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Formulation and Evaluation of Gastroretentive Dosage Form of Ofloxacin

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Original Research Article

ABSTRACT

The aim of the present investigation was to develop and evaluate gastroretentive drug delivery tablets (GRDDTs) of ofloxacin using different polymers such as HPMC K4M, HPMC K15M, Polyethylene oxide WSR 303, Carbopol 971P, Xanthan Gum in different ratios for local action in gastric region to eradicate *Helicobacter pylori* infection. The GRDDTs were prepared by wet granulation method and evaluated for physical characteristics such as hardness, thickness, friability, drug content and floating properties. The optimized formula F4 showed better sustained drug release and which also had good floating properties and fitted best to be Korsmeyer-Peppas model with R^2 value of 0.9848. As the n value for the Korsmeyer- Peppas model was found be less than 0.45 it follows Fickian diffusion mechanism. FT-IR result showed that there is no drug excipient interaction. *In vivo* radiographic studies were conducted with $BaSO_4$ loaded tablets to examine the increased gastric residence time of the prepared tablets. The study revealed that the tablet remained in the stomach for 300±10min which indicates the increase in the gastric residence time for the effective localized action of the ofloxacin in the treatment of *Helicobacter pylori* caused peptic ulcer.

***Key words*:** Ofloxacin, *Helicobacter pylori*, gastric residence time, gastroretentive drug delivery system.

INTRODUCTION

Over the past three decades the oral controlled release dosage forms have been developed due to their significant advantages such as patient compliance, ease of administration and flexibility in formulation. There are several difficulties in this approach such as inability to restrain and locate the controlled drug delivery system within the desired region of gastro intestinal tract due to gastric motility and gastric emptying which leads to reduced efficacy of the administered dosage (Rouge *et al.*, 1996). To overcome these problems oral controlled dosage form with gastro retentive properties were developed (Streubel *et al.*, 2006). Gastroretentive dosage forms are suitable for local drug delivery to the stomach and small intestine (Ali *et al.*, 2005). In case of many drugs which are released in the stomach have the greatest therapeutic effect while their release is prolonged in a continuous and controlled manner. This type of drug delivery system will have relatively less side effect and removes the need of repeated dosages (Hwang *et al.*, 1998).

Various approaches are available to increase gastric residence time of oral dosage form in the stomach which includes floating systems (Deshpande *et al.*, 1997), swelling and expanding systems (Urquhart and Theeuwes., 1984), bioadhesive systems (Alvisi *et al.*, 1996), modified shape systems (Cargill *et al.*, 1988), high density systems (Bechgaard and Ladefoged., 1978) and other delayed gastric emptying devices (Groning and Heun., 1989; Groning and Heun., 1984). The buoyant preparation increases gastric residence time of dosage form and also gives sustain release (Sing

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and Kim., 2000). Based on the mechanism of buoyancy, two types of technologies are developed in the floating systems. They are non effervescent and effervescent systems. Non effervescent systems prepared by using poly-acrylate, polycarbonate, polystyrene as excipients swells unrestrained via inhibition of gastric fluid to an extent which will prevent their exit from stomach (Garg and Gupta., 2008). Effervescent system utilizes matrices prepared by using swellable polymers like methocel, polysaccharides and effervescent compounds like sodium bicarbonate, citric acid or tartaric acid (Rubinstein and Friend., 1994).

Drugs suitable for floating drug delivery system includes drugs with narrow absorption window in GI tract, drugs which are mostly absorbed from stomach and upper part of GIT, drugs that act locally in the stomach, drugs that degrades in the colon, drugs which have poor solubility at alkaline pH. Several factors influence the gastric retention time of dosage forms such as density, size, shape, single or multiple unit formulation (Coupe *et al.* 1991), nature of meal, caloric content, frequency of feed (Mazer *et al.*,1998; Agyilirah *et al.*, 1991; Sangekar *et al.*, 1987; Muller-Lissner *et al.*, 1981; Oth *et al.*, 1992; Moore *et al.*, 1984; Mojaverian *et al.*, 1985), gender, age, posture (Mojaverian *et al.*, 1988).

Ofloxacin is a flouroquinolone, broad spectrum antibiotic, rapidly well absorbed from the gastrointestinal tract. Half life of ofloxacin is 9 hours and is used in the treatment of gentio urinary, respiratory, gastrointestinal, skin and soft tissue infections. Boldhane and Kuchekar., (2009) developed a gastroretentive drug delivery systems of metformin hydrochloride. Their study has shown that the metformin gastro-retentive tablets prepared using sodium alginate and sodium carboxy methylcellulose can successfully be employed as a once a day oral controlled release drug delivery system. Jagadale *et al.*, (2009) developed a gastroreten-tive drug delivery system of propranolol hydrochloride. Their investigation indicated that the tablets formulated using HPC, sodium alginate, HPMC E15 LV failed to produce matrix of required strength, while formulation containing xanthan gum showed good drug retaining abilities but floating abilities were found to be poor. Finally, floating tablets were formulated with HPMC K4M and HPC. Gambhire *et al.*, (2007) formulated a floating drug delivery system of diltiazem hydrochloride using polymers such as hydroxypropyl methyl cellulose K100M CR and compritol 888 ATO, alone and in combination. They have investigated the effect of sodium bicarbonate and succinic acid on drug release. The high level of both methocel K100M CR and compritol 888 ATO favored the preparation of floating controlled release of diltiazem tablets. They have observed that incorporation of succinic acid in the formulation nullified the effect of the acidic dissolution media on the drug release in that formulation, methocel K100M CR retards the release by diffusion mechanism and compritol 888 ATO decreases the hydration of matrix and retards the release by erosion mechanism owing to its hydrophobic property. Together, these polymers retard the release of drug using different mechanisms. Mahesh *et al.*, (2006) reported Novel sustained release, swellable and bioadhesive gastro retentive drug delivery system for ofloxacin. Mahesh *et al.*, (2005) proposed a new strategy for the development of gastroretentive dosage forms for ofloxacin preferably once daily. The design of the delivery system was based on the sustained release formulation, with floating and swelling features in order to prolong the gastric retention time of the drug delivery systems. They tried different polymers, such as psyllium husk, HPMC K100M, crospovidone and its combinations in order to get the desired sustained release profile over a period of 24 hours. They found that in vitro drug release rate increased with increasing amount of crospovidone due to the increased water uptake, and hence increased driving force for drug release.

MATERIALS AND METHODS

Ofloxacin was a generous gift sample from Ranbaxy Laboratories Ltd, Gurgaon New Delhi, India. Polyethylene oxide WSR 303 was gift sample from Ra Chem Pharma Ltd, Hyderabad, India. Hydroxy propyl methyl cellulose (HPMC K4M and HPMC K100M), Carbopol 971P,

xanthan gum and Avicel 112 were gifted by Orchid Health Care Pvt Ltd, Chennai, India. All other chemicals used were of analytical grade.

Preparation Method of Ofloxacin Floating Tablets

Drug, polymer and sodium bicarbonate were weighed and passed through sieve with mesh #40 and were mixed homogeneously in a poly-bag for about 5-10 mins and was taken in a mortar. 5% PVP K30 in isopropyl alcohol was used as granulating agent. The wet mass was passed through mesh #14 and dried in hot air oven at 50°C for 30 mins. and dried granules were sieved through mesh #16. Finally well formed granules were lubricated with magnesium stearate and talc. Formulation compositions of all batches were shown in Table 1.

Evaluation of Floating Tablets

The prepared floating tablets were evaluated for hardness, thickness and friability which were measured by a hardness tester (Monsanto, Germany), vernier calipers (Mitutoyo Corporation, Japan) and friability test apparatus (Campbell Electronics friabilator, India) respectively. The drug content in each formulation was determined by triturating ten tablets in a mortar and amount equivalent to one average tablet was accurately weighed and dissolved in 100ml 0.1 N HCl taken in a 250 ml volumetric flask. The flask was kept on mechanical shaker for overnight, later was filtered through a filter paper and the first few ml were discarded. The filtrate was sufficiently diluted and the absorbance was recorded against the blank at 293 nm using UV- Visible spectrophotometer.

In vitro buoyancy studies

The in vitro buoyancy was determined by floating lag time and floating duration in a 100 ml glass beaker containing 0.1N HCl.

In vitro drug release studies

The in vitro drug release study was conducted using the USP dissolution apparatus-II (paddle method) and 900ml of 0.1N HCl (pH 1.2) as dissolution release medium. The study was conducted at 37 ± 0.5°C and at paddle rotation of 50 rpm. The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at predetermined time intervals of 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hours. The volume of dissolution fluid was adjusted to 900 ml by replacing 5ml of fresh dissolution medium after each sampling. The release studies were performed in triplicate, and the mean values were plotted versus time. Each sample was analyzed at 293nm using double beam UV - Visible Spectrophotometer against reagent blank.

Drug release kinetics

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order (Donbrow *et al.*, 1980), first order (Merchant *et al.*, 2006), Higuchi (Higuchi T., 1963) and Korsmeyer-Peppas (Korsmeyer *et al.*, 1983) release model.

Fourier Transform Infrared Spectroscopy Studies

Fourier transform infrared spectra of the ofloxacin pure drug, polymer, physical mixture of drug and excipients and placebo were obtained using Fourier Transform Infrared Spectrophotometer (Bruker Model: Alpha-T, Ettlingen, Germany). Samples were prepared using KBr disks by means of hydraulic pellet press at a pressure of 7-10 tons. The samples were scanned from 4000 to 400cm^{-1}.

In vivo confirmation of buoyancy by using radiographic studies

For this study the tablets of optimized batch (F4) were prepared by replacing half of the amount of drug with barium sulfate. After overnight fasting of three healthy volunteers they were fed with low calorie food and allowed to take water after these tablets were administered orally. Radiographs were obtained at predetermined time intervals (1hr., 2hrs., 3 hrs. and 5hrs.). The Institutional Human Ethical Committee approved the protocol for this study.

Table 1. Formulation composition of gastroretentive tablets of Ofloxacin.

Code	Drug (mg)	HPMC K4M (mg)	HPMC K 15M (mg)	PEO (mg)	Carbopol 971P (mg)	Xanthan Gum (mg)	SBC (mg)	Avicel 112 (mg)
F1	400	95	-	-	-	-	190	246
F2	400	190	-	-	-	-	190	151
F3	400	285	-	-	-	-	190	56
F4	400	-	95	-	-	-	190	246
F5	400	-	190	-	-	-	190	151
F6	400	-	285	-	-	-	190	56
F7	400	-	-	95	-	-	190	246
F8	400	-	-	190	-	-	190	151
F9	400	-	-	285	-	-	190	56
F10	400	-	-	-	95	-	190	246
F11	400	-	-	-	190	-	190	151
F12	400	-	-	-	285	-	190	56
F13	400	-	-	-	-	95	190	246
F14	400	-	-	-	-	190	190	151
F15	400	-	-	-	-	285	190	56

HPMC- Hydroxy Propyl Methyl Cellulose; PEO- Polyethylene Oxide; SBC- Sodium Bicarbonate; All formulations contained 1% Magnesium Stearate and 1% Talc.

Table 2. Physical evaluation parameters of gastroretentive tablets of Ofloxacin.

Code	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	951.16 ± 1.2	6.0 ± 0.5	5.51 ± 0.01	0.34	98.0 ± 0.3
F2	950.80 ± 2.6	5.5 ± 0.5	5.42 ± 0.04	0.25	98.7 ± 0.2
F3	950.22 ± 3.4	6.0 ± 0.5	5.61 ± 0.07	0.42	98.5 ± 0.1
F4	949.11 ± 4.5	5.0 ± 0.1	5.56 ± 0.05	0.29	98.7 ± 0.2
F5	948.65 ± 2.5	5.4 ± 0.4	5.80 ± 0.02	0.36	94.1 ± 0.5
F6	952.21 ± 1.5	6.0 ± 0.5	5.73 ± 0.03	0.45	98.5 ± 0.1
F7	953.11 ± 1.3	5.5 ± 0.5	5.64 ± 0.09	0.22	95.0 ± 1.1
F8	950.28 ± 21	6.5 ± 0.5	5.89 ± 0.05	0.28	92.0 ± 1.8
F9	951.65 ± 1.7	5.5 ± 0.5	5.77 ± 0.04	0.37	94.5 ± 1.3
F10	952.09 ± 2.4	6.5 ± 0.3	5.68 ± 0.08	0.44	91.5 ± 2.3
F11	951.18 ± 3.5	5.4 ± 0.2	5.72 ± 0.06	0.24	93.0 ± 2.0
F12	950.51 ± 4.3	5.5 ± 0.5	5.65 ± 0.04	0.31	92.0 ± 1.9
F13	951.19 ± 1.4	6.0 ± 0.1	5.79 ± 0.07	0.27	95.0 ± 0.9
F14	952.32 ± 2.9	5.5 ± 0.4	5.37 ± 0.05	0.35	97.5 ± 0.6
F15	950.29 ± 1.5	5.6 ± 0.2	5.64 ± 0.08	0.21	96.2 ± 1.5

Table 3. Floating properties of gastroretentive tablets of Ofloxacin.

Code	Floating Lag Time (s)	Total Floating Time (h)
F1	09	01
F2	11	03
F3	20	05
F4	28	>12
F5	32	>12
F6	38	>12
F7	60	08
F8	126	>12
F9	189	>12
F10	80	09
F11	140	06
F12	200	04
F13	600	>12
F14	1100	>12
F15	1800	>12

Table 4. Regression Coefficient (R^2) Values of Drug Release Data Obtained from Various Kinetic Models and n Value According to Krosmeyer–Peppas.

Code	Zero-Order	First Order	Higuchi	Krosmeyer–Peppas	
	R^2	R^2	R^2	R^2	n
F1	0.610	0.451	0.864	0.905	0.151
F2	0.685	0.516	0.911	0.960	0.215
F3	0.825	0.394	0.971	0.963	0.354
F4	0.805	0.886	0.961	0.984	0.335
F5	0.817	0.961	0.966	0.976	0.327
F6	0.903	0.967	0.987	0.975	0.431
F7	0.863	0.972	0.983	0.981	0.427
F8	0.979	0.891	0.922	0.905	0.675
F9	0.968	0.985	0.960	0.992	0.787
F10	0.826	0.963	0.981	0.979	0.388
F11	0.932	0.982	0.985	0.982	0.666
F12	0.946	0.978	0.965	0.923	0.339
F13	0.839	0.910	0.973	0.975	0.336
F14	0.856	0.913	0.913	0.989	0.362
F15	0.831	0.862	0.862	0.933	0.320

Table 5. Characteristic peaks of pure drug, polymer, physical mixture of optimized formulation and placebo in FTIR spectra.

Sl. No	Compound	Group	Type of vibration	Peaks (cm^{-1})
1	**Pure drug**	C-F	C-F Stretching	1457.70
		C=C-O-C	C-O Stretching	1072.31
		$-CH_3$	C-H Stretching	2968.12
		-COOH	C=O Stretching	1711.55
		-COOH	O-H Stretching	2755.71
		Aromatic	Ar-H Stretching	3042.49
		Hydrocarbons	C=C Stretching	1620.57,1548.28, 1520.88,1457.70
2	**Polymer**	$-CH_2$-OH	O-H Stretching	3402.52
		$-CH_2$-OH	C-O Stretching	1048.84
		CH-OH	C-O Stretching	1314.09
		C-O-CH_3	C-H Stretching	2873.29
3	**Physical mixture of optimized formulation**	C-F	C-F Stretching	1458.32
		C=C-O-C	C-O Stretching	1072.18
		$-CH_3$	C-H Stretching	2968.65
		-COOH	C=O Stretching	1712.29
		-COOH	O-H Stretching	2756.75
		Aromatic	Ar-H Stretching	3042.87
		Hydrocarbons	C=C Stretching	1620.72,1549.34, 1520.78,1456.32
		$-CH_2$-OH	O-H Stretching	3378.63
		$-CH_2$-OH	C-O Stretching	1054.39
		CH-OH	C-O Stretching	1304.91
		C-O-CH_3	C-H Stretching	2834.43-2866.62
4	**Placebo**	$-CH_2$-OH	O-H Stretching	3332.65
		$-CH_2$-OH	C-O Stretching	1051.67
		CH-OH	C-O Stretching	1313.91
		C-O-CH_3	C-H Stretching	2882.76

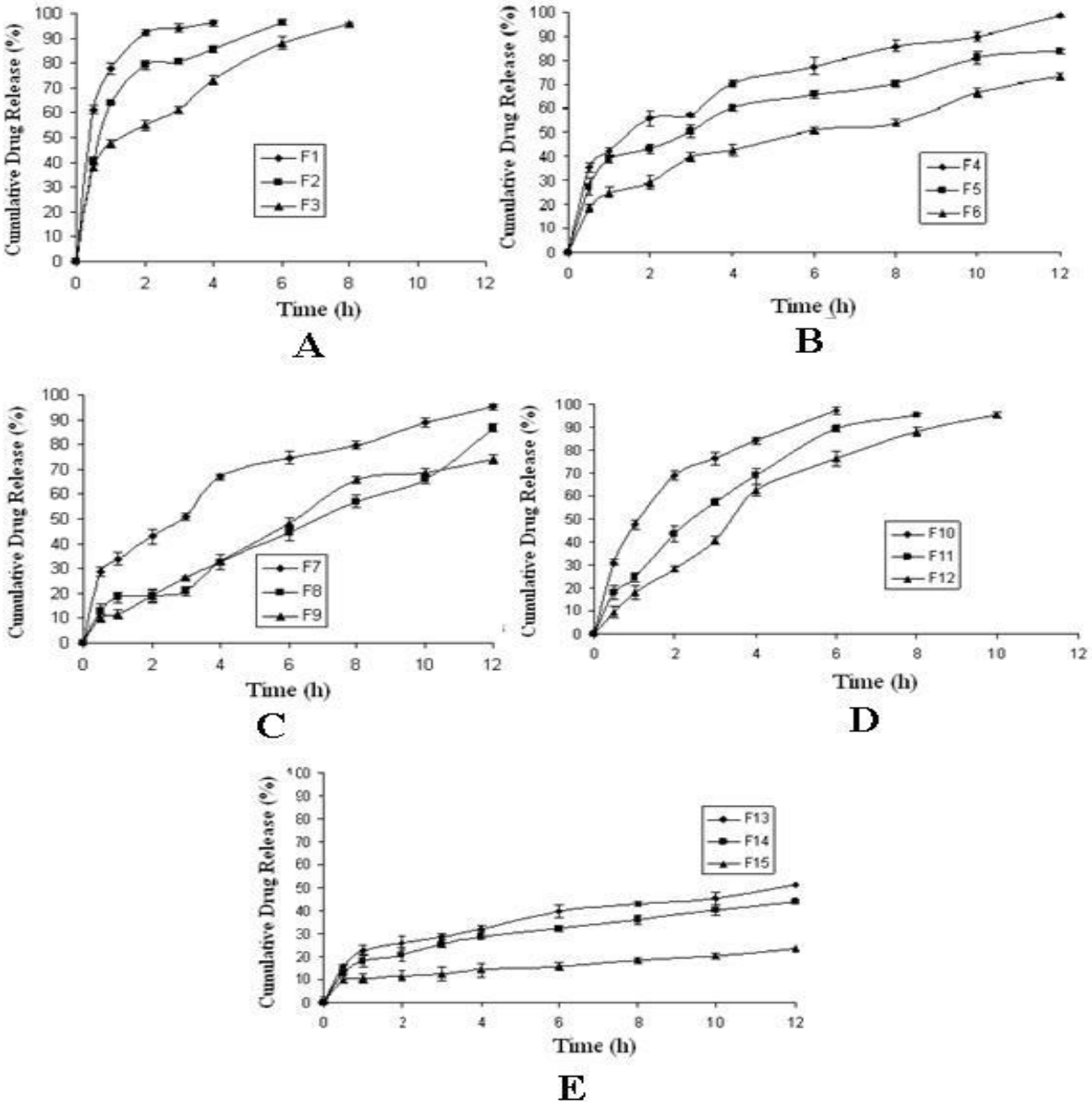

Figure 1. *In vitro* Drug Release Profile of Ofloxacin Tablets Prepared with (A) HPMC K4 M; (B) HPMC K15 M; (C) PEO; (D) Carbopol 971P (E) Xanthan Gum

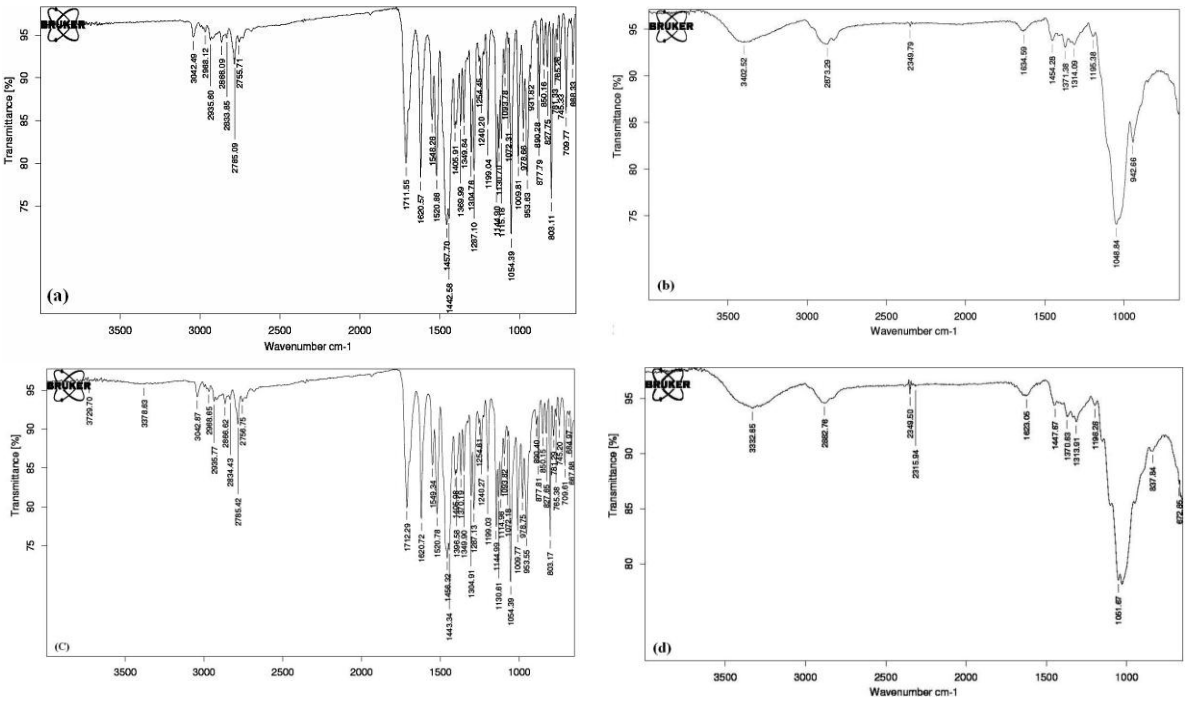

Figure 2. The FTIR spectra. a) pure drug b) polymer c) physical mixture of optimized formulation d) Placebo

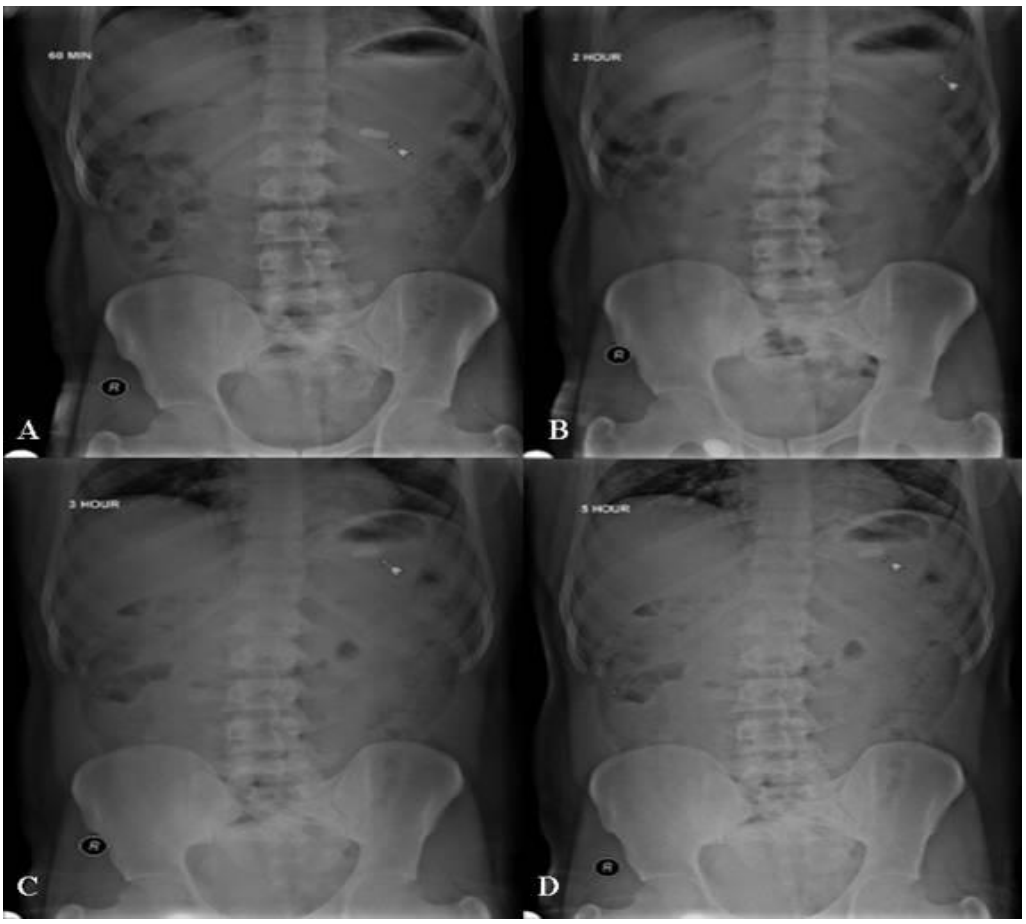

Figure 3. Radiographic images showing the presence of floating tablet in the stomach at different time periods (the tablet is indicated with an arrow). The tablet altered its position in the stomach. Images were taken after: A) 1 h, B) 2 h, C) 3 h and D) 5 h after tablet administration.

RESULT AND DISCUSSION

Evaluation of floating tablets

All formulations were tested for physical parameters like hardness, thickness, weight variation, and friability and results were shown in Table 2. The best formulation (F4) showed hardness of 5.0 ± 0.1kg/cm^2, thickness of 5.56 ± 0.05 mm, friability of 0.29% and the drug content of all the formulations was determined and was found to be within the permissible limit and in vitro floating evaluation parameters were showed in Table 3.

As the amount of HPMC K4M decreased, TFT decreased probably because of the poor gelling strength. In the case of HPMC K15M and PEO, TFT increased this is because of increased gel strength of matrices which prevents escape of evolved CO_2 from matrices, leading to decreased density. As the amount of carbopol 971P increased, TFT decreased which may be due to high affinity of carbopol towards water, which promotes water penetration into tablet matrices, leading to increased density. Xanthan Gum will have the nature of high viscosity therefore sodium bicarbonate takes more time to react with dissolution medium which leads to increase in the floating lag time.

In vitro drug release studies

In vitro drug release profile for all prepared formulations were depicted in Figure 1. The formulations containing HPMC K4M showed poor integrity. Further attempt were made to improve the integrity by increasing the polymer percentage but were unable to show the desired integrity within the highest possible concentration of the polymer in the formulation. The formulation F1 which contain least (10%) amount of polymer showed drug release to the extent of 96.18% within 4 hours. When the polymer concentration is increased to 20% of total weight of the tablet (F2), 96.49% of drug release was achieved within 6 hours. Further increment of the polymer to 30% (F3) has resulted in 95.68% of drug release in 8 hours. The formulations containing HPMC K15M have shown sustaining effect on the release of drug from the floating matrix tablets, but the increase in the concentration of the same polymer in the formulation retards the release of drug from the tablet. Formulation F4 gave the best results which retarded the drug release 98.80% for 12hours and hence it was considered as the optimized formulation. The formulation F5 had drug release of 83.69% in 12hours and F6 had drug release of 73.01% in 12 hours. The formulations which contain PEO show retarded effect on drug release with the increase in the polymer ratio. The formulation F7 which contain polymer ratio 10% of total tablet weight dissolved in the dissolution medium at about 8 hours.

With other formulations the tablet floated more than 12hours. The formulations which contain carbopol showed retarded effect on drug release when there was increase in the polymer ratio. However, it has a disadvantage where increase in the polymer ratio leads to decrease in the floating time which is due to increase in the density. Xanthan gum has sustaining effect on the release of drug from the floating matrix tablets but the increase in the concentration of the same polymer in the formulation retards the release of drug from the tablet. The release of drug from all formulation was less than 55% within 12 hours.

Drug Release Kinetics

Regression coefficient value (R^2) and n values for all formulation were shown in Table 4. The release profile of optimized formula F4, fitted best to Korsmeyer-Peppas model with R^2 value of 0.9848. As the n value for the Korsmeyer-Peppas model was found to be less than 0.45 it follows Fickian diffusion mechanism.

Fourier Transform Infrared Spectroscopy Studies

FTIR spectra and Characteristic peaks for pure drug, polymer, physical mixture of optimized formulation, and placebo were represented in Figure 2 and Table 5 respectively. Pure drug characteristic peaks were observed in pure drug and physical mixture of optimized formulation only but not in pure polymer and placebo. Polymer chrematistic peaks were observed in polymer, physical mixture of optimized formulation and placebo. Therefore, from this FTIR study can be concluding that the pure drug has no interaction with excipients.

In vivo confirmation of buoyancy by using radiographic studies

In vivo studies were conducted on healthy human volunteers to find the gastric residence time of the optimized formulation (F4). The studies were based on X-ray radiography. Images were taken at different time points to find the location of the tablet shown in Figure 3. The radiograms were taken for every 1hr and the tablet was found floating on the gastric content for about 300±10 min.

CONCLUSION

Gastroretentive drug delivery tablets of ofloxacin were developed to enhance gastric residence time and there by eradication of Helicobacter pylori infection. The optimized formula F4 showed better sustained drug release and which also had good floating properties. The release profile of optimized formula, fitted best to Korsmeyer-Peppas model with R^2 value of 0.9848. As the n value for the Korsmeyer-Peppas model was found be less than 0.45 it follows Fickian diffusion mechanism. In vivo radiographic studies revealed that the tablets remained in the stomach for 300±10 min which indicates the increase in the gastric residence time.

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