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Development and radiographical evaluation of floating tablets with combination of Amoxicillin Trihydrate and Ranitidine Hydrochloride

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ABSTRACT

Stomach Specific Floating Tablets (SSFT) with a combination of Amoxicillin-Trihydrate (AT) and Ranitidine Hydrochloride (RH) were developed by using different grades of Hydroxypropylmethylcellulose (HPMCK) (i.e.HPMCK $_{100}$M, HPMCK$_4$M and HPMCK$_{15}$M), to treat patients with H. pylori-infected duodenal ulcer. Floating tablets were prepared by direct compression method, developed formulations were evaluated for different pre-compression and post-compression parameters like angle of repose, compressibility index, hardness, weight variation, floating lag time, content uniformity, and in-vitro drug release. In-Vitro release of two drugs (Amoxicillin-Trihydrate and Ranitidine hydrochloride) from the developed formulation was estimated by the Simultaneous Estimation method (Vierordt's Method). The optimized formulation was subjected to Radio graphical evaluation by incorporating the $BaSO_4$, a radio-opaque substance by replacing a part of the drug from the optimized formulation of into the formulation and then it was administered to the healthy human volunteers to find out the in-vivo residence time. In-vivo X-ray studies were conducted both in fed condition, as well as fasted condition the optimized formulation showed a gastric residence time of more in fed state than that of fasting state. From these studies it was clearly observed that the floating tablets should be given to patients after a standard food and with frequent intake of water.

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INTRODUCTION

Oral administration of drugs got upper hand in drug delivery systems (Meenakshi Jassal *et al.,* 2015). During the past decades, many oral conventional drug delivery systems have been formulated and prepared to act as drug carrier and reservoir from which the active pharmaceutical ingredient can be released. The oral route is preferred at most of the times for drug administration due to its low cost, noninvasive administration which enhances patient compliance (*Mosab Arafat et al.,* 2015). However, the developed conventional oral dosage forms have many pitfalls because of its overdose due to multiple times administration of dosage form to a patient this disadvantage was overcome by developing the extended-release formulations (AAH Abdellatif, 2018) like sustained oral release and controlled release formulations. These formulations optimize the biopharmaceutical, pharmacokinetic and pharmacodynamic properties (Mayur Karvekar *et al.,* 2017) of active pharmaceutical ingredient in such a way decreases the frequency (Vishal Sachdeva *et al.,* 2013) of dosing to

an extent to that of daily once administration of dosage form is sufficient to maintain the drug levels in therapeutic window.

Extended-release formulations have shown good in-vitro drug release patterns. However, they failed to maintain the drug levels in therapeutic window in blood for some drugs, this is mainly due to the drugs showing the site specificity in solubility and pharmacokinetics (mainly absorption of the drugs) this variability of pharmacokinetics of drugs is mainly due to the physiological variation in gastrointestinal tract, gastric transit and gastric residence time (Carla M. *et al.,* 2016). Gastric residence time plays a vital role in the overall transit time of dosage form. Gastric residence time of oral extended release dosage form was less than 12 hours, Drug absorption from the gastrointestinal tract is a complex process, and it was subjected to many variables such as the extent of gastrointestinal tract drug absorption is related to the extent of contact time with the small intestinal mucosa, this issue leads to development of gastroretentive drug delivery systems which will enhance the gastric residence of formulation (Vivek K. *et al.,* 2011) for predetermined time.

Floating drug delivery systems (Satinderkakar *et al., 2015;* Shirwaikar *et al.,* 2006) is one of the approaches for retaining the drug delivery system in the stomach for prolonged times based on the bulk density of the formulation. These are the formulations with a bulk density lower than that of gastric fluids, so they remain floating in the stomach for a prolonged time, without being affected by the gastric emptying rate.

While the formulation buoyant on contents of the stomach and the drug was released slowly from the dosage form slowly at a determined rate, peptic ulcer disease and particularly duodenal ulcer disease was thought to have a multifactorial pathogenesis peptic ulcer disease is mainly focused on abnormalities in the secretion of gastric acid and infection due to H. pylori, eradication of H. pylori and suppression of gastric acid secretion were the main strategy in treating the duodenal ulcer disease (Gisbert J. P. *et al.,* 2009) and has resulted in very high duodenal ulcer healing rates and a dramatic reduction in disease recurrence rate. Combination of ranitidine and amoxicillin (Dettmer A. *et al.,* 1995). is very effective and well-tolerated therapy in curing the H. pylori-infected duodenal ulcer patients.

Amoxicillin Trihydrate is a bactericidal β-lactam moderate-spectrum antibiotic used in treating bacterial infections. Maximum absorption of Amoxicillin Trihydrate occurs from the upper part of the gastrointestinal tract (Narendar Dudhipala *et al.,* 2016) after oral administration. The half-life of Amoxicillin Trihydrate was 1 – 2 hours. Ranitidine hydrochloride is histamine H2 -receptor antagonist was widely used in treating the duodenal ulcers. Bioavailability of Ranitidine was 50%, it was mainly due to its site of absorption from the initial part of small intestine and metabolism by colonic flora (Jain S. *et al.,* 2010) was responsible for the poor bioavailability of ranitidine.

In the present research floating tablets with a combination of Amoxicillin-Trihydrate and Ranitidine hydrochloride were prepared by using different viscosity grades of Hydroxypropylmethylcellulose. Amoxicillin-Trihydrate and Ranitidine hydrochloride were having the maximum absorption from the upper part of the gastrointestinal tract, and Ranitidine hydrochloride is metabolized by colonic flora; this makes the drugs suitable for developing as a gastroretentive floating tablets. In-vitro drug release from the developed formulation was estimated with UV spectrophotometer by Vierordt's Simultaneous Estimation method.

MATERIALS

Ranitidine Hydrochloride was provided as gif sample from M/s Aurobindo Pharma Ltd. Hyderabad, India. Amoxicillin-Trihydrate was received as, generous gift sample from Alkem Laboratories, Mumbai. Hydroxypropyl methylcellulose ($HPMCK_{100}M$, $HPMCK_4M$ and $HPMCK_{15}M$) was received as a gift sample from Euro Drugs Ltd. Sodium bicarbonate ($NaHCO_3$) Magnesium Stearate (MS), Microcrystalline cellulose (MCC) (Avicel PH101), and talc were purchased from S.D. Fine-Chem. Ltd., Mumbai, India. All other reagents used in the research were of analytical grade.

METHODOLOGY

Formulation and Development of Floating Tablets with a combination of Amoxicillin-Trihydrate and Ranitidine Hydrochloride

Floating tablets with **a** combination of Amoxicillin-Trihydrate and Ranitidine Hydrochloride were prepared by direct compression method. Accurately weighed quantities of polymer and microcrystalline cellulose were taken in a mortar and mixed homogenously, to this mixture required quantity of Amoxicillin trihydrate and Ranitidine hydrochloride were added and mixed with a pestle, sodium bicarbonate was taken separately in a mortar and powdered with a pestle. The powder is then passed through sieve no 40, and accurate quantity was weighed. The total content was transferred to a plastic bag and mixed for 3 minutes, and blended appropriately with talc and magnesium stearate. This powder mixture was subjected to different Preformulation studies, and floating tablets were compressed with a tablet compression machine by

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using 12 mm punch set. The composition of developed 9 formulations was shown in the Table.1, before optimizing the amount or percentage of polymer required to have a required release of drugs, the concentration of sodium bicarbonate required to keep tablets buoyancy was optimized.

Pre-formulation parameters

Construction of Calibration Curve and Analysis of In-Vitro Dissolution Sample: Standard stock solution of Amoxicillin-Trihydrate and Ranitidine Hydrochloride (1mg/ml) were prepared separately in 0.1N HCl, for the selection of analytical wavelength (λmax) concentrations were prepared from standard stock solution by diluting the standard stock solutions with 0.1N HCl, prepared sample solutions were subjected to scanning in the spectrum mode from 200-400nm, by using UV-visible spectrophotometer. The wavelength with maximum absorption was chosen for further construction of calibration curve and analysis. Calibration curve was constructed by recording Absorptivities at λmax of Amoxicillin-Trihydrate for Amoxicillin-Trihydrate as well as for Ranitidine Hydrochloride and other Absorptivities were recorded at λmax of Ranitidine Hydrochloride for Amoxicillin-Trihydrate as well as for Ranitidine Hydrochloride calibration curve and analysis of dissolution samples were done by using Vierordt's Simultaneous Estimation method (Giriraj P. *et al.,* 2014).

Vierordt's Method: This method of analysis is based on the absorption of drugs (X and Y) at the wavelength Maximum of the other. The quantification analysis of amoxicillin trihydrate and Ranitidine in a binary mixture were performed with the following equations: Cx= (A2 ay 1 - A 1 ay 2)/ a x 2 ay1 – ax1 a y2 (eqn1), CY= (A1 ax2- A2 ax1)/ax2ay1-ax1ay2 (Eqn2), where CX and CY are the concentrations of X and Y respectively in the diluted sample, ax1 and ax2 are Absorptivity's of x at λ1 and λ2 and ay1 and ay2 are the absorptivity of Y at λ1 and λ2 are A1 and A2 respectively

Fourier-transform infrared spectroscopy: Fourier-transform infrared (FT-IR) spectroscopy studies were carried out for pure drugs drug and for the 1:1 Physical mixture of drugs and excipients[14] by using FT-IR (Bruker., India). These samples were analyzed in the range of wave numbers 4000 and 400cm-1. FT-IR spectral analysis of pure drugs Amoxicillin-Trihydrate, Ranitidine Hydrochloride and Excipients was carried out to screen the chemical composition changes in drugs after combining the drugs with the excipients The pure drugs, mixture of drugs and excipients were mixed appropriately and were placed under the knob of Bruker FT-IR scanned in wavelength, the spectra were analyzed and interpreted.

Powder characterization: Determination of various Preformulation characteristic is crucial in formulation development Preformulation parameters (Ananthakumar R. *et al.,* 2014*;* Faria Gias Senjoti *et al.,* 2016; Sarovar Reddy V. *et al.,* 2018). Such as the angle of repose, bulk density, tapped density, Carr's index and Hausner ratio are very important in the characterization of the property and compression behavior of powder or granules before the tablet was compressed because they decide the quality of the product, in turn, reflect the same in formulation integrity and efficiency.

Post-Compression Evaluation: Prepared tablets were evaluated for hardness, thickness, friability floating lag time, total in-vitro floating time, drug content, in-vitro dissolution studies, stability and radiographic studies.

Hardness and Thickness: The compressed floating tablets of Amoxicillin-Trihydrate and Ranitidine Hydrochloride were evaluated for hardness (Aswatha H.N. *et al.,* 2010) and thickness. The thickness of tablets was measured by using Vernier caliper. The hardness of the developed tablets was done by using Monsanto hardness tester.

Weight variation: Twenty tablets from each composition/formulation were weighed, and their average weight was determined (Jyoti Rathore *et al., 2015*) and was determined by using formula.

Percentage of Weight variation = $(W_A–W_I)$ x 100/ W_A

W_I is the initial weight of tablet & W_A is the average weight of the tablet

Friability

Friability of tablets was determined (Ara N. Patel *et al., 2011*) by using Roche friabilator, ten tablets were taken randomly from prepared batch/ formulation and their sum of initial weight (W_1) was recorded by using weighing balance, then friabilator was run at 25 rpm for 4 minutes, then final weight of ten tablets was recorded as final weight (W_2) percentage of friability was calculated by using formula;

Percentage Friability = $[[(W_1) - (W_2)]/ (W_2)] \times 100]$

Floating lag time

Floating lag time was the time taken for tablet to raise to the surface of the medium this was carried out (Basavaraj K Nanjwade *et al., 2012*) by dropping a tablet into 250 ml beaker containing 200 ml of 0.1 N HCl, and recording the time taken by tablet to rise to surface of 0.1 N HCl.

In-Vitro Total Floating Time: It was the total duration for which tablet remains floating on the surface of the medium. This was done (Kumar Sachin

et al., 2018) by dropping a tablet into 250 ml of 0.1 N HCl and recording total buoyancy time of tablet on the surface of 0.1 N HCl.

Drug Content (Assay)

The content of both the drugs in the developed formulations were evaluated and was determined accordingly by standards and the active ingredients in each of the 6 tested tablets were evaluated and should lie within the range of according to IP ten tablets were crushed in motor and pestle and triturated to get uniform mixture, equivalent weight of tablet was weighed from crushed tablets and it was transferred to a 100mL volumetric flask containing 70 mL of 0.1N HCl. It was shaken for 1h, and then it was filtered through a Whatman filter paper and diluted to 100mL with 0.1N HCl. From this resulted solution 1ml was taken, diluted to 50mL with 0.1N HCl and absorbance was measured against a blank at λmax of Amoxicillin-Trihydrate, and Ranitidine Hydrochloride and content of both drugs were analyzed by using Vierordt's Simultaneous Estimation method.

In-vitro Drug Release Studies

The in-vitro drug release study was carried out for all the developed floating tablets in USP Type-II dissolution apparatus in 900mL of 0.1N HCl at a temperature of 37±0.5°C, the speed of the basket was set at 50 rotations per minute. Sampling was done at different predetermined time intervals as follows 0.5, 1, 2, 3, 4, 6, 8, 9, 10, 12 hours and 5mL of the sample was collected and replaced by fresh preheated (37±0.5°C) 0.1N HCl to maintain sink conditions. Samples withdrawn were filtered through Whatman filter paper (No.1), and the amount drug in each sample was analyzed by Vierordt's Simultaneous Estimation method.

Kinetic Analysis of Dissolution Data

There are number of kinetic models, which described the overall release of drug from the dosage forms. Because qualitative and quantitative changes in a formulation may alter the drug release.

The data recorded from the in-vitro drug release studies were analyzed by various kinetic models to find out and to explain the drug release mechanism (Kumar Sachin *et al.,* 2018) from the floating tablets of Amoxicillin-Trihydrate and Ranitidine Hydrochloride in this research, the drug release data were subjected to different kinetics models like zero-order, first-order, Higuchi, and Korsmeyer-Peppas. The best fit of data was analyzed by using the values of (R^2). In Korsmeyer–Peppas model: $F = K_P t^n$: where F indicates the fraction of drug released at time point t, K_P represents the rate constant and n is the release exponent, suggestive of the drug release mechanism. An n value is less than or equal to 0.5 it represents the Fickian release mechanism and the value of n ranging between 0.5 and 1 represents non-Fickian release mechanism When the n value is greater than or equal to 1, it represents case-II transport, and this is due to the polymer dissolution and polymeric chain expansion or relaxation.

Radiographic Studies

Radiographic studies were conducted in healthy human volunteers (Arun B. Reddy *et al.,* 2018) to find out the in –vivo gastric resident time of optimized formulation, this study was conducted in healthy male subjects (mean age 24 year: mean weight 60±10 kg) formulation was made opaque by replacing the 10 % of Amoxicillin-Trihydrate with $BaSO_4$. An optimized formulation containing 10% of $BaSO_4$. Were evaluated for any change in the floating lag time and total floating time Formulation with $BaSO_4$ was administered to healthy male human volunteer after taking informed consent. The study was carried in human volunteers with permission from Institutional Human ethics committee and their Approval no: REF. No: ICE /RVSIMS/2017/09. The radiographic study was conducted in healthy human volunteers in fasting condition and fed condition. In the fasted state the human volunteer's fasted overnight then capsule was administered with 150 ml water then after volunteers were not allowed to eat anything for two hours. In fed state after a regular meal, the formulation was administered to volunteers immediately with 250 ml of water, the composition of an optimized formulation containing $BaSO_4$ shown in Table.2

Stability Studies

Stability studies were carried out for the optimized formulation accordingly to the guidelines of International Conference on Harmonization (Nelson Kenneth *et al.,* 2015*;* Shah UH Patel BK. *et al.,* 2012) (ICH) guidelines. The optimized formulation was enclosed in polyethylene bottle and placed in a stability chambers 75± 5% Relative Humidity at 40 ± 2°C for 3 months, and post-compression evaluation test was conducted for the formulations stored in stability chambers at intervals of 30 days, 60 days and 90 days At predetermined time intervals, the tablets were examined for hardness, drug content, buoyancy and drug release these tablets were evaluated for parameters like hardness, drug content, floating lag time total floating time and in-vitro drug release studies.

RESULTS AND DISCUSSION

Simultaneous Spectrophotometric Determination of Amoxicillin Trihydrate and Ranitidine Hydrochloride

The standard graph and whole analysis were performed in a pH of 1.2(0.1N HCl). Vierordt's Method issued for Simultaneous estimation is based on the Absorptivities of Amoxicillin and Ranitidine Hydrochloride at the wavelength maximum of the other. The wavelengths selected were 231nm and 313nm based on their $\lambda_{max.}$ (λ_{max} of Amoxicillin Trihydrate is 231nm, $\lambda_{max\ of}$ Ranitidine Hydrochloride is 313nm)

Drug-Excipients Compatibility Studies

FT-IR spectrum for pure drugs and physical mixture of formulation with drug and polymer were recorded in the range of 4000-400 cm^{-1}. The FT-IR spectrum of AT revealed the stretching frequency for C-H, C=C, OH, CH_3, C-N, N-H at 2969.02, 1482.03, 3499, 1119.57, 3154.04 cm^{-1} respectively and bending frequency for N-H and CH_3 groups at 1518.12 and 1312.30 cm^{-1} respectively and RH spectrum had stretching frequency for C-H, C=C, OH, CH_3, C-N, N-H at 2950.32, 1470.19, 1003.87, 3167.56 respectively and bending frequency for N-H and CH group at 1619.40 and 1377.99 cm^{-1}. The FT-IR spectrum of the formulation with drugs AT, RH along with polymer HPMC K_4M have shown stretching frequencies for C-H, C=C, OH, C-N, N-H at 2915.88, 1456.39, 1019.04, 3182.61 cm^{-1} respectively and bending frequency for N-H and CH at 1619.40 and 1377.99 cm^{-1}. FT-IR spectrum for the formulation with drugs AT, RH an along with polymer HPMC $K_{100}M$ have shown stretching frequencies for C-H, C=C, OH, CH_3, C-N, N-H at 2910.27, 1454.77, 3422.00, 1020.89, 3171.52 cm^{-1} and bending frequency for N-H and CH at 1519.02 and 1376.30 cm^{-1} respectively. The FT-IR spectrum of formulations with pure drugs and polymer have not shown any major shift in the stretching and bending frequency of vital groups in the drugs when compared to that of FT-IR spectrums of pure drugs shown in the Figure.1, this reveals that the absence of incompatibility between pure drugs and other components used for formulation development.

Characterization of Powder Blend

The Pre-formulation studies like Angle of repose, Compressibility index (CI) and Hausner's ratio were calculated values were shown in Table 4.

Powder blend of all the formulations containing the drugs polymer diluents glidant and lubricant were evaluated for powder parameters and values are in the range as follows values of angle of repose were in the range of 25.5° to 29.4° these values indicate powder has good flow property, values of bulk density powder blend of all the formulations were in the range of 0.358 to 0.378 g/cc and the values of tapped density of powder blend of all the formulations were in the range of 0.434 to 0.482(g/cc), values of CI of all the formulation powder blend were in the range between 16.55 to 20.4% this indicates that developed composition of all the formulations are having good enough compressibility properties so tablet can be prepared by direct compression method without any difficulty. Powder blend of all the formulations have shown Hausner's ratio values in the range of 1.19 to 1.25 indicating the powder has fair Compressibility properties, above values, indicate all the powder properties of developed formulations were good.

Characterization of Floating Tablets

All the developed 9 formulations were tested for physical parameters of tablets like Weight variation, Thickness, Hardness, Friability, drug content and in-vitro drug release in 0.1N HCl the values of results were found to be as follows. Weight variation of all the developed formulation was in the range of 989±2.9 to998±3.2 mg these values indicate they are in pharmacopeial limits. The hardness of the floating tablets was in between 5.1±0.48 to 5.6±0.51 kg/cm^2 this value indicates that the developed formulations have enough mechanical strength. Friability of the tablets was found to be less than 0.55 %. Assay was performed for all the developed 9 formulations to determine the content of AT and RH in the formulations and the percentage of AT was found to be in the range 96.45±2.76% to 101.78±1.85 % and values for RH were in the range of 96.46±1.12% to 99.85±1.54% which indicates values of drug content of both the drugs were within the acceptable limits and found to be within the pharmacopoeias limits. The results of the tests were shown in Table.5**.** Below the drug content of all the formulations were determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

All the developed nine formulations of floating tablets were showing the total In-vitro floating time for above 12 hours in 200 ml of 0.1n HCl. Floating lag time of all the formulation was in the range of 40±2.34 to 63±3.93 seconds, this indicates tablets were showing the floating lag time less than 2 minutes of time. Values of floating lag time and total floating time of floating tablets with a combination of AT and RH were shown in Table 6.

In-Vitro drug release Studies of Floating Tablets with a combination of Amoxicillin-Trihydrate and Ranitidine Hydrochloride: The in-vitro drug release study was carried out for all the

Table 1: Composition of Developed Formulation of Floating Tablets

Components (Milligrams)	FTAR1	FTAR2	FTAR3	FTAR4	FTAR5	FTAR6	FTAR7	FTAR8	FTAR9
AT	500	500	500	500	500	500	500	500	500
RH	150	150	150	150	150	150	150	150	150
HPMC $K_{100}M$	120	150	180	-	-	-	-	-	-
HPMC K_4M	-	-	-	120	150	180	-	-	-
HPMC$K^{15}M$	-	-	-	-	-	-	120	150	180
NaHCO3	80	80	80	80	80	80	80	80	80
MCC	120	100	80	120	100	80	120	100	80
Magnesium Stearate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10
Total Weight	1000	1000	1000	1000	1000	1000	1000	1000	1000

FTAR: Floating Tablets of Amoxicillin-Trihydrate and Ranitidine Hydrochloride

Table 2: Composition of Optimized Formulation of Floating Tablets With BaSO4

Ingredients	Weight (Milligrams)
Amoxicillin Trihydrate	400
Ranitidine	150
$BaSO_4$	100
HPMCK_4M	150
Sodium bicarbonate	80
MCC	100
Talc	10
Magnesium Stearate	10
Total weight	1000

Table 3: the wave number of vital groups in Amoxicillin Tri-Hydrate, Ranitidine, and Formulations with HPMC K4M, HPMC K100M

Functional group	Amoxicillin trihydrate	Ranitidine Hydrochloride	Formulation with HPMC K_4M	Formulation with HPMC $K_{100}M$
C-H stretching	2969.02	2950.32	2915.88	2910.27
C=C aromatic stretching	1482.03	1470.19	1456.39	1454.77
OH stretching phenolic	3499.75	-	3421.53	3422.00
N-H bending	1518.12	1619.40	1575.77	1519.02
CH bending	1312.30	1377.99	1406.35	1376.30
C-N stretching	1119.57	1003.87	1019.04	1020.89
N-H stretching	3154.04	3167.56	3182.61	3171.52

Table 4: Pre-Formulation Studies of Powder Blend

Formulation	Angle of repose	Bulk Density (g/cc)	Tapped Density (g/cc)	CI (%)	Hausner's Ratio
FTAR 1	27.5°	0.375	0.459	18.33	1.22
FTAR 2	26.8°	0.358	0.445	19.55	1.24
FTAR 3	29.4°	0.374	0.468	20.08	1.25
FTAR 4	28.0°	0.361	0.434	19.12	1.20
FTAR 5	27.1°	0.381	0.479	20.4	1.25
FTAR 6	26.4°	0.375	0.462	18.83	1.23
FTAR 7	25.5°	0.369	0.451	20.39	1.22
FTAR 8	26.7°	0.378	0.453	16.55	1.19
FTAR 9	28.9°	0.391	0.482	18.87	1.23

developed floating tablets in USP Type -II dissolution apparatus in 900mL of 0.1N HCl at a temperature of 37±0.5°C, the speed of the basket was set at 50 rotations per minute and samples were analyzed by Vierordt's Method of Simultaneous estimation is based on the Absorptivities of Amoxicillin Trihydrate and Ranitidine Hydrochloride (FAT: Cumulative percentage of Amoxicillin-Trihydrate

Table 5: Evaluation of Prepared Floating Tablets (Post-Compression evaluations)

Formulation	[a]Weight Variation(mg)	[b]Hardness (kg/cm^2)	[c]Friability (%)	[b]Thickness (mm)	[b] Drug content (%)	
					AT	RT
FTAR 1	990±2.7	5.5±0.52	0.25	8.36±0.09	97.98±1.58	99.53±1.73
FTAR 2	996±2.3	5.1±0.48	0.31	8.58±0.15	98.92±2.32	99.85±1.54
FTAR 3	997±2.4	5.2±0.42	0.39	8.31±0.21	101.78±1.85	98.72±2.42
FTAR 4	989±2.9	5.3±0.48	0.52	8.47±0.18	96.45±2.76	97.95±2.53
FTAR 5	993±3.1	5.4±0.41	0.47	8.29±0.06	97.94±2.34	96.85±1.68
FTAR 6	985±3.8	5.5±0.52	0.34	8.51±0.29	99.98±1.79	96.46±1.12
FTAR 7	994±3.34	5.6±0.51	0.27	8.43±0.08	98.57±1.56	97.46±2.45
FTAR 8	998±3.2	5.2±0.42	0.37	8.61±0.38	99.69±1.95	97.59±1.79
FTAR 9	986±2.3	5.3±0.48	0.29	8.35±0.41	97.96±2.26	97.69±2.31

Mean ± SD: a-n=20, b-n=6; Friability, c-n=10

Table 6: In-Vito Floating Cauterization of Floating Developed Floating Tablets

S.No	Formulations	Floating Lag Time(Seconds)	Total Floating Time
1	FTAR 1	40±2.34	>12hrs
2	FTAR 2	53±2.71	>12hrs
3	FTAR 3	45±3.25	>12hrs
4	FTAR 4	49±4.96	>12hrs
5	FTAR 5	42±2.34	>12hrs
6	FTAR 6	63±3.93	>12hrs
7	FTAR 7	50±2.51	>12hrs
8	FTAR 8	40±2.37	>12hrs
9	FTAR 9	61±4.26	>12hrs

Table 7: Kinetics of Drugs Release from Optimized Formulation of Floating Tablets

S. No	Formulation	Zero-order R^2	First order R^2	Higuchi model R^2	Peppas Model R^2	Peppas n
1	FAT5	0.9350	0.8510	0.9954	0.9949	0.5114
2	FR 5	0.9091	0.9566	0.9949	0.9901	0.5094

Table 8: Evaluation of tablets with Baso4 for In-Vivo X-Ray studies

Parameters	Optimized batch	Tablets containing $BaSO_4$
Hardness	5.4±0.41kg/cm^3	5.6±0.56 kg/cm^3
Thickness	8.29±0.06mm	8.41.±0.15mm
Floating time	42±2.34sec	57± 3.61sec
Floating duration time	More than 12hours	More than 12 hours

Table 9: Stability Studies of Optimized Formulation

PARAMETER		0th Day	30th Day	60th Day	90th Day
Hardness (kg/cm^2)		5.4±0.41	5.51±0.39	5.59±0.72	5.69±0.48
Drug content (%)	AT	97.94±2.34	97.23±2.12	96.45±1.53	96.23±1.34
	RAN	96.85±1.68	96.71± 1.62	96.72±1.58	96.64±1.55
Floating lag time (Sec)		42±2.34	40±1.34	43±2.25	43±3.82
Duration of Floating (hrs)		>12	>12	>12	>12

release from formulations, FR: Cumulative percentage of Ranitidine Hydrochloride release from formulations, D:P Drug to polymer Ratio in the formulations).

Formulation FTAR1, FTAR2 and FTAR3 containing HPMC $K_{100}M$ as a polymer of varying concentration, i.e. Amoxicillin Trihydrate to polymer ratio 1:0.24, have shown Amoxicillin Trihydrate release of 93.23±3.14 % in 12 hours, Amoxicillin Trihydrate to polymer ratio 1: 0.30 have shown Amoxicillin Trihydrate release of 87.33±2.98 in 12 hours, Amoxicillin Trihydrate to polymer ratio 1:0.36 have shown Amoxicillin Trihydrate release of 81.89±2.45 in 12 hours, as shown cumulate percentage of drug release a and Ranitidine Hydrochloride to polymer ratio 1:0.8, have shown the Ranitidine Hydrochloride release of 92.84±2 in 12 hours. Ranitidine Hydrochloride to polymer ratio 1:1, have shown the Ranitidine Hydrochloride release of 84.36±1.35in 12 hours and. Ranitidine Hydrochloride to polymer ratio 1:1.2, have shown the Ranitidine Hydrochloride release of 81.63±3.4412 hours.

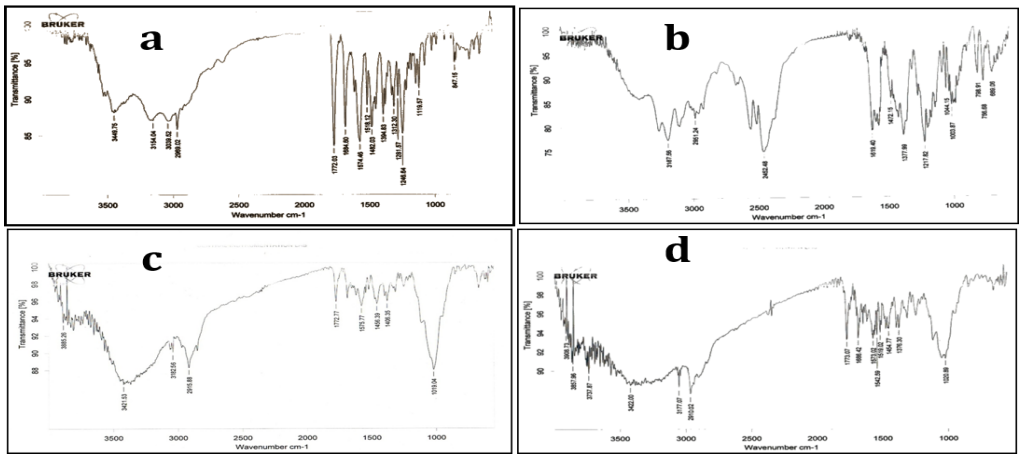

Figure 1: The Wave Number of Stretching and Bending Frequency of vital groups; a: FT-IR spectrum of Amoxicillin-Trihydrate; b: FT-IR spectrum of Ranitidine Hydrochloride; c: FT-IR spectrum of Amoxicillin-Trihydrate and Ranitidine Hydrochloride with HPMC K_4M; d: FT-IR spectrum of Amoxicillin-Trihydrate and Ranitidine Hydrochloride with HPMC $K_{100}M$.

Formulation FTAR4, FTAR5 and FTAR6 containing HPMC K_4M as a polymer of varying concentration, i.e. Amoxicillin Trihydrate to polymer ratio 1:0.24, have released 97.14±1.56 % of Amoxicillin Trihydrate in 10 hours, Amoxicillin Trihydrate to polymer ratio 1: 0.30 have released 98.56±2.91 % of

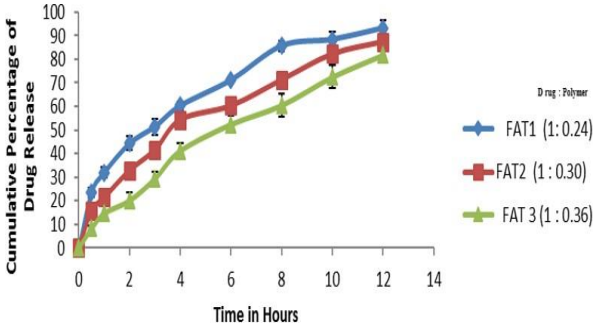

Figure 2: Graphical Representation of cumulative percentage of In-Vitro AT Release from Formulation Containing Different Ratios of HPMC $K_{100}M$

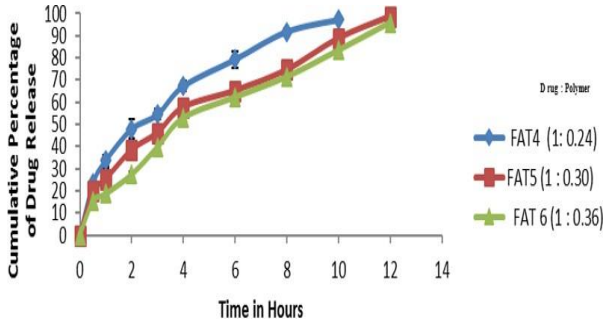

Figure 3: Graphical Representation of cumulative percentage of In-Vitro AT Release from Formulation Containing Different Ratios of HPMC K_4M

Amoxicillin Trihydrate in 12 hours, Amoxicillin Trihydrate to polymer ratio 1:0.36 have 95.67±1.62% released Amoxicillin Trihydrate in 12 hours, as shown cumulate percentage of drug release a and Ranitidine Hydrochloride to polymer ratio 1:0.8, have shown the Ranitidine Hydrochloride release of 97.58±1.28% in 12 hours and Ranitidine Hydrochloride to polymer ratio 1:1, have shown the Ranitidine Hydrochloride release of 94.52±1.08% in 12 hours and. Ranitidine Hydrochloride to polymer ratio 1:1.2, have shown the Ranitidine Hydrochloride release of 88.56±1.87% in 12 hours.

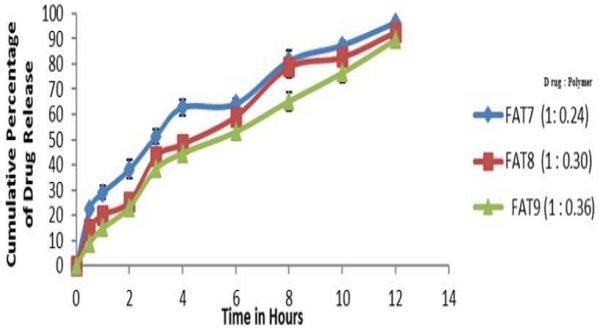

Figure 4: Graphical Representation of cumulative percentage of In-Vitro AT Release from Formulation Containing Different Ratios of HPMC $K_{15}M$

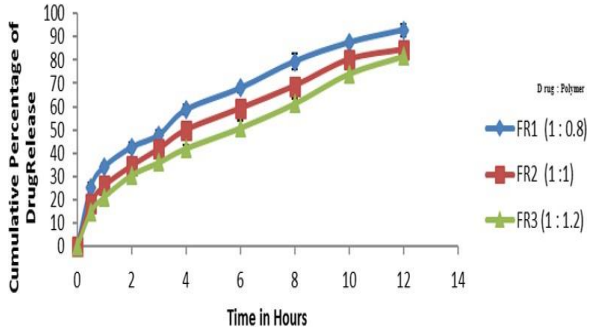

Figure 5: Graphical Representation of cumulative percentage of In-Vitro RH Release from Formulation Containing Different Ratios of HPMC $K_{100}M$

Formulation FTAR7, FTAR8 and FTAR9 containing HPMC $K_{15}M$ as a polymer of varying concentration,

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i.e. Amoxicillin Trihydrate to polymer ratio 1:0.24, have shown Amoxicillin Trihydrate release of 96.58±1.68% in 12 hours, Amoxicillin Trihydrate to polymer ratio 1: 0.30 have shown Amoxicillin Trihydrate release of 92.56±2.24 % in 12 hours, Amoxicillin Trihydrate to polymer ratio 1:0.36 have shown Amoxicillin Trihydrate release of 89.52±3.6% in 12 hours, as shown cumulate percentage of drug release a and Ranitidine Hydrochloride to polymer ratio 1:0.8 have shown the Ranitidine Hydrochloride release of 94.36±1.76 % in 12 hours and Ranitidine Hydrochloride to polymer ratio 1:1, have shown the Ranitidine Hydrochloride release of 88.30±1.85% in 12 hours and. Ranitidine Hydrochloride to polymer ratio 1:1.2, have shown the Ranitidine Hydrochloride release of 83.94±1.56 % in 12 hours. From the obtained dissolution data formulation FTAR7 having the HPMC $K_{15}M$ as polymer has shown the release 98.56±2.91% of Amoxicillin Trihydrate and 94.52±1.08% of Ranitidine Hydrochloride in 12 hours was considered as optimized formulation. The cumulative percentage of Amoxicillin Trihydrate release from developed formulation was shown in Figure.1, 2 & 3 and the cumulative percentage of Ranitidine Hydrochloride from developed formulation was shown in the Figure.4, 5&6.

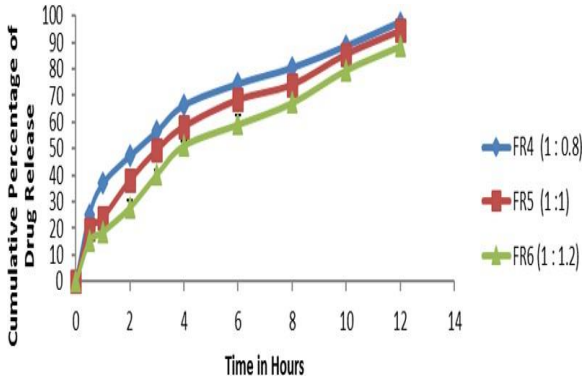

Figure 6: Graphical Representation of cumulative percentage of In-Vitro RH Release from Formulation Containing Different Ratios of HPMC K_4M

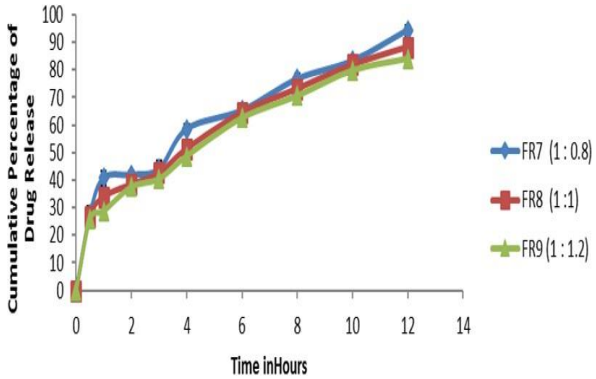

Figure 7: Graphical Representation of cumulative percentage of In-Vitro RH Release from Formulation Containing Different Ratios of HPMC $K_{15}M$

The dissolution values of optimized formulations were further processed to kinetic models to determine order and mechanism of release for both the drugs regression coefficient value (R^2) for zero order was found to be 0.9350, R^2 of first order was found to be 0.8510 for the Amoxicillin Trihydrate, so the order of Amoxicillin Trihydrate, release from the optimized formulation was zero as linearity was greater for plots zero order than that of first-order plots. R^2 of Higuchi was found to be 0.9954, R^2 of Peppas was found to be 0.9949, i.e. Linearity for the Higuchi plots was greater than that of linearity of Peppas, and the values of the release exponent was recorded as 0.5114 this value indicates Non-Fickian Diffusion, this indicates the drug release from the formulation is governed by polymer rearrangement for Amoxicillin Trihydrate release from optimized formulation, whereas for release of Ranitidine Hydrochloride from optimized formulation followed first order with R^2 0.9566 and shown the Non-Fickian Diffusion with n value 0.5094. The difference in the order of drug releases from both the drugs is due to the difference in the drug doses in the formulation and difference in the drug to polymer ratios; the R^2 values were shown in Table.7

Mechanism and Order of Drug Release

Mechanism and Order of Drug Release from the optimized formulation. FAT5: Amoxicillin Trihydrate, FR5: Ranitidine Hydrochloride

In-Vivo of Optimized Formulation of Floating Tablets (X-RAY STUDIES)

To evaluate gastric resident time of optimized Amoxicillin trihydrate and Ranitidine floating tablets $BaSO_4$ was added by replacing a part of Amoxicillin trihydrate in formulation composition floating tablets were evaluated for physical parameters values were shown in the Table 8. Additions of $BaSO_4$ to the formulation has not altered the physical parameters too much and not altered the in-Vitro total floating time of tablets. In-vivo x-ray studies in healthy human volunteers w**ere** conducted (results were shown in the (Figure. 8& 9) with permission from Institutional Human ethics committee and their Approval no: ICE/RVSIMS/2017/09.

The behavior of the floating tablet in the stomach of human volunteers was observed in real time using a radiographic imaging technique. In radiographic images made 30min after the administration, the tablets were observed in the human stomach. In the next picture taken at 1 hr, significant changes were detected. The tablet had altered its

position and turned around. This provided evidence that the tablets did not adhere to the gastric mucosa, but on the contrary, floating on the gastric fluid. The tablet containing the drug remained in the stomach for up to 1.5 hrs in a fasting condition. Thereafter they changed the position. After 3 hrs radiograms show that the tablet left the stomach. In fed condition when the tablets were given to human volunteers, the tablet presence was observed in the stomach even after 6 hrs of the tablet was administered this can be seen from the radiograms. One glass of water (200ml) was administered to volunteers in both cases after half an hour to help to float.

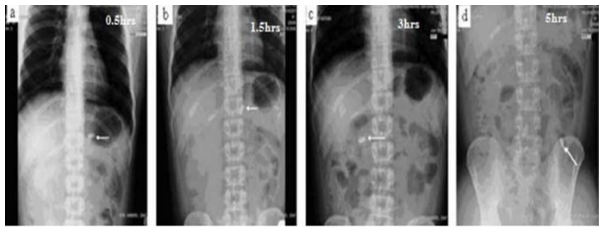

Figure 8: Radiographic images (a & b) showing the presence of a BaSO4-loaded floating tablet in the stomach and image (c & d) shows the displacement of tablet from the stomach due to housekeeper waves in fasting condition (the tablet is indicated with an arrow). The tablet altered its position in the stomach. Images were taken at: a) 0.5 h, b) 1.5 hr, c) 3hr and d) 5 hr after tablet administration (n=3 subjects).

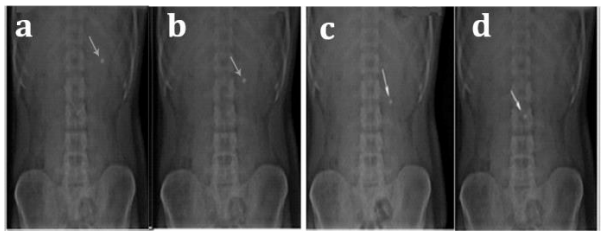

Figure 9: Radiographic images (a & b) showing the presence of a BaSO4-loaded floating tablet in the stomach and image (c & d) shows the displacement of tablet from the stomach due to housekeeper waves in fasting condition (the tablet is indicated with an arrow). The tablet altered its position in the stomach. Images were taken at: a) 0.5 h, b) 1.5 hr, c) 3hr and d) 5 hr after tablet administration (n=3 subjects).

Three-month stability studies data was shown in the table.9 hardness of tablets were slightly increased, and drug content of both the drugs was slightly reduced; there were no major changes indicates developed formulation were stable.

CONCLUSION

Stomach Specific Floating Tablets (SSFT) with combination of Amoxicillin-Trihydrate and Ranitidine Hydrochloride were developed successfully by using different grades of Hydroxypropylmethylcellulose and evaluated for Pre formulation parameters and post-compression parameters all the values are in acceptable limits The optimized formulation was subjected to Radiographical evaluation by incorporating the $BASO_4$ a radio-opaque substance by replacing a part of drug from optimized formulation have resided in stomach up to 1.5 hours in fasting state and up to 6 hours in fed state in healthy male human volunteers.

REFERENCES

Abdellatif. AAH. (2018) Design of Sustained Action Dosage Forms; Mini-Review. Pharm Anal Acta. 9(7), 1-5.

Ananthakumar.J, Raja. N, Mohan P, Ruckmani K. (2013) Design and Evaluation of Intragastric Buoyant Tablets of Metformin Hydrochloride. International Journal of Pharmacy and Pharmaceutical Sciences. 5(3), 479-484.

Ara N. Patel, Falguni M. Patel, Kamal Singh Rathore. (2011) Formulation and characterization of floating tablets of Diltiazem hydrochloride. Journal of Pharmaceutical and Biomedical Sciences. 9(9), 1-6.

Arun B. Reddy, Narendar D. Reddy. (2017) Development of Multiple-Unit Floating Drug Delivery System of Clarithromycin: Formulation, in vitro Dissolution by Modified Dissolution Apparatus, in vivo Radiographic Studies in Human Volunteers. Drug Res.76 (7), 1-7.

Aswatha Ram H. N, Prachiti Lachake, Ujjwal Kaushik, Shreedhara C.S. (2010) Formulation and evaluation of floating tablets of liquorice extract. Pharmacognosy Research. 2(5), 304-308.

Basavaraj K Nanjwade, Sagar A Adichwal, Veerendra K Nanjwade, Kishori R Gaikwad, Sachin A. Thakare and FV Manvi. (2012) Development and Evaluation of Gastroretentive Floating Tablets of Glipizide Based on Effervescent Technology. J Drug Metab Toxicol 3(3), 1-6.

Carla M. Lopes, Catarina Bettencourt, Alessandra Rossi, Francesca Buttini, Pedro Barata. (2016) Overview of gastro-retentive drug delivery systems for improving drug bioavailability. International Journal of Pharmaceutics. 510, 144-58.

Faria Gias Senjoti, Syed Mahmood, Juliana Md. Jaffri, Uttam Kumar Mandal. (2016) Design and In-vitro Evaluation of Sustained Release Floating Tablets of Metformin HCl Based on Effervescence and Swelling. Iranian Journal of Pharmaceutical Research. 15 (1), 53-70.

Giriraj.P, Sivakkumar.T. (2014) New Simple Spectrophotometric Method for the Simultaneous Estimation of Paracetamol and Flupirtine Maleate in Pure and Pharmaceutical Dosage Form. International Journal of Spectroscopy. 1-6.

Gisbert J. P, Calvet. X. (1995) Review article: Helicobacter pylori-negative duodenal ulcer disease. Alimentary Pharmacology & Therapeutics. 30, 2009 791–815. Dettmer A. Ranitidine and amoxicillin for the eradication of Helicobacter pylori in patients with duodenal ulcer. Arzneimittel forschung. 45(5): 604-7.

Jain S, Srinath MS, Narendra C, Reddy SN, Sindhu A. (2010) Development of a Floating Dosage Form of Ranitidine Hydrochloride by Statistical Optimization Technique. Journal of Young Pharmacists. 2 (4), 342-349.

Jyoti Rathore1, Hitesh Kumar Parmar1. (2015) Formulation and Evaluation of Floating Tablets of Norfloxacin. International Journal of Pharma Sciences and Research. 6(2), 23-27.

Kumar Sachin, Mazumder Rupa. (2018) Preparation and Characterization of Floating Tablets of Venlafaxine Hydrochloride: An Approach for Depression Treatment. Asian Journal of Pharmaceutics. 12 (1), S296-S303.

Mayur Karvekar, Arshad Bashir Khan. (2017) A Brief Review on Sustained Release Matrix Type Drug Delivery System. Journal of pharmaceutical research 16(3), 282-289.

Meenakshi Jassal, Ujjwal Nautiyal, Jyotsana Kundlas, Devendra Singh. (2015) A review: Gastroretentive drug delivery system. *Indian journal of pharmaceutical and biological research.* 3(1), 2015, 82-92.

Mosab Arafat. (2015) Approaches to Achieve an Oral Controlled Release Drug Delivery System Using Polymers: A Recent Review. International Journal of Pharmacy and Pharmaceutical Sciences. 7(7), 16-21.

Narendar Dudhipala, Karthik Yadav Janga, Ramesh Bomma. (2016) Preparation, In Vitro and Ex Vivo Evaluation, of Amoxycillin Trihydrate Floating-Bioadhesive, Drug Delivery System for Eradication of Helicobacter pylori,J Bioequiv Availab. 8(3), 118-124.

Nelson Kenneth, Varadarajan Parthasarathy, Chikkanna Narendra, Prakasam Kalya (2015) Development and Evaluation of Oral Controlled Release Matrix Tablets of Lamivudine Optimization and in Vitro-In Vivo Studies. International Journal of Pharmacy and Pharmaceutical Sciences.7(1), 95-101.

Sarovar Reddy. V, Badarinat A. V, Gnana Prakash. K. (2018) Formulation and Evaluation of Floating Tablets of Ciprofloxacin Hydrochloride. Asian Journal of Pharmaceutics. 12 (2), 106-114.

Satinderkakar, Ramandeep Singh, Shallusandhan. (2015) Gastro retentive drug delivery systems: A review. African Journal of Pharmacy and Pharmacology. 9(12), 405-4017.

Shah UH, Patel BK. Patel MR. (2012) Formulation and evaluation of controlled release matrix tablet of Diltiazem HCl by using HPMC and guar gum as polymeric matrix material. Ars Pharmaceutica.53(4), 16-20.

Shende M.A, Chatur S. V, Marathe R. P. Design and Fabrication of Amoxicillin Trihydrate Floating Matrices. Journal of Pharmacy Research. 5(9), 4830-4835.

Shirwaikar, Kumar, Jacob S. M. R, Rashi S, Ravi W. (2012) Recent developments in floating drug delivery systems for gastric retention of drugs, an overview. *Indian Drugs*. *43*(9), 2006, 697-704.

Vishal Sachdeva, Shoaib Alam. Md, Ramesh Kumar, Mahesh Kumar Kataria. (2013) Oral multiunit pellet extended release dosage form: A review. International Current Pharmaceutical Journal. 2(10), 177-184.

Vivek K. Pawar, Shaswat Kansal, Garima Garg, Rajendra Awasthi, Deepak Singodia, and Giriraj T. Kulkarni. (2011) Gastro retentive dosage forms: A review with special emphasis on floating drug delivery systems. Drug Delivery. 18(2), 97–110.