indicative of terpenoid group of compounds present in the aqueous neem extract. Above peaks were seen in FTIR spectra of neem extract and physical mixture of neem extract and excipient which suggested physical compatibility between them.

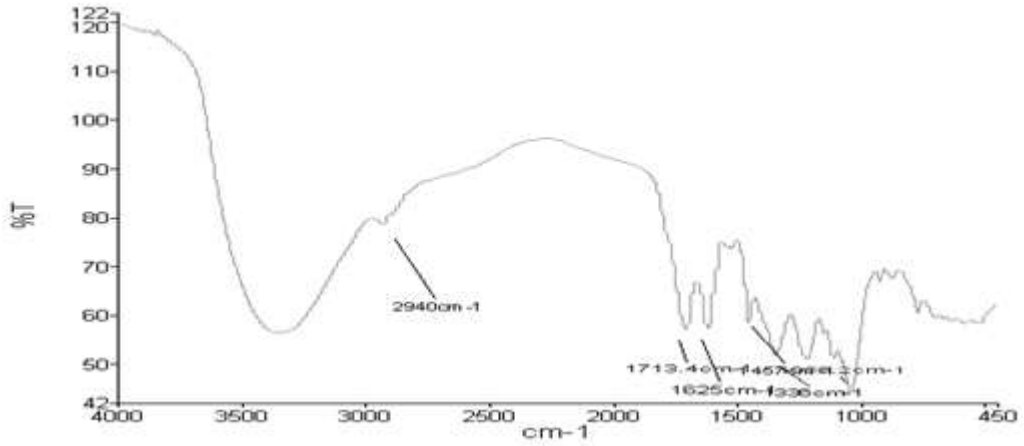

Figure 2: FTIR spectra of hydroalcoholic extract of *A. indica*

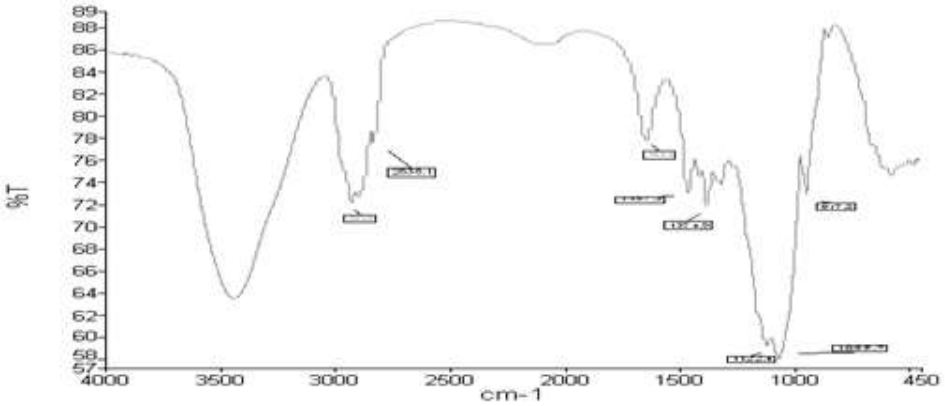

Figure 3:FTIR spectra of HPMC K100M

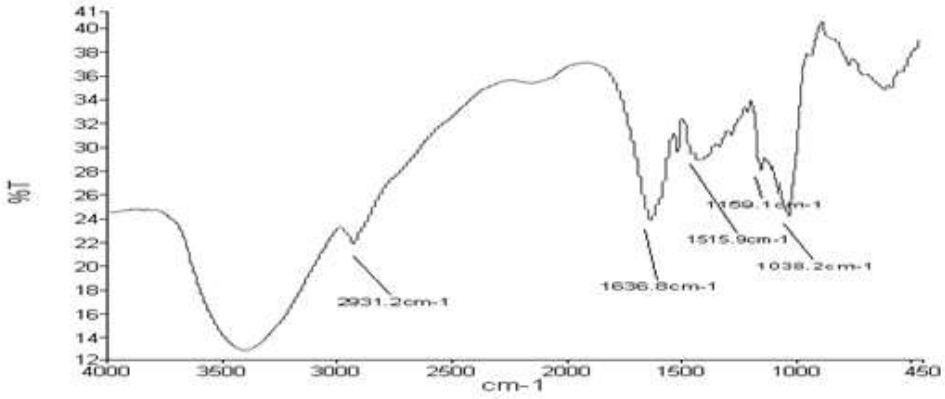

Figure 4: FTIR spectra of sodium bicarbonate

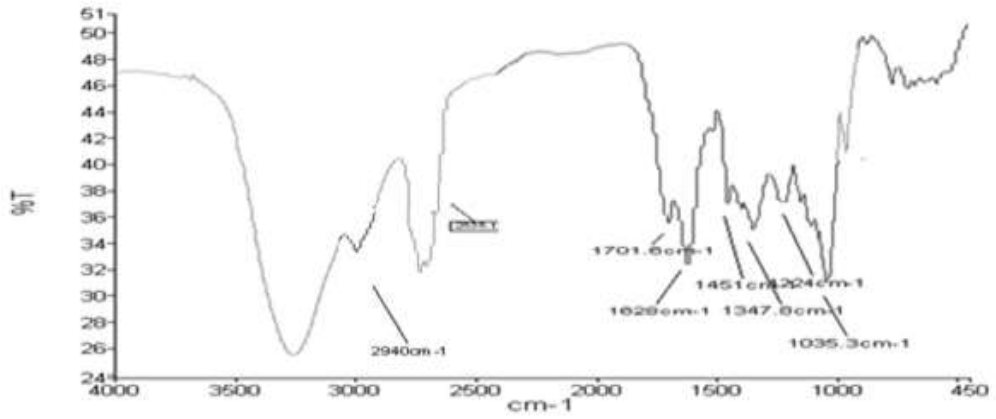

Figure 5: FTIR spectra of physical mixture of neem extract, HPMC and sodium bicarbonate

Evaluation of powder blend

Powder blends of seven formulations (A1 to A7) were evaluated for angle of repose, bulk density and Carr's compressibility index (Table 3). The results showed that the pre compressed blend has good flow property. The angle of repose for all formulation was found between 24-30 except A1 and A3, which represents excellent flow property. Compressibility index value was minimum for A5 (13.18) and maximum for A1 as 17.30.

Table 3: Evaluation of Powder Blend

Formulation No.	Angle of Repose (°)	LBD (g/cm^2)	TBD (g/cm^2)	Compressibility Index
A1	23.54±1.2	0.4137±0.05	0.5064±0.09	17.30±1.3
A2	24.57±0.5	0.5678±0.04	0.6542±0.06	13.20±0.9
A3	22.24±0.8	0.5490±0.1	0.6341±0.07	13.42±0.5
A4	26.07±0.4	0.4675±0.06	0.5462±0.04	14.40±0.6
A5	25.54±2.1	0.4642±0.05	0.5231±0.05	13.18±1.2
A6	24.46±1.3	0.5548±0.03	0.6742±0.05	17.20±2.1
A7	27.36±1.4	0.5450±0.02	0.6473±0.06	15.81±0.9

*Data is expressed as mean± S.D

Evaluation of floating tablets

Various formulations of floating tablet were evaluated for physical parameters such as hardness, thickness, weight variation, % friability, drug content and swelling index, the results are shown in Table 4. The total weight of each formulation was maintained constant; the weight variations of the tablets were within the permissible limits. Tablet thickness was also used to assess the quality of tablets. The thickness of floating tablets ranged from 8.36 to 8.68 mm. Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion with % friability being less than 1%. Drug content in all formulations was calculated and the presence of active ingredient ranged between acceptable limit of 95 to 105%. There was

marked variation in swelling index for various formulations.

Table 4: Post compression evaluation of formulations

Formulation no.	Tablet weight (mg)	Tablet thi-ckness (mm)	Friability %	% drug content	Hardness (kg/cm^2)	Swelling index	Buoyancy lag time (sec.)
A1	505.1 ±0.56	8.54±0.07	0.551±0.06	97.45±0.56	3.1±0.13	178.45±2.34	298±2.28
A2	526.4 ±0.14	8.64±0.04	0.641 ±0.10	98.27±0.75	3.3±0.25	234.66±3.75	271±1.5
A3	552 ±0.35	8.58±0.03	0.66±0.15	98.17±0.34	3.2±0.06	245.56±2.56	239 ± 1.76
A4	513.5 ±0.95	8.50±0.05	0.531 ±0.09	97.96±0.78	3.1±0.15	201.45±1.34	212 ± 1.8
A5	535.6 ±0.23	8.43±0.08	0.634±0.13	98.59±1.56	3.4±0.08	256.55±3.13	302 ± 2.57
A6	515.3 ±0.87	8.36±0.02	0.426±0.16	96.39±0.50	3.3±0.12	208.44±1.57	252 ± 1.2
A7	534.2 ±0.98	8.68±0.10	0.723±0.15	97.19±1.34	3.5±0.34	205.45±2.18	294 ± 2.73

*Data is expressed as mean± S.D

The *in vitro* buoyancy studies in 0.1 N HCl (pH 1.2), revealed buoyancy variations for all the formulations (Table 5). Sodium bicarbonate was used as the effervescent base which generates carbon-di-oxide gas in the presence of hydrochloric acid present in dissolution medium. The gas generated was trapped and protected within the gel (formed by hydration of HPMC K100M and psyllium husk), thus decreasing the density of the tablet. As the density of the tablet falls below 1 (density of water), the tablet becomes buoyant. The tablet mass decreased progressively due to liberation of CO_2 and release of drug from the matrix. On the other hand, as solvent penetrated the polymer layer, the swelling of HPMC K100 M caused an increase in volume of the tablet. The combined effect was a net reduction in density of the tablets, which prolongs the duration of floatation beyond 12 h. The buoyancy lag time of all formulations was in the range 3 to 5 min. Effect of different concentrations of psyllium husk on *in vitro* release was as shown in figure 6. As the concentration of psyllium husk increased from 75 (A1) to 125 mg (A3) per tablet, the percent cumulative drug release in 12 h decreased with 96.33 ±1.9 %, 95.99 ± 1.4 and 91.66 ±2.6 for A1, A2 and A3 respectively. The slow release of the drug was attributed to the gelling properties of psyllium husk. Effect of different concentrations of HPMC K100M on in vitro release was as shown in figure 7. As the concentration of HPMC K100M was increased from 40 (A4) to 60 mg (A5), drug release decreased from 98.77 ± 2.3 % to 94.53 ± 1.89 %. With the increase in polymer concentration there was an increase in the diffusion path length of the drug, retarding the drug release. The effect of sodium bicarbonate on in vitro drug was shown in figure 8. In such systems, sodium bicarbonate acts as a gas-generating agent. As the concentration was increased from 90 (A6) to 110 mg (A7) per tablet, the drug release was decreased from 96.03 ± 1.7 % to 90.55 ± 2.4 %.

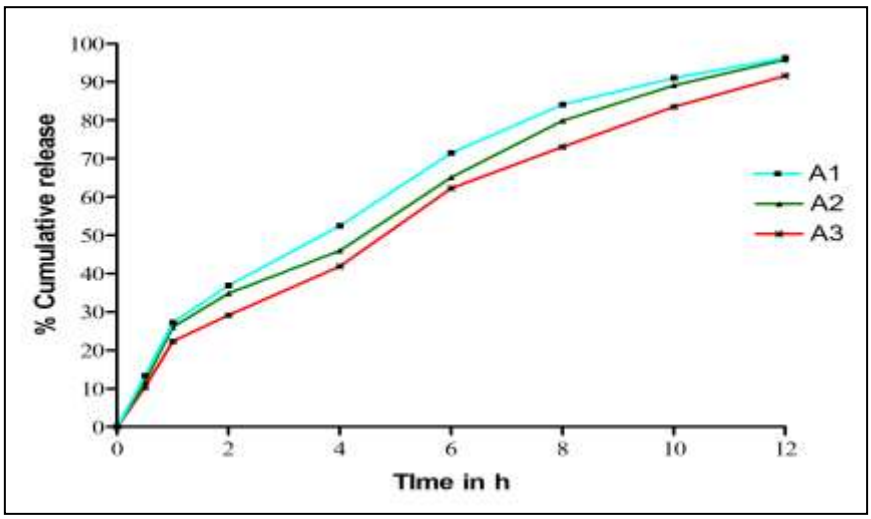

Figure 6: *In vitro* drug dissolution study for A1, A2 and A3

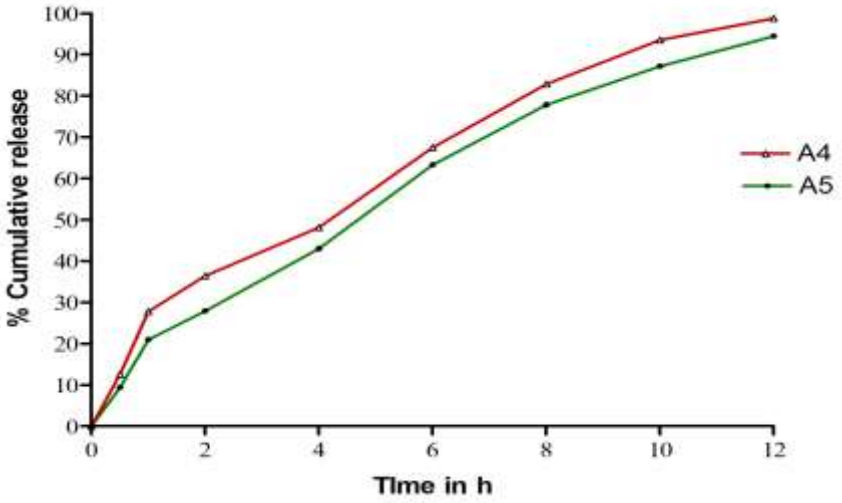

Figure 7: *In vitro* drug dissolution study for A4 and A 5

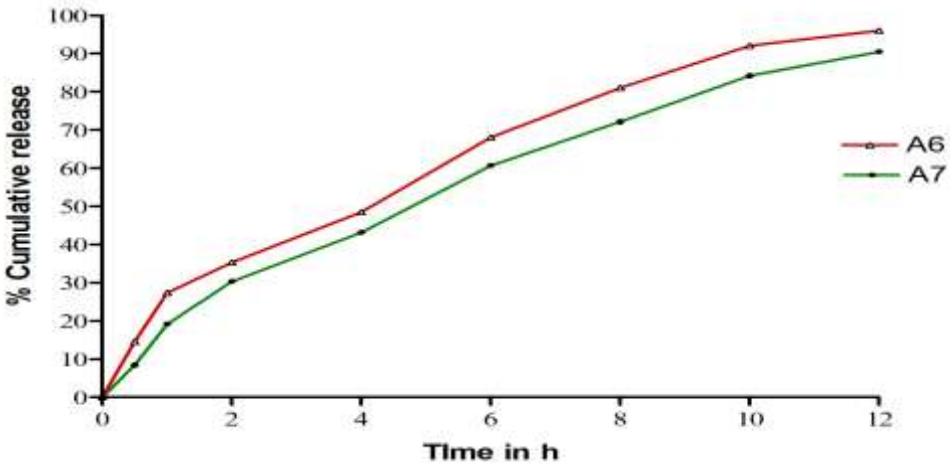

Figure 8: ***In vitro* drug dissolution study for A6 and A7**

Optimization of tablet formulation

Based upon the buoyancy time and % cumulative drug release, the formulations were optimized. The buoyancy time of all formulations was found in the range 3-5 min. The % cumulative drug release was in the range 90.55 -98.77%. The optimized formulation was found to be A4 with the buoyancy time 212 seconds and % cumulative drug release 98.77%.

Mathematical modeling and release kinetics

The release pattern of all the formulations was calculated using PCP Disso v2.0.8.5 software. All the formulations were fitted for zero order release, first order release, higuchi matrix model, Hixson and crowell powder dissolution model and korsmeyer- peppas model. The data obtained are represented in Table 5. None of the formulations followed first-order kinetics, which was confirmed by the poor correlation coefficient values. All formulations best fitted both zero-order (R^2 =0.9534–0.9871) and Korsemeyer and Peppas equation (R2 =0.9734-0.9926). The value for diffusional exponent n was found between 0.5 (suggesting Fickian diffusion controlled drug release) and 1.0 (swelling-controlled drug release). For all formulations, the value of n was in the range 0.5523-0.8178 indicating non-Fickian anomalous transport wherein the drug release mechanism was controlled by both diffusion and polymer swelling.

Table 5: Release Kinetics for various formulations

Formulation code	Zero order Correlation coefficient (R^2)	First order Correlation coefficient (R^2)	Matrix Correlation coefficient (R^2)	Hixson crowell Correlation Coefficient (R^2)	Korsmeyer-Peppas		Best fit model
					Correlation Coefficient (R^2)	Diffusional exponent (n)	
A1	0.9652	0.9089	0.9455	0.9890	0.9843	0.7962	Zero order
A2	0.9766	0.9118	0.9723	0.9095	0.9915	0.5523	Korsmeye
A3	0.9534	0.8657	0.9534	0.9863	0.9874	0.6213	Zero order
A4	0.9540	0.9260	0.9422	0.9715	0.9926	0.8154	Korsmeye
A5	0.9603	0.9244	0.9219	0.9348	0.9734	0.4815	Korsmeye
A6	0.9547	0.9160	0.9633	0.9941	0.9886	0.8178	Hixson
A7	0.9871	0.9201	0.9657	0.9502	0.9814	0.5214	Korsmeye

***In vivo* gastro retention study**

The digital X-ray obtained for radio-opaque placebo tablet in rabbit provides the evidence of floating nature of formulation in the rabbit's stomach. The $BaSO_4$ tagged formulations, similar to formulation A4 were observed in the stomach region as shown in Figure 9. It was observed that formulation kept floating in the rabbit stomach till 10 hours.

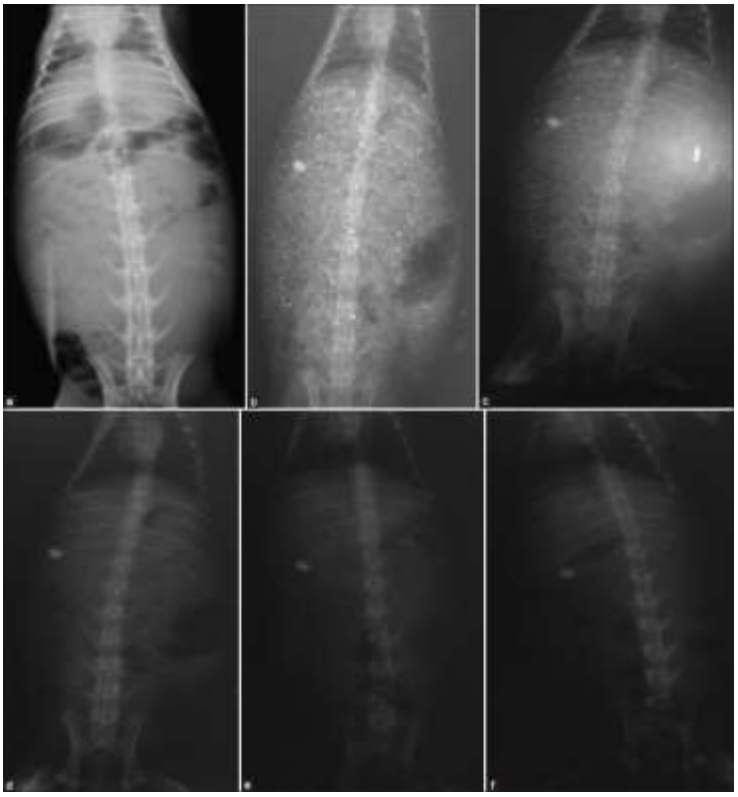

Figure 9: X-ray photographs at different time intervals of gastroretentive floating tablets (a) X-ray at 0 h. (b) X-ray after 2 h. (c) X-ray after 4 h. (d) X-ray after 6 h. (e) X-ray after 8 h. (f) X-ray after 10 h

CONCLUSION

Floating tablets of hydroalcoholic neem leaf extract using psyllium husk, HPMC K100M, talc, sodium bicarbonate, and magnesium stearate were prepared. Formulated tablets were within acceptable limits for various physicochemical evaluations for tablets like tablet dimensions, hardness, uniformity of weight, friability, buoyancy time, and in vitro drug release. Psyllium husk could be a promising natural polymer for controlling drug release from gastro retentive floating drug delivery systems in combination with synthetic polymer like HPMC K 100M. Combination of polymer has enhanced the floating duration and controlled the drug release from the formulation. From FTIR studies, it was concluded that no interactions exists between drug and polymers. Formulation A4 showed good floating behavior along with better--controlled drug release in comparison to other prepared formulations. Formulated floating tablets best fitted to Korsmeyer-Peppas model and zero-order kinetics. The drug release mechanism was found to be non fickain type and controlled by diffusion through the swollen matrix. *In vivo* gastric retention study in rabbits confirmed the floating behavior of $BaSO_4$ tagged formulation similar to the

optimized formulation till 10hour. Floating tablets of aqueous extract of neem leaves can be formulated as an approach to increase gastric residence time, thereby improving its bioavailability.

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