Asian Journal of Pharmaceutical Education and Research
Vol -11, Issue-3, July- September 2022
ISSN:2278 7496

RESEARCH ARTICLE Impact Factor: 7.014

FORMULATION AND EVALUATION OF MOXIFLOXACIN BIOADHESIVE TABLETS

Kanika Dhote, Vinod Dhote*

Truba Institute of Pharmacy, Bhopal

*Corresponding Author's E mail: vinoddhote@gmail.com

Received 17 May 2022; Revised 27 May 2022; Accepted 17 June 2022, Available online 15 July 2022.

Cite this article as: Dhote K, Dhote V. Formulation and Evaluation of Moxifloxacin Bioadhesive Tablets. Asian Journal of Pharmaceutical Education and Research. 2022; 11(3): 135-146.

https://dx.doi.org/10.38164/AJPER/11.3.2022.135-146

ABSTRACT

Gastroretentive Moxifloxacin floating tablets for the eradication of Helicobacter pylori (*H. pylori*) were prepared using the matrix forming polymer hydroxypropyl methylcellulose (HPMC K15M), in different ratios by wet granulation method. Buoyancy of formulated tablets was achieved by an addition of an effervescent mixture consisting of sodium bicarbonate to some formulations. The prepared floating tablets were characterize for weight variation, thickness, friability, hardness, drug content, in vitro buoyancy, water uptake and in vitro release. The prepared floating tablets revealed satisfactory physicochemical characteristics. Incorporation of gas-generating agent improved the floating parameters. HPMC K15M floating tablet formulation (CF1) offered the best controlled drug release (>8 h) along with floating lag time <1 s and total floating time >24 h. The value of (n) in case of CF1 (n = 0.37) revealed a Fickian diffusion mechanism of formulated floating tablets.

Keywords: Gastroretentive, floating tablets, *H. pylori*, *I* , Fickian diffusion, Moxifloxacin.

INTRODUCTION

The oral route of administration still persists to be the most prefer route due to its assorted advantages comprise ease of ingestion, pain averting, adaptability and most importantly patient conformity. Out of them the most popular dosage forms being tablets and capsules [1-2]. Tablets are the solid dosage forms usually prepared with the aid of suitable pharmaceutical excipients [2].

Floating drug delivery systems are those systems having a bulk density less than that of the gastric fluids and thus these systems remain buoyant for a prolonged period of time in the stomach without being affected by the gastric emptying rate. The drug is released slowly at the desired rate from the system and after release of the drug; the residual system is emptied from the stomach [3]. Most of the floating systems previously reported are single unit systems such as tablets and capsules.

Helicobacter pylori (H. pylori) infection is the causative organism in chronic active gastritis, duodenal ulcers and gastric adenocarcinoma [4]. This bacterium is highly adapted for colonization in the human stomach; the majority of these bacteria are free living in the gastric mucus layer although about 20% is in close contact with epithelial cells [5]. Antimicrobial resistance, patient's poor compliance with the antibiotic regimen, and drug-related side effects are said to be the major problems with eradication of H. pylori [6]. Moxifloxacin is a new semi-synthetic antimicrobial 14-membered macrolide exhibiting a broad in vitro antibacterial spectrum. Moxifloxacin appears to have more activity against *Mycoplasma pneumoniae* and *Chlamydia trachomatis*. Furthermore, Moxifloxacin (in combination with its microbiologically active metabolite, 14-hydroxyMoxifloxacin) has shown an additive or even synergistic activity against Haemophilus injluenzae, a species that often is resistant of intermediate susceptibility to erythromycin. The 14-hydroxy-Moxifloxacin itself is twice as active as the parent compound [7].

MATERIALS AND METHODS

Materials

Moxifloxacin, Gum Acacia, HPMC K15 M, Sodium Bicarbonate, PVP K30, Lactose, Magnesium Stearate and Talc all ingredients were of analytical grade.

Preparation of Floating Granules by wet granulation technique

All ingredients were weighed, and mixed using the geometric dilution technique except magnesium stearate and talc. Resulting mixture was granulated using PVP K-30 within isopropyl alcohol. Finally wet coherent mass were passed through a sieve no. # 16 to get uniform granules and then dried in thermostatic hot air oven at a temperature of 60^0C; finally sieved through sieve no. # 20/44 sieves. Resulting dried granules were mixed with sodium bicarbonate used as a gas-generating agent. Then, homogeneously blended mixture Magnesium stearate was then added as 2% and compressed with the 13.7 mm flat punch in rotary tablet press [8-11].

Evaluation of the pre-compression parameters of powder mixtures

Pre-compression parameters: bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio [12], were measured.

Table 1: Composition of Moxifloxacin Floating Tablets

Ingredients (mg)	MB1	MB2	MB3	MB 4	MB 5	MB 6
Moxifloxacin	250	250	250	250	250	250
Gum Acacia	40	40	40	40	70	70
HPMC K15 M	20	40	30	30	20	40
Sodium Bicarbonate	20	20	10	30	10	10
PVP K30	15	15	15	15	15	15
Lactose	70	50	70	50	60	40
Magnesium Stearate	15	15	15	15	10	10
Talc	15	15	15	15	10	10
Total weight	450	450	450	450	450	450

Evaluation of the post-compression parameters

Compressed tablets were characterized for weight variation, crushing strength, diameter, thickness and friability as follows:

Weight variation

The weight variation test was conducted by weighing 20 randomly selected floating tablets individually [13]. The average weight and standard deviation were calculated.

Diameter and thickness for tablets

The diameter and thickness of ten randomly selected floating tablets from each formulation were measured with a Vernier caliper scale. The average and standard deviation were reported [14].

Crushing strength/ hardness test

Crushing strength of the floating tablets was determined using the tablet hardness tester. Hardness was determined using six tablets from each formulation and crushing strength that just caused the tablet to break was recorded [1]. The average of 6 records expressed in Newton was used.

Friability test for tablets

Friability test was carried out by using Roche friability tester [15]

Content uniformity test

20 tablets were randomly weighed and crushed using mortar and pestle and equivalent weight ~100 mg was dissolved in 10 ml methanol in a 100 ml volumetric flask and allowed to stand for 10 minutes. Then, 0.1 N HCl with 1% SLS solution was added and volume was made up to 100 ml which was then filtered through Whatmann filter paper # 41. 5 ml of this resulting solution was further diluted to 100 ml with 0.1 N HCl with 1% SLS solution. The absorbance was taken in UV-visible spectrophotometer at λmax

290 nm using 0.1 N HCl with 1% SLS solution as blank and the drug concentration in each tablet was calculated, after suitable dilution. The drug content in each tablet was compared to the label claim [14, 16].

Floating lag time and floating duration

Floating lag time is the time required by tablets to emerge at the surface when introduced in the dissolution medium and floating duration is the duration for which it remained buoyant. It was determined using a 0.1 N HCl filled (250 ml) in glass beaker [6, 17-18].

***In vitro* floating studies**

The *in vitro* buoyancy was characterized by floating lag time and total floating time. The test was performed using a USP dissolution apparatus type-II (basket) using 900 ml of 0.1 N HCl buffer solution at 100 rpm at 37 ± 0.5°C. The time required for the formulation to rise to the surface of the dissolution medium and the duration for which the formulation constantly floated on the dissolution medium were noted as floating lag time and total time, respectively[18-19].

***In vitro* buoyancy studies**

To study the *in vitro* buoyancy, an effervescent approach was adopted. Sodium bicarbonate was added as a gas-generating agent. As the dissolution medium (0.1 N HCl) got imbibed into the tablet matrix, the acidic fluid interacted with Sodium bicarbonate resulting in the generation of CO_2. The generated gas was entrapped and protected within the gel, formed by the hydration of polymer and gum acacia, and thereby decreased the density of the tablet [20].

Drug release data were analyzed according to zero order, first order, Higuchi, Hixon-Crowell, Peppas and Weibull kinetic equations [10]. DD Solver, an add-in program for Microsoft Excel, for modeling and comparison of drug release profiles was used [21]. The model with the highest coefficient of determination (R^2) was considered to be the best fitting one.

Water-uptake study

The swelling of the polymers was measured by their ability to absorb water and swell. The water uptake study of the tablet was done using a USP dissolution apparatus type-II (basket) in 900 ml of pH 1.2 Hydrochloric acid buffer at 100 rpm. The medium was maintained at 37 ± 0.5°C throughout the study. At regular time intervals, the tablets were withdrawn, blotted to remove excess water, and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake (WU) as [22-23]:

$$\mathbf{WU\ (\%)} = \frac{\textbf{Weight of Swollen tablet- Initial weight of tablet}}{\textbf{Initial weight of tablet}} \times 100$$

The swelling of the polymers used could be determined by water uptake of the tablet. The percent swelling of the tablet was determined at different time intervals.

In-vitro release profile

Release of the prepared tablets was determined up to 9 hr. using U.S.P. II (type II) dissolution rate test apparatus. Nine hundred ml of 0.1 N HCl was used as dissolution medium. The rotation of paddle was fixed at 75 r.p.m. and the temperature of 37+0.5ºC was maintained throughout the experiment. Samples of 1 ml were withdrawn at known time intervals and were replaced with same volume of fresh dissolution media after each withdrawal. The samples were analyzed spectrophotometerically for drug contents on double beam UV/Visible spectrophotometer (Shimadzu UV- 1700) at 290 nm. The results in the form of percent cumulative drug released [7, 12, 14, 20].

Results and discussion

Pre-compression parameters of powder mixtures

The angle of repose of the powder mixture for all formulations (CF1–CF6) ranged from 22.50 to 26.30 indicating excellent flow properties[24-25]. Bulk and tapped density of the powder mixture for all formulations varied from 0. 3417 to 0.5437gm/cm3 and from 0.3941 to 0. 5502 gm/cm^3, respectively. Compressibility indices ranged from 14.15 to 18.91. The results of flow properties are acceptable for granules [26].The values of compressibility indices further confirmed the good compressibility of the prepared granules [13].

Table 2: Pre-compression parameters of powder mixtures

Formula code	Bulk density gm/ml	Tapped density gm/ml	Angle of repose (θ)	Carr's index %
MB 1	0.3417±0.024	0.4214±0.025	22.50±1.21	18.91±0.87
MB 2	0.5218±0.039	0.4336±0.072	24.62±1.34	14.15±0.79
MB 3	0.3321±0.061	0.3941±0.074	22.32±1.64	16.29±1.32
MB 4	0.4129±0.062	0.4457±0.035	24.03±1.25	15.81±0.43
MB 5	0.4652±0.042	0.5156±0.045	25.07±1.25	15.43±0.41
MB 6	0.5437±0.025	0.5502±0.010	26.30±1.31	14.59±1.37

Post-compression parameters for tablets

Concerning appearance, the floating tablets were whitish-buff or white in color, all were round concave, with smooth surface in both sides and no visible cracks were observed.

The mean diameter of floating tablets was 4.0± 0.0 mm while mean thickness ranged from 4.0 to 4.2 mm. Mean hardness was in the range of 4.4–6.1 Kg/cm^2 indicating that the floating tablets are of sufficient strength to withstand physical abrasion [27]. The percentage friability for all formulations was less than 1% which is an indication of satisfactory mechanical resistance of the floating tablets [13]. The formulated tablets showed no evidence of capping, cracking, cleavage or breaking after being removed from the friabilator. The percentage of mean drug content ranged from 95.7–98.3% which met the standard pharmacopeial requirements (90–110%) [28]. Since the mixtures of powders used were free flowing, the obtained floating tablets were of uniform weight due to uniform die fill. The mean weight of formulated tablets was 450± 0.0 mg, (n= 20). The USP specification is generally ±5% [22]. This means that no difference was observed in the weight of individual floating tablets from the labeled weight indicating uniformity of weight.

Table 3: Post-compression evaluation of floating tablets

Batch	Weight Variation	Content Uniformity* (%)	Hardness* (Kg/cm^2)	Thickness* (mm)	Friability * (%)	Floating lag* time(s)
MB 1	450.25± 0.83	99.35±0.93	4.6±0.18	4.0±0.48	0.57±0.17	62±1.3
MB 2	450.76± 0.19	98.45±0.53	6.1±0.30	4.1±0.56	0.34±0.37	66±2.2
MB 3	450.78± 0.64	99.21±0.76	5.5±0.62	4.1±0.68	0.30±0.06	90±1.7
MB 4	450.39± 0.36	96.53±0.36	5.8±0.23	4.1±0.77	0.38±0.34	35±1.5
MB 5	450.38± 0.59	100.01±0.64	4.8±0.64	4.0±0.68	0.55±0.86	89±1.6
MB 6	450.34± 0.49	102.03±0.52	4.6±0.76	4.2±0.59	0.59±0.76	95±2.7

(*n=3)

In vitro buoyancy test

In the present study the floating system employed sodium bicarbonate ($NaHCO_3$) and citric acid in an optimized ratio (2:1) as gas forming mixture [29]. This ratio was used in order to provide the shortest possible floating lag time and floating duration of up to 24 h. Sodium bicarbonate induced effervescence that leads to pore formation and consequently, rapid hydration of the floating tablets matrices thus enhancing their floating ability [30]. Floating lag time for the formulation was found to be 35-95 s. Effect of Sodium bicarbonate on onset and duration of floatation of floating tablet containing Moxifloxacin showed onset and dutration of floating ranges from 32-92 s and 16-24h respectively.

Table 4: Effect of Sodium bicarbonate on onset and duration of floatation of effervescent floating tablet of Moxifloxacin

Amount of sodium bicarbonate (mg)	Onset of floating (s)*	Duration of floating (h)*
10	92±3.86	16±0.81
20	62±2.96	21±0.36
30	32±2.50	24±0.69
40	27±0.05	18±0.75

*Standard deviation, n=3

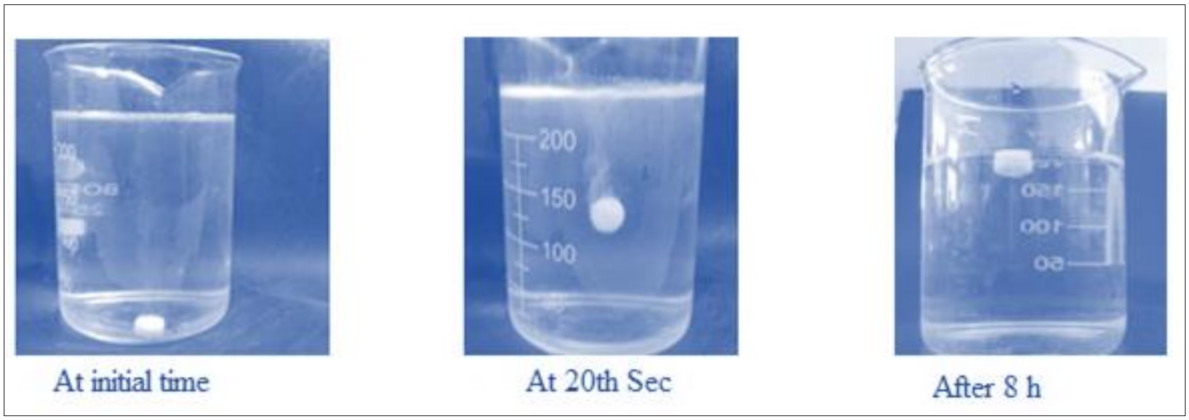

Fig. 1: Photographs of *in vitro* floating behavior floating tablet at different time intervals

Consequently, faster and higher swelling of the tablet led to an increase in the dimensions of the tablet, leading to increasing the gel barrier and thus decreasing diffusion rates [31-33]. So the drug release was found to be high initially and then gradually decreased, this was true especially in CF4. The swelling behavior of tablet from 0 min to 8 h is shown in fig. 2.

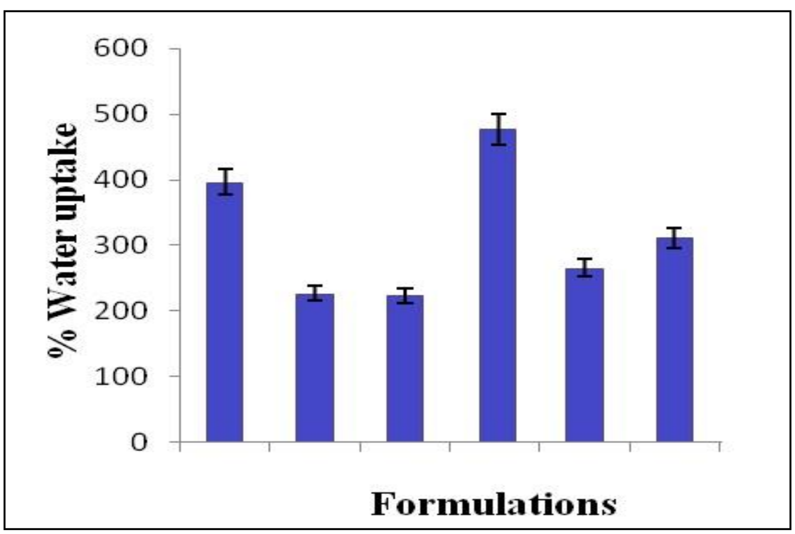

Fig. 2: Effect of various concentrations of ingredients on swelling index of floating tablets of Moxifloxacin at the end of 8 h

There was no significant difference observed in the swelling property by varying the concentration of Sodium bicarbonate. The drug release was found to be high initially and then gradually decreased this was true especially in CF4.

***In-vitro* release profile**

The release profiles of Moxifloxacin from floating tablets are shown in Figure 3. Concerning effervescent formulations CF1, CF3 and CF5: Formula CF1 exhibited burst release since about 30% drug released in 1h min. Whereas, formulae CF3 and CF5 released 17% and 21% Moxifloxacin, respectively, in 1h. The initial burst effect for CF1 could be due to rapid dissolution of the drug from the surface while the HPMC K15M undergoes hydration to form a protective gel layer [34-35]. Concerning effervescent formulations CF2, CF4 and CF6. Formula CF2 exhibited burst release since about 15% drug released in 1h min. Whereas, formulae CF4 and CF6 released 12% and 15% Moxifloxacin, respectively, in 1h.The addition of polymer PVP K30 in the matrix decreased the drug release in the acidic medium by forming an insoluble mass that acts as a barrier to drug diffusion [36] and, consequently, the initial burst effect was decreased.

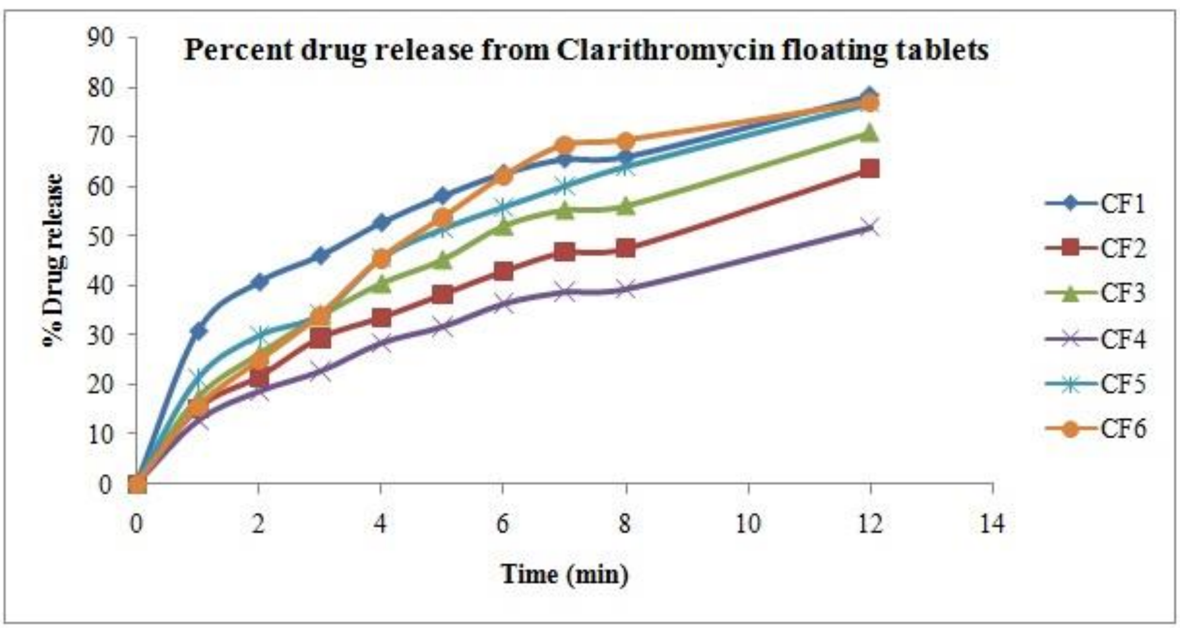

Fig. 3: In-vitro drug release from Moxifloxacin floating tablets

The release kinetics of Moxifloxacin from floating tablets can be obtained from *in-vitro* release data were treated according to the model-dependent methods, zero order, first order, Higuchi model, Korsmeyer–Peppas model, Hixson–Crowell model and Weibull equation. Criteria for selecting the most appropriate model was based on best fit indicated by the value of coefficient of determination (R^2) nearer to 1 [11].

Concerning CF1, CF2 and CF4 the highest values of R^2 were obtained after fitting the data into Peppas equation. The value of (n) allows the release to be characterized as either Fickian diffusion n 6 0.5, anomalous diffusion (non-Fickian) (0.5< n< 1) or zero-order release (n =1) [11-12]. The n values for CF2 and CF4 were 0.57 and 0.56 respectively, that indicated anomalous diffusion (non-Fickian) which refers to a combination of both diffusion and erosion controlled-drug release [22]. Whereas, the value of (n) in case of CF1 (n = 0.37) revealed a Fickian diffusion mechanism of formulated floating tablets.

Table 5: Drug release Kinetics for floating tablets

Batch	Korsmeyer – Peppas			Matrix		Mechanism of drug release	Release kinetics
	n	R^2	k	R^2	k		
MB 1	0.3771	0.9981	31.1077	0.9811	24.7943	Fickian	Peppas
MB 2	0.5737	0.9981	15.1110	0.9950	17.3367	Non-Fickian	Peppas
MB 3	0.5714	0.9975	17.8613	0.9966	20.3088	Non-Fickian	Peppas
MB 4	0.5675	0.9981	12.6702	0.9956	14.3660	Non-Fickian	Peppas
MB 5	0.5380	0.9948	20.8757	0.9967	22.3909	Non-Fickian	Matrix
MB 6	0.6997	0.9868	16.2306	0.9775	23.3020	Non-Fickian	Peppas

CONCLUSION

Obtained results for the Moxifloxacin floating tablets, HPMC K15 M floating-tablet formulation (CF1) offered controlled release along with floating lag time <1 s and total floating time >24 h. The optimized formula (CF1) showed the absence of interaction between drug and the used polymer/additives which confirmed the compatibility among its ingredients. In vivo studies can provide a definite proof that prolonged gastric residence could be obtained. Thus, the studied can be studied for the in-vivo correlation to study retention of tablet in the stomach of the volunteer over the tested period providing localized drug release.

REFERENCES

1. Al Remawia M, Al-akayleh F, Salem M, Shami AM and Badwan A. Application of excipient made from Chitosan-Xanthan as a single component for the controlled release of ambroxol tablet. J. Excipients Food. Chem. 2013; 4: 48–57.
2. Bano R, Gauhar S, Naqvi SBS and Mahmood S. Pharmaceutical evaluation of different brands of Moxifloxacin tablets (250 mg) available in local market of Karachi (Pakistan). Int. J. Curr. Pharm. Res. 2011; 3, 15–22.
3. Sharma S, Prashar M and Sahu RK. Floating drug delivery system: Incredible revolution. Pharmacologyonline 2011; 3: 1039–1054.
4. Khalifa MM, Sharaf RR and Aziz RK. Helicobacter pylori: a poor man's gut pathogen. Gut Pathog. 2010; 2: 1–12.
5. Hessey S, Spencer J, Wyatt J, Sobala G, Rathbone B, Axon A and Dixon M. Bacterial adhesion and disease activity in Helicobacter associated chronic gastritis. Gut. 1990; 31: 134–138.
6. Bardonnet P, Faivre V, Pugh W, Piffaretti J and Falson F. Gastroretentive dosage forms: overview and special case of Helicobacter pylori. J. Control Release. 2006;111: 1–18.
7. Basak S and Jayakumar Reddy B. Formulation and release behaviour of sustained release ambroxol hydrochloride HPMC matrix tablet. Indian J. Pharm. Sci. 2006; 68: 594–598.
8. Chinthala, CSK, Kota KSR, Hadassah M, Metilda EH and Sridevi S. Formulation and evaluation of gastroretentive floating tablets of gabapentin using effervescent technology. Int. J. Pharm. Biomed. Res. 2012; 3: 202–208.
9. Christian V, Ghedia T and Gajjar V. A review on floating drug delivery system as a part of GRDDS. Int. J. Pharm. Res. Dev. 2011; 3: 233–241.
10. Costa P and Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci. 2001; 13: 123–133.
11. Couto RO, Martins FS, Chaul LT, Conceicao EC and Freitas LAP. Spray drying of Eugenia dysenterica extract: effects of in-process parameters on product quality. Revista Brasileira de Farmacognosia 2013, 23, 115–123.
12. Hadi MA, Babu VL and Pal N. Formulation and evaluation of sustained release matrix tablets of glimepiride based on combination of hydrophilic and hydrophobic polymers. J. Appl. Pharm. Sci. 2012; 2: 101–107.
13. Rao NGR, Hadi MA, Panchal H and Reddy BM. Formulation and evaluation of biphasic drug delivery system of Montelukast sodium for chronotherapy. World J. Pharm. Res. 2012; 1: 757–775.

14. Dash S, Murthy PN, Nath L and Chowdhury P., Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol. Pharm. 2010; 67: 217–223.
15. Doodipala N, Palem C, Reddy S and Rao Y. Pharmaceutical development and clinical pharmacokinetic evaluation of gastroretentive floating matrix tablets of Moxifloxacin. Int. J. Pharm. Sci. Nanotech. 2011; 4: 1463–1469.
16. Garg A and Gupta, M. Taste masking and formulation development & evaluation of mouth dissolving tablets of levocetrizine dihydrochloride. J. Drug Deliv. Ther. 2013; 3: 123–130.
17. Gisbert JP and Pajares JM. Treatment of Helicobacter pylori infection: the past and the future. Eur. J. Intern. Med. 2010; 21: 357–359.
18. Gutierrez-Sanchez PE, Hernandez-Leon A and Villafuerte-Robles L. Effect of sodium bicarbonate on the properties of metronidazole floating matrix tablets. Drug Dev. Ind. Pharm. 2008; 34: 171–180.
19. Pandey SP, Khan A, Dhote V, Dhote K and Jain DK. Formulation Development of Sustained Release Matrix Tablet Containing Metformin Hydrochloride and Study of Various Factors Affecting Dissolution Rate. Sch Acad J Pharm 2019; 8 (3): 57–73.
20. Shukla T, Khare P, Thakur N, Dhote V, Chandel HS. Exploring the Use of Sodium Benzoate as Hydrotrope for the Estimation of Lornoxicam in their Marketed Formulation. Pharmaceutical Methods. 5(1): 14-19
21. Patel P, Rai JP, Jain DK and Banweer J. Formulation, development and evaluation of cefaclor extended release matrix tablet. Int J Pharm Pharm Sci. 2012; 4(4): 355-357.
22. Dhote K, Dhote V, Khatri K and Dhote K. Phytochemical screening and pharmacological activity in Punica granatum. Asian Journal of Pharmaceutical Education and Research. 2015;4(4):290-7.
23. Li S, Lin S, Daggy BP, Mirchandani HL and Chien YW. Effect of HPMC and Carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int. J. Pharm. 2003; 253: 13–22.
24. Hadi MA, Babu VL and Pal N. Formulation and evaluation of sustained release matrix tablets of glimepiride based on combination of hydrophilic and hydrophobic polymers. J. Appl. Pharm. Sci. 2012; 2: 101–107.
25. Manivannan R and Chakole V. Formulation and development of extended release floating tablet of atenolol. Int. J. Recent Adv. Pharm. Res. 2011; 3: 25–30.
26. Mouzam MI, Dehghan M, Asif S, Sahuji T and Chudiwal, P. Preparation of a novel floating ring capsule-type dosage form for stomach specific delivery. Saudi Pharm. J. 2011; 19: 85–93.

27. Ishak RAH, Awad GAS, Mortada ND and Nour SAK. Preparation, in vitro and in vivo evaluation of stomach-specific metronidazole-loaded alginate beads as local anti-Helicobacter pylori therapy. J. Control Release. 2007; 119: 207–214.
28. Kassab NM, Amaral MS, Singh AK and Santoro MIRM. Development and validation of UV spectrophotometric method for determination of Moxifloxacin in pharmaceutical dosage forms. Quı´m Nova. 2010; 33: 968–971.
29. Dhote V, Dhote K, Mishra DK. Formulation and Characterization of Microbeads as a Carrier for the Controlled Release of Rioprostil. Asian J Pharmacy Pharmacol. 2015; 1(1): 27-32
30. Pradhan A, Jain P, Pal M, Chauhan M and Jain DK. Qualitative and quantitative determination of phytochemical contents of hydroalcoholic extract of salmalia malabarica. Pharmacologyonline. 2019; 1:21-26.
31. Dhote K, Dhote V, Mishra DK. Management of Diabetes mellitus: Herbal remedies Asian Journal of Biomaterial Research. 2015; 1(1):12-16.
32. Sawicki W. Pharmacokinetics of verapamil and norverapamil from controlled release floating pellets in humans. Eur J Pharm Biopharm. 2002;53(1):29-35.
33. Klausner EA, Lavy E, Friedman M and Hoffman A. Expandable gastroretentive dosage forms. J Control Release. 2003;90(2):143-62.
34. Dave BS, Amin AF and Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. AAPS PharmSciTech. 2004;5(2): 1-10.
35. Ponchel G and Irache J. Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. Adv Drug Deliv Rev. 1998;34(2-3):191-219.
36. Dhote V, Dhote K, Pandey SP, Shukla T, Maheshwari R, Mishra DK. Fundamentals of polymers science applied in pharmaceutical product development Basic Fundamentals of Drug Delivery. 2018; 85-112