ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

Preformulative studies for floating tablet of ofloxacin

Tiwari Diwakar *and Kheri Rajat
Lakshmi Narain College of Pharmacy, Bhopal, (M.P.) - India

Abstract

In the present study the effect of formulation variables on drug release and floating properties of ofloxacin drug delivery system was investigated. In formulating Gastric Floating Drug Delivery System (GFDDS) hydroxy propyle methylcellulose (HPMC) of different viscosity grades and carbopol were used. Interaction terms and main effects of the above formulations were evaluated quantitatively by utilizing various systems like MS, IR, and UV in different buffers. It was concluded that both HPMC viscosity and the presence of carbopol and their interaction had significant impact on the release and floating properties if the delivery system. It was observed that there was decrease in the release rate with an increase in the viscosity of the polymeric system.

Keywords: Preformulation, Floating tablets, Ofloxacin

Introduction

The novel design of oral controlled drug delivery system was primarily aimed at achieving more predictable and increased bioavailability of drugs. Some drugs restrain and localize the drug delivery system within the specific region of GIT, this variability cause unpredictable bioavailability and time for Cmax[1]. Gastric emptying time for humans generally vary from 2-3 hrs[2-3], this cause incomplete drug absorption of drug which is primarily absorbed in stomach and upper part of intestine[4]. Incomplete release or absorption of drugs is the major cause of diminished efficacy of administered dose.[5-6] To overcome these problems a specific drug delivery is designed for a specific region of GIT, which offers numerous advantages, especially for drugs exhibiting an absorption window for drugs with a stability problem. Specific drug delivery remains in contact with the absorbing membrane which maximizes the drug absorption[7].

Ofloxacin is used for treatment of bacterial infection, it is incompletely absorbed from GIT and has oral bioavailability of only 32%, while the remaining is excreted unchanged in feces due to poor absorption in lower GIT[8-9]. It is also important to distinguish between bacterial and viral infection[10] because they both can cause symptoms such as malaise, fever and chills[11-12]. This makes it difficult to distinguish them from each other[13]. Its elimination half life is 7 to 9 hrs[14-15]. Hence it is suitable for design of a gastro retentive floating drug delivery system for improved bioavailability[16-18].

Ofloxacin – General properties

- Molecular formula - $C_{18}H_{20}FN_3O_4$ [19].
- Molecular weight – 361.3675[20].
- Route of administration – oral or ophthalmic route.
- Physical state – solid.
- Melting point – 250 – 257° C[21].
- Water solubility – 28.3 mg/ml.
- LogP/Hydrophobicity – 2.1.
- Protein binding – 32%.
- Half life – 6 - 9 hrs.
- Absorption – Bioavailability of ofloxacin in tablet formulation is approximately 98%.

*** Corresponding Author:**
E-mail:Diwakar2185@gmail.com, Mob.

ISSN: 0976-7126

Material and methods

Preformulation studies

Preformulation studies are needed to ensure the development of a stable as well as therapeutically effective and safe dosage form[22-23]. The preformulation studies, performed in this research include identification of drug, solubility analysis, partition coefficient and drug compatibility[24-25].

Test for identification of ofloxacin[26-29]

Physical appearance: White to off-white crystalline powder.

Melting point: Determined by using melting point apparatus (Tempo India) and found sharp at 250 – 257°C.

Pka determination: It is a measure of unionized drug at certain pH.

For acidic compounds –

$$P^H = Pka + \log (\text{ionized drug})/ (\text{unionized drug})$$

For basic compounds –

$$P^H = Pka + \log (\text{unionized drug})/ (\text{ionized drug}).$$

Solubility studies: For quantitative solubility studies, known amount of drug (10mg) was suspended in a series of different solvents and shaken for 24 hrs. Using wrist action shaker (York India). Solubility of ofloxacin in different solvents is recorded in table 1.

Partition coefficient: [30-32] It is defined as the ratio of unionized drug distributed b/ w organic and aqueous phase at equilibrium.

Po/w = (C oil/C water) equilibrium.

Drugs having value of P > 1 = Lipophillic drug

P< 1 = Hydrophilic drug.

Preparation of buffers and reagents [34]

- Sodium hydroxide solution 0.2 M – 8.0 gm of sodium hydroxide was dissolved in distilled water and diluted to 1000 ml with distilled water.
- Potassium dihydrogen phosphate solution 0.2 M – 27.218 gm of potassium dihydrogen phosphate was dissolved in distilled water and diluted to 1000 ml.
- Hydrochloride acid solution 0.1 N – 8.5 ml of concentrated HCl was diluted with distilled water and volume was made up to 1000 ml with distilled water pH (1.2) was adjusted with dilute HCL.
- Phosphate buffer solution P^H 6.8 – 250 ml of 0.2 M potassium dihydrogen phosphate was placed in 1000 ml volumetric flask. 112 ml of 0.2 M sodium hydroxide was added and then volume was adjusted with distilled water up to 1000 ml. P^H was adjusted to 6.8 with dilute sodium hydroxide.

Determination of absorption maxima (λmax)/wavelength maxima [35] **–**

The standard sock solution of ofloxacin was prepared by dissolving 50 mg of drug in 0.5 N Acetic acid in 100 ml volumetric flask. Stock solution of Ofloxacin was further diluted in 0.5 N acetic acid to get standard solution concentration of 100 mcg/ml. The resulting solution was then scanned between 292 -296 nm. UV visible spectrophotometer (shimadzu 1601 UV Japan). The λmax was found to be at 295 nm as shown in figure 1.

Mass spectrum [35] **–**

It was reported by Clark that the mass spectrum of ofloxacin shows principal ions at m/z 71,375, 70,246,305 and 290 (Clark, 2006) as shown in Figure 2.

Infrared spectrum [35] **–**

The infrared spectrum of ofloxacin in a KBr pellet for wave number range of 2000 – 650 cm^{-1} is presented in. The principal peaks are at wave number 1459,1621,1715,1086 cm^{-1}. Few IR bands are shown in table 2.

UV spectrum –

Figure 3 shows the UV spectra of ofloxacin in aqueous acid (225,226,256 and 326 nm) and aqueous base (288 and 332 nm). The UV spectrum of levofloxacin in ethanol has bands at 226 and 300 nm (Clark, 2006).

Preparation of standard curve of ofloxacin in different solutions [36] **-**

Preparation of standard curve of ofloxacin in water –

Accurately weighted 10 mg of ofloxacin was dissolved in double distilled water and volume was made up to 100 ml. This resulted in 100 mg/ml stock solution. The aliquots of 0.2ml,0.4ml up to 2 ml of stock solution were taken into series of 10 ml volumetric flasks and volume was made up to the mark with double distilled water. The solution were filtered through whattmann No. 1 filter paper and filtrate analyzed at λmax 295.00 nm by using UV visible

ISSN: 0976-7126

spectrophotometer (shimadzu UV - 1601). The standard curve was plotted between absorbance and concentration as shown in figure 4, table 3.

Standard curve of ofloxacin in phosphate buffer solution (P^H 7.4 and 2.4) –

For the preparation of standard curve in PBS P^H 7.4 and 2.4, all dilution and measurement were made same as discussed in previous section except the double distilled water was replaced with phosphate buffer saline P^H 7.4 and 2.4. The absorbance of different drug solution was taken at λmax 295.00 nm against a reagent blank. The standard curve was plotted between absorbance and concentration.

Absorbance value of ofloxacin in PBS P^H 7.4 (λmax = 295.00 nm) as shown in table 4.

Standard curve of ofloxacin in PBS pH 7.4 (λmax 295.00 nm) as shown in figure 5.

Concentration and absorbance of ofloxacin in PBS P^H 2.4 at λmax 295.00 nm as shown in table 5.

Standard curve of ofloxacin in PBS pH 2.4 (λmax 295.00 nm) as shown in figure 6.

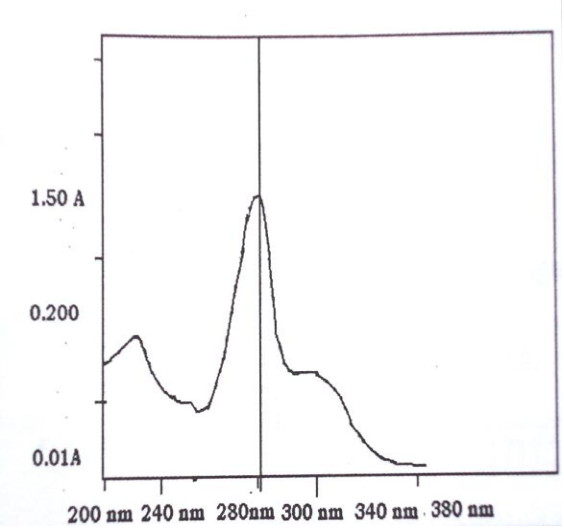
Results and Conclusion

Ofloxacin sample was identified and tested for purity as per tests given in pharmacopoeia of India (1996). The infrared spectrum of provided 0.1 mg was found to be concordant with the reference infrared spectrum of ofloxacin given by Florey (1973). From the various drug identification tests it was found that the present drug sample of ofloxacin is pure. Solubility studies in different solvents at room temperature revealed that it is soluble in distilled water and insoluble in acetone and ethanol etc.

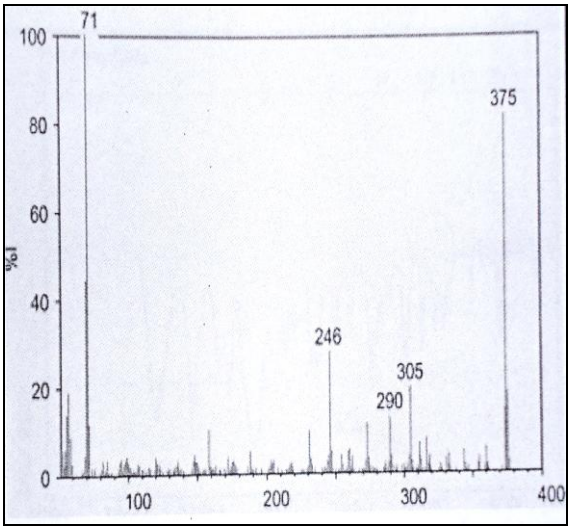
Partition coefficient value of ofloxacin has also revealed its hydrophilic nature as it was found to be 0.154 in n-octanol/water system and 0.105 in n-octanol/PBS pH 7.4. The spectrophotometric method of analysis of ofloxacin at λmax 295 nm was found to be reproducible and highly sensitive.

Drug compatibility of the drug with excipients was observed by determining UV maxima and found to be no significant change in absorption maxima. The drug is compatible in these ingredients in the formulation.

The standard curve of ofloxacin were prepared in different medium at λmax 295 nm and the absorbance data obtained subjected to linear regression. The correlation coefficient were found to be 0.9978 and 0.9989, for standard curve of drug in distil water and PBS (pH 7.4), which are very close to 1 and indicating good linearity.



(1)

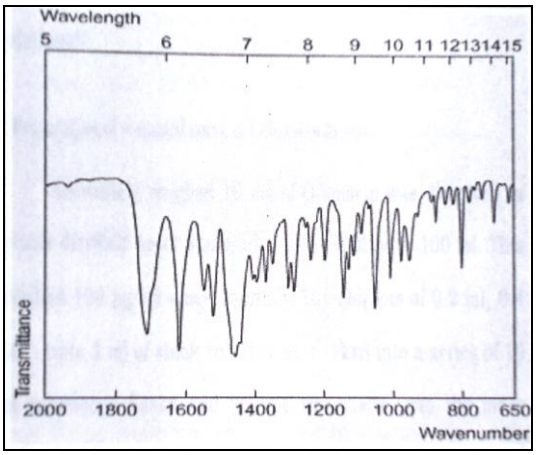


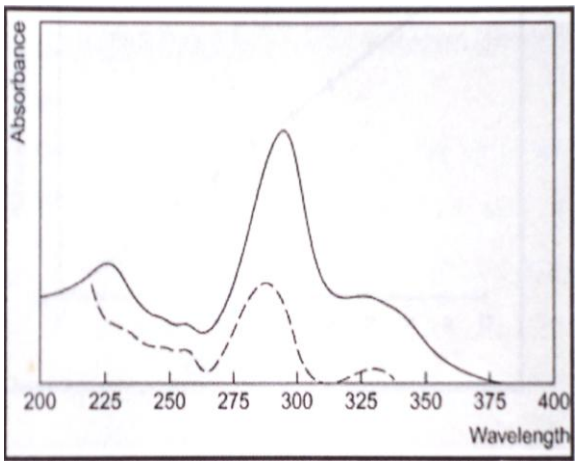
(2)

Fig. 1 : Absorption maxima (λmax)/wavelength maxima of ofloxacin

Fig. 2 : Mass spectrum of ofloxacin (adapted from Clarkes analysis of drugs and poisons)

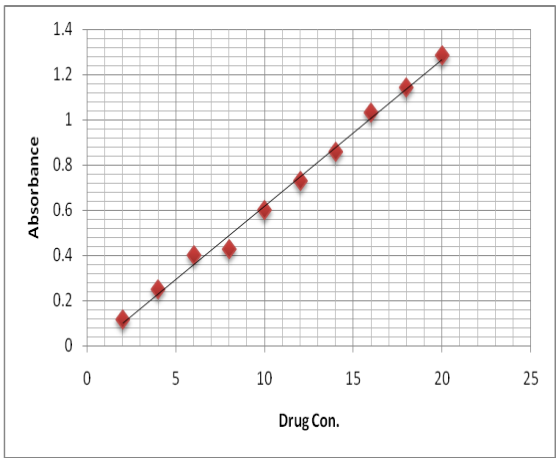
ISSN: 0976-7126

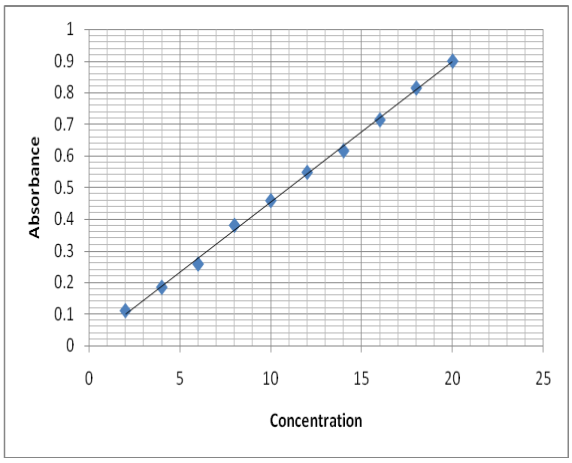




(3) **(4)**

Fig. 3 : Infrared spectrum of ofloxacin
Fig. 4 : UV spectrum of ofloxacin (adapted from clarkes analysis of drugs and poisons)





(5) **(6)**

Fig. 5: Standard curve of ofloxacin in water at λmax 295 nm.
Fig. 6: Standard curve of ofloxacin in PBS pH 7.4 (λmax 295 nm).

ISSN: 0976-7126

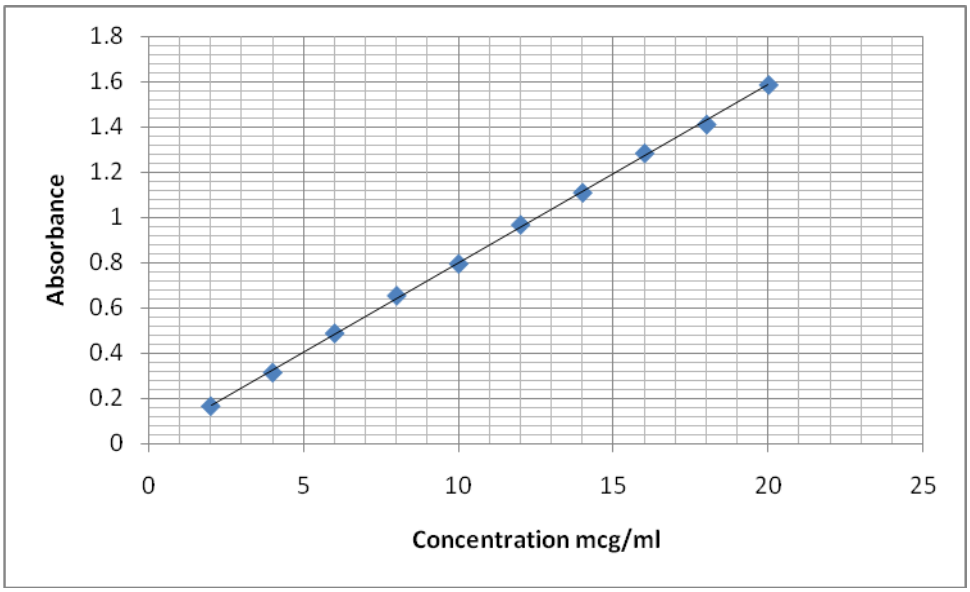


Fig. 7: Standard curve of ofloxacin in PBS pH 2.4 (λmax 295 nm)

Table 1 : Solubility of ofloxacin in different solvent systems at 250°C.

Solvent	Solubility
Water	+++
0.1 NaOH	-
Methylene Chloride	++
PBS (pH 5.6)	+
PBS (pH 7.4)	-
Ethanol	++
Methanol	+
Chloroform	++
Ethyl acetate	++
DCM	++
Ether	-

Table 2 : According to USP change in solubility of ofloxacin at 250°C with the change in pH.

pH	Solubility parameter	Parts/solvent	Mcg/ml
2-5	Soluble	1 in 30	60
7.5	Slightly soluble	1 in 100-1000	30
9	Freely soluble	1 in 1	4
0.1 N HCl	Soluble	1 in 17	58
pH Buffer	Slightly soluble	1 in 116	8.6
pH 6.8 Buffer	Slightly soluble	1 in 263	3.8

Abbr.: Signs - +++, Freely soluble (<1 part), ++ Slightly soluble (1-10 parts), +, sparingly soluble (10-30 parts), -, practically insoluble (>10,000 parts).

ISSN: 0976-7126

Table 3: Important band frequencies in IR spectrum of ofloxacin sample

Group name	Standard (cm^{-1})	Sample (cm^{-1})
NH stretch	3124	3130
C=O stretch	1716 and 1657	1713.2 and 1660
CH plane deformation	1245	1247
CH out of deformation	813	814.77
C-F	1028	1006
Benzene ring	1495	1500

Table 4: Absorbance value of ofloxacin in DW at λmax 295 nm

Drug Conc. (µg/ml)	Absorbance (observed)	Absorbance (regressed)	Statistical parameter
2	0.1142	0.1096	Equation of line : y=0.0641x-0.0185 r^2=0.9953
4	0.2516	0.2377	
6	0.4003	0.3658	
8	0.4285	0.4939	
10	0.6012	0.6220	
12	0.7299	0.7502	
14	0.8590	0.8783	
16	1.0300	1.0064	
18	1.1432	1.1345	
20	1.2846	1.2626	

Table 5: Absorbance value of ofloxacin in PBS pH 7.4 (λmax 295 nm)

Drug con. (µg/ml)	Absorbance (observed)	Absorbance (Regressed)	Statistical parameter
2	0.1106	0.0974	Equation of line: y = 0.0445x+0.0083 r^2 = 0.9986
4	0.1848	0.1864	
6	0.2583	0.2755	
8	0.3809	0.3645	
10	0.4590	0.4536	
12	0.5485	0.5426	
14	0.6167	0.6316	
16	0.7146	0.7207	
18	0.8153	0.8097	
20	0.9004	0.8988	

Table 6: Concentration and absorbance of ofloxacin PBS pH 2.4 (λmax 295 nm).

Con. (µg/ml)	Absorbance	Regressed	Eq. of line
2	0.1647	0.1677	y = 0.0788x+0.0101 r^2 = 0.9995
4	0.313	0.3253	
6	0.4871	0.4829	
8	0.6536	0.6405	
10	0.7948	0.7981	
12	0.9675	0.9557	
14	1.1096	1.1133	
16	1.2843	1.2709	
18	1.4116	1.4285	
20	1.5867	1.5861	

ISSN: 0976-7126

An attempt of preformulative study for formulation and evaluation of floating drug delivery system containing ofloxacin as a model drug. Ofloxacin is rapidly absorbed after oral administration with a half life of 6 – 8 hrs. and has no difference in the amount of absorption between the stomach, ileum and colon. Hence the floating dosage form can be developed. However it will be prepared by dry granulation method because low flow rate to die; direct compression will not be acceptable. In the preformulation study it was found that estimation of ofloxacin is carried out by shimadzu – 1601 UV spectrophotometer at λmax 295 nm in 0.1N HCl had a good reproducibility and this method was used in the study. The linear regression coefficient was found to be closer to 1 at the concentration range 2 – 16. The regression equation generated was

$$y = mx + c.$$

By using this regression coefficient equation the assay content of drug and % CDR was calculated.

Precoated –TLC chromatography was carried out to check for the possible drug excipients interaction. The Rf values of the drug and excipients used in the study were similar. The value of all excipients is nearing to 0.10 cm. This established that the drug (ofloxacin) and all the excipients used in the study showed no interaction between them and indicated that they were compatible with each other.

Formulation and optimization of a sustained floating drug delivery system of ofloxacin by using high viscosity grade of polymer (HPMC, carbopol), gas generating agent (sodium bicarbonate), aerosol, PVP K30, and magnesium stearate. Kinetic mechanism of data indicated zero order release of ofloxacin from dosage form.

Dry granulation procedure to manufacture matrix tablets and gastro retentive tablets were established, As a part of an ongoing research on the formulation and evaluation of floating drug delivery system containing ofloxacin system as a model drug, different excipients were tested for the compatibility with ofloxacin such as TLC studies which revealed that no chemical interaction occur with other excipients. Matrix tablets of ofloxacin using hydrophilic polymers i.e., HPMC, HEC, Crosspovidone and carbopol were found to be good without chipping, capping and sticking therefore tablets can be formulated.

Thus it can be concluded from the results obtained that HPMC, HEC and sodium bicarbonate showed differences in their behavior in sustain release of ofloxacin from tablets embedded granular particulates. The combined HPMC and sodium alginate due to its quick hydration and swelling might have created more channels for quick release of drug. The enhanced drug release in combined HPMC and sodium bicarbonate system can be attributed to its wicking action.

References

1. Ohkubo T., Kudo M., Sugawara K., Determination of ofloxacin in human serum by high performance liquid chromatography with column switching. Anal – sci. Oct 1991; 7(5): 741-743.
2. Le-coguic A., Bidault R., Farinotti R., Daulphi determination of ofloxacin in plasma ad urine by liquid chromatography. J-chromatogram, Biomed Appl. 29 Dec 1988; 78 (J. Chromatogr., 434): 320 – 323.
3. Argekar A.P., Kapadia S.U., Raj S.V., Kunjir S.S., Quantitative determination of lomefloxacin, ofloxacin, pefloxacin and exrofloxacin in pharmaceutical dosage, bulk drugs and process monitoring of enrofloxacin by RPHPLC. Indian-drugs. Jun 1996; 33(6): 261-266.
4. Macek J., Ptacek P., Determination of ofloxacin in human plasma using HPLC and fluorescence detection. Bunseki-Kagaku. Nov 1989; 38(11): 650-652.
5. Rang H.P., Dale M.M., Ritter J.M., Pharmacology1999, 4, 700-701.
6. United States Pharmacopoeia (USP-NF XXIV), Rockville MD 20852; United States Pharmacopoeia Inc., 1985, 2149-2151.
7. Willard H.H., Merritt L.L., Jr. Dean J.A., Frank A.S., Instrumental method of analysis. CBS publishers and Distributors, New Delhi, 7, 1986, 1-5.
8. Mathur S.C., Kumar Y., Murugesan N., Rathore Y.ks., Sethi P.D., Spectrophotometric determination of ofloxacin in pharmaceutical formulation. Indian- Drugs, May 1992; 29(8): 376-377.
9. Kraas E., Hirrle A., Determination of ofloxacin in biological fluid using HPLC with florometric detection. Fresenius-z-anal-chem., Jun 1986; 324(3-2):354.
10. Brahma N., Kwon H.K., Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Cintr Rel 2000; 63: 235-259.

ISSN: 0976-7126

11. Zhang H., Hong Y.C., YU C., LI D.K., Qiu Z.F., Determination of ofloxacin granules by UV spectrophotometry. Yaowu-fenxi-zazhi, 1996; 16(1):9-12.
12. Swarbrick J., Boylan J.C., Optimization techniques in formulation and processing. Pharmaceutical encyclopedia, 12: marcel dekker (NY); 1990.
13. Brijesh S.D., Avani F.A., Madhabhai M.P., Gastroretentive drug delivery system of ranitidine hydrochloride formulation and in vitro evaluation. AAPS Pharm Sci Tech 2004; 5(2): 1-6.
14. Abdul W.B., Larry F.L., Solonic metabolism of ranitidine, implications for its delivery and absorption. Int J Pharm 2001; 227: 157-165.
15. Bertram K.G., Basic and clinical pharmacology 2007, 10, 766-769.
16. Tripathi K. D., Essentials of Medicinal Pharmacology, 2008, 6, 688-693.
17. Bennett P.N., Brown M.J., Clinical Pharmacology 2006, 9, 232-233.
18. Arthur H.K., Handbook of excipients. 3rd ed. Pharmaceutical press: American pharmaceutical association; 2000.
19. Streubel A., Siepmann J., Bodmeier R., Floating matrix tablets based on low density foam powder effects of formulation and processing parameters on drug release. Euro J Pharm Sci 2003; 18: 37-45.
20. Tadakazu T., Yoshiharu M., Preparation of amoxicillin intragastric buoyant sustained release tablets and the dissolution characteristics. J Cont Rel 2005; Article in press. Accepted 24 Oct. 2005.
21. Lynne W., John H.C., John T.F., Amoxicillin release from a floating dosage form based on Alginates Int J Pharm 2000; 210: 45-49.
22. Hoffman A., David S., Eran L., Sara R., Eytan K., ichael F., Pharmacokinetic and pharmacodynamic aspects of gastro retentive dosage forms. Int J Pharm 2004; 277: 141-153.
23. Ibrahim E.G., Development and in vitro evaluation of novel floating chitosan microcapsules for oral use: comparison with non-floating chitosan microspheres. Int J Pharm 2002; 249: 7-21.
24. Kiran K.M., Manish H.S., Anant K., Mahadik K.R., Anant P., Effect of drug solubility and different excipients on floating behavior and release from glyceryl monooleae matrices. Int J Pharm 2004; 272: 151-160.
25. Midhat V., Sabira H., Fatima S., Amina H., Elvedina V., Ediba H., Stability of ranitidine in inject able solutions. Int J Pharm 2003; 256: 109-115.
26. Burns S.J., Corness D., Hay G., Higginbottom S., Whelan I., Attwood D., Barnwell S.G., Development and validation of an in vitro dissolution method for a floating dosage form with biphasic release characteristic. Int J Pharm 1995; 121: 37-44.
27. Shoufeng L., Senshang L., Bruce P.D., Haresh L.M., Chien Y.W., Effect of formulation variables on the floating properties of gastric floating drug delivery system. Drug Dev Int Pharm 2002; 28(7): 787-793.
28. Dorozynski R., Jachowicz P., Kulinowaski S., Kwiecinski, Szybinski K.,Skora T., et al., The macromolecular polymers for the preparation of hydrodynamic ally balanced system-methods of evaluation. Drug Dev Int Pharm 2004; 30(9): 947-957.
29. Igani H.M., Timmermans J., Moes A.J., Conception and in vivo investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. Int J Pharm 1987; 35: 157-164.
30. Srinath M.S., Narendra C., Prakash B.R., Formulation and Evaluation of a sublingual tablet coating terbutaline sulphate: optimization and in vivo studies. Ars Pharm 2005; 46(2): 139-158.
31. Narendra C., Srinath M.S., Prakash R.B., Development of three layered buckle compact containing metroprolol tart rate by statically optimization technique. Int J Pharm 2005; 304: 102-114.
32. Shoufeng L., Senshang L., Bruce P.D., Haresh L.M., Chien Y.W., 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.
33. Sasa B., Julijana K., Franc V., Polona V., Bojan Z., optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000; 195: 125-135.
34. Cheuh H.R., Zia H., Rhodes C.T., Optimization of sotatol floating and bioadhesive extended release tablet formulation. Drug Dev Int Pharm 1995; 21(5):1725-1747.
35. Luiz A.L.S., George G.O., Pedro R.P., Peter C.S., Optimization of tablets containing a high dose of spray-Dried plant extract: A Technical Note. AAPS Pharm Sci Tech 2005; 6 (3): 367-371.

ISSN: 0976-7126

36. Chih H., Huang H.M., Shu Y.H., Ching Y.S., Chang B.L., Simultaneous high performance liquid chromatographic analysis for famotedine, Ranitidine HCl, Cimitidine, and Nizatidine in commercial products. Drug Dev Int Pharm 1999; 25(3): 379-385.