Saudi Pharmaceutical Journal (2011) **19**, 85–93

King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Preparation of a novel floating ring capsule-type dosage form for stomach specific delivery

Md. Ismail Mouzam [a,*], M.H.G. Dehghan [a], Shaikh Asif [b], Trupti Sahuji [a], Pooja Chudiwal [a]

[a] *Department of Pharmaceutical Technology, Y.B. Chavan College of Pharmacy, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, India*
[b] *Wockhardt Research Centre, MIDC Industrial Area, Aurangabad, India*

Received 7 July 2010; accepted 7 January 2011
Available online 18 January 2011

KEYWORDS

New floating ring capsule;
Stomach specific delivery;
Polymers;
In vitro drug release

Abstract Study objectives were to develop a unique floating ring capsule dosage form which combines gastric soluble and insoluble portions, and to evaluate its suitability for stomach specific drug delivery. New floating ring capsules were developed using different polymers and were compared for various parameters. The formulation with HPMC and sodium CMC has better floating properties. The effects of polymers concentration on drug release were studies by *in vitro* release studies. The interaction studies of combined drug with polymers were determined using FT-IR spectroscopy. The entrapped air within the gel barrier and lower densities of HPMC and sodium CMC resulted in better floating behavior. Steady slow gel formations showed prolonged drug release. The *in vitro* release rates were generally found to be faster with low concentration of carbopol showing release within 2 h, while formulations containing high amount of HPMC showed release in 8 h. In particular, the higher concentration of HPMC formulation shows the best drug release performance. A very low change in peak shift was observed only with sodium alginate formulations. Further, FT-IR measurements confirmed the absence of any chemical interactions.

* Corresponding author. Address: Department of Pharmaceutical Technology, Y.B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Rauza Bagh, P.O. Box 33, Aurangabad 431001, Maharashtra, India. Tel.: +91 2402381307; mobile: +91 9860440856; fax: +91 2402381129.
E-mail address: mdismail1111@rediffmail.com (M.I. Mouzam).

Peer review under responsibility of King Saud University.
doi:10.1016/j.jsps.2011.01.004

ELSEVIER **Production and hosting by Elsevier**

Results indicate that new floating ring capsule is a promise dosage form for stomach specific delivery.

1. Introduction

During past few decades *Helicobacter pylori (H. pylori*) has been recognized as a major gastric pathogen responsible for chronic active gastritis, duodenal ulcers and gastric adenocarcinoma (Megraud and Lamouliatte, 1992; Forman et al., 1994). Levofloxacin hemihydrate is considered to be effective for the treatment of *H. pylori* (Cavallaro et al., 2005; Enrico et al., 2006). Oral ingestion is the predominant and most preferable route for drug delivery (Chien, 1992). Always there was interest in the development of novel capsules of hard gelatin capsules (Sarah et al., 2010; Takashi et al., 1998). One could envision utilizing the time-delayed systems to target relatively specific regions of the GI tract for drug release. RingCap, a patented technology could be an example of such development. The intent of such technology was to provide a delivery system with reliable and reproducible drug release characteristics (Wong et al., 1996, 1997).

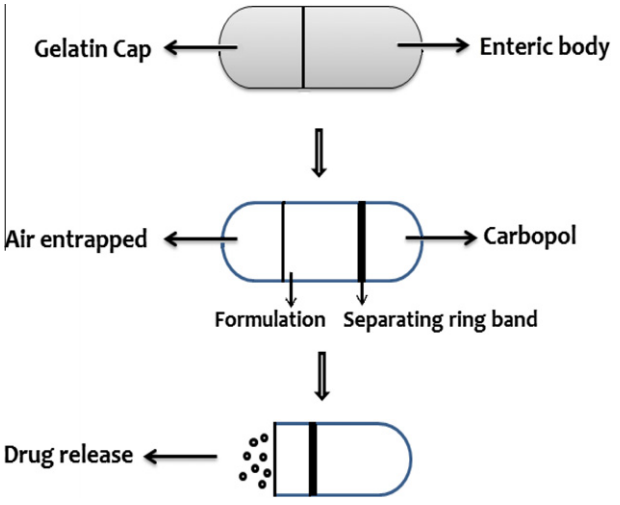

Figure 1 Schematic drawing of the steps involved in the drug release. (1) Filled capsule with enteric body and gelatin cap. (2) Entrapped air and gelatin cap get dissolved. (3) Drug release.

Table 1 Studied formulations.

Code of formulation	Sodium alginate (mg)	Carbopol 934 (mg)	HPMC (mg)	Sodium CMC (mg)
F1	100	–	–	–
F2	200			
F3		100		
F4		200		
F5			100	
F6			200	
F7				100
F8				200

All the capsules formulations contain 250 mg levofloxacin.

Thus, it is believed that delivery of antibiotic through a floating drug delivery system may result in incomplete removal of the organisms in the fundal area of the gastric mucosa due to bactericidal drug levels being reached in this area, and might lead to better reported treatment of peptic ulcer disease (Brahma et al., 2000).

Various authors report alginate and HPMC that were able to float on gastric contents and provided SR characteristics (Davis et al., 1986; Muller-Lissner et al., 1981; Sheth and Tossounian, 1984). Further Washington et al. (1986) suggested that the formulation consists of a mixture of alginate, forms a gel of alginic acid. The gel becomes buoyant by entrapping the gas bubbles and floats on the gastric contents as a viscous layer. Furthermore, cellulose ether polymers (HPMC) have a bulk density of less than unity in gastric fluids, and formulation containing sodium CMC exhibited better release from the capsules (Nathalie et al., 1997).

The aim of this study was to develop a new floating ringcap delivery system (NFRCDS) in cross-linked hard gelatin capsule shell. The effect of the preparative parameters, e.g., amount of the various polymers, the floating ability and drug release properties of the NFRCDS were evaluated.

1.1. Design of dosage form

The NFRCDS was developed by first rectification of enteric body and the gelatin cap. In enteric body carbopol was placed first and then over this circular separating ringband of 1 mm thickness was placed. Mixture of levofloxacin and polymer were prepared as shown in Table 1 and placed over the separating band (Fig. 1). There after gelatin cap was joined over the enteric body. After ingestion of the capsule, the acidic environment quickly dissolves the gelatin cap, but the enteric body still remains intact. As a result, the formulation mixture gets exposed to the acidic environment only from a side. This exposed dry mixture gets hydrated and gradually erodes or swells, at the same time drug dissolves in the gel and diffuses out to the aqueous acidic environment. The deep located drug inside the capsule body gets thrusted towards exposed acidic environment by the separating ringband with the aid of swelling carbopol polymer. This formulation does not involve gas generation. Air is trapped inside the less dense powder bulk drug which accounts for the buoyant behavior of the capsule.

2. Materials

Levofloxacin was supplied by Wockhardt Research Ltd. (Aurangabad, India). Hard gelatin capsules (#0) were obtained from Concept Pharmaceuticals Ltd. (Associated Capsules, Mumbai, India, Lot No.: DKR10387). Hydroxypropyl methylcellulose (HPMC, Lot No.: GA228766) with Mw of 100,000 and viscosity 118,567 mPa s was from Dow Chemical Co. (Midland, MI, USA). Sodium carboxymethylcellulose (sodium CMC, BNo.: 61799305001046, Mw 250,000) and 4279 cP s viscosity as a 2% aqueous solution were purchased from Merck, Mumbai (India). Sodium alginate (BNo.:

544308) with Mw of 150,000 and 302 cP s viscosity as a 2% aqueous solution were provided from LobaChemie (Mumbai, India), and Carbopol-934 (Lot No.: 000044726) with Mw 39,400 and 501 cP s viscosity as a 2% aqueous solution were procured from Himedia Lab Ltd. (Mumbai, India). All other reagents used were of analytical grade. Capsule filling machines used were of ACG-Worldwide, MF-30 (Mumbai, India).

3. Methods

3.1. Preparation of separating ringcap band

It was prepared by making 2% HMPC solution in water, followed by the addition of 5% glycerol which was preoptimized. Then the mixture was poured to petridish and was allowed to dry at 45 °C. The dried film was cut uniformly into circular rings with punch, each having 1 mm thickness and diameter of 5.1 mm.

3.2. Preparation of enteric gelatin body

Enteric gelatin bodies were prepared by crosslinking technique as described previously by Pina and Sousa (2002). Hard gelatin body was separated from the cap. The formaldehyde solution was prepared and the separated gelatin body was immersed for 15 min followed by drying.

3.3. Preparation of new floating ring capsules

Enteric gelatin bodies were filled with 50 mg powder carbopol, then a separating ringcap band was placed. A mixture of levofloxacin and polymer as described in Table 1 was filled over it with light compression and finally the capsule body was sealed with hard gelatin cap (Fig. 2).

3.4. In vitro buoyancy studies

The *in vitro* buoyancy was determined by the floating time (Rosa et al., 1994). The capsules were placed in a beaker containing 100 mL of 0.1 mol L^{-1} HCl. The floating duration of all capsules were determined by visual observation.

Figure 2 New levofloxacin floating ring capsule.

3.5. Infrared spectroscopic studies

The spectra were recorded on Jasco-5300 FT-IR system. Infrared (IR) spectroscopic analysis was carried out on the mixtures to evaluate possible interactions between the drug and the carrier. Samples were prepared by KBr disc method (2 mg sample in 200 mg KBr) and examined in the transmission mode. Individual polymer, levofloxacin and drug/polymer mixture were run as controls. The scanning range was 400–4000 cm^{-1} and the resolution was 1 cm^{-1}. The recorded spectrum was subjected to analysis by Essential FT-IR V 1.5 software, USA.

3.6. In vitro drug release

In vitro drug release studies were conducted using the USP type II (paddle) dissolution apparatus (TDT-06T, Electrolab, India). Hydrochloric acid (0.1 N) 900 mL was used as medium. The study was conducted at 37 ± 0.5 °C and at paddle rotation of 50 rpm. Samples of 5 mL were collected at predetermined time intervals and replaced with fresh medium. The samples were filtered and absorbance of solutions was measured at 294 nm using Shimadzu UV 1800 spectrophotometer (Thakkar et al., 2008). The studies were performed in triplicate.

3.7. Mathematical drug release models

The different mathematical models may be applied for describing the kinetics of the drug release process from capsules. The kinetics of drug release from capsule formulations were determined by finding the best fit of the release data to zero order, first order, Hixson–Crowell, Higuchi, and Korsmeyer–Peppas plots, respectively.

3.7.1. Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) is represented by

$$Q_t = Q_0 + K_0 t$$

where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q = 0$) and K_0 is the zero order release constant. The exponential n equal to 1 is considered to follow zero order kinetics (case II transport).

3.7.2. First order kinetics

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967). The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices (Mulye and Turco, 1995), release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount drug released by unit of time diminishes:

$$Q_t = Q_0 \, e^{-K_1 t}$$

where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_1 is the first order release constant.

3.7.3. Higuchi model

Higuchi (1961, 1963) developed several theoretical models to study release of high and low water soluble drugs incorporated in the semi-solid and/or solid matrices. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. The simplified Higuchi's model is given as

$$Q_t = K_H t^{1/2}$$

where K_H is Higuchi's rate constant, and Q_t is the amount of drug released at time t. If a plot of square root of time vs cumulative amount of drug released yields a straight line, and the slope is 1 or more than 1, then the particular dosage form is considered to follow Higuchi kinetics of drug release. Under some experimental situations the release mechanism deviates from the Fick's equation, following an anomalous behavior (non-Fickian release).

3.7.4. Korsmeyer–Peppas model

Korsmeyer et al. (1983) developed a simple, semi-empirical, relating exponentially the drug release to the lapsed time:

$$Q_t/Q_\alpha = Kt^n$$

where K is the constant comprising a structural and geometric characteristics of the tablets; and n is the release exponent indicative of the drug release mechanism, is the function of t is Q_t/Q_α (fractional release of drug). Peppas (1985) used this n value in order to characterize different release mechanisms. If the n value is 0.5 or less, the release mechanism follows Fickian diffusion controlled release, and higher values ($0.5 < n < 1$) for mass transfer follow anomalous non-Fickian transport mechanism.

3.7.5. Hixson–Crowell model

When this model is used, it is assumed that the release rate is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix. It is given as follows

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

where W_0 is the initial amount of drug, W_t is the remaining amount of drug in dosage form at time t, and K_s is a constant incorporating the surface volume.

Table 2 Floating time for the various formulations.

Code of formulation	Floating time (h)
F1	2.5
F2	3.5
F3	0.75
F4	0.5
F5	5
F6	8
F7	3
F8	8

4. Results and discussion

*4.1. **In vitro** buoyancy studies*

The investigated model drug levofloxacin has pH dependent solubility, true density is $\rho = 1.48$ g/cm^3 and the single dose is very high, so it was a real challenge to form a floating capsule which will ensure a constant drug release for a period of 8 h. The air entrapped in dense powder during filling operation of capsules aids for the buoyancy phenomena. Sodium alginate formulations tend to float for lesser time, might be because of water penetration tends to withdraw the entrapped air from the non-compressed formulation, leading to abrupt loss of floating strength. This result correlates with the result obtained by Timmermans and Moes (1990). It indirectly suggests reduction in the penetration of water could lead to floating of capsules for prolonged period of time. Formulations containing HMPC and sodium CMC have better floating properties (Table 2). This could be due to their low apparent densities (bulk density of HPMC was 0.547 g/cm^3 and for sodium CMC 0.52 g/cm^3). Higher HPMC and sodium CMC levels were related to a lower density and thus improved floating behavior. Further when a large amount of sodium CMC was contained in the formulations, a part of sodium CMC located around the capsules was rapidly dissolved to form a gel barrier, which resulted in the entrapped air hardly being able to escape, leading to floating of formulations (Shan-Yang and Pei-Chin, 1992). The floating was continued over 8 h for formulations F6 and F8, respectively.

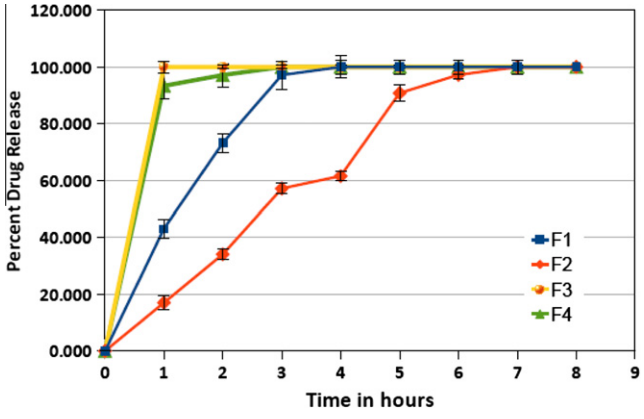

Figure 3 Comparison of influence of formulation variables on *in vitro* drug release from new levofloxacin floating ring capsules.

The formulation containing carbopol have negative effect on floating behavior of the delivery system and the results correlates with the study conducted by Shoufeng et al. (2003). This was been explained by the moisture isotherm of carbopol, which illustrates that carbopol has a much higher moisture absorption curve compared to HPMC, which in turn shows a corresponding decrease in the floating property.

4.2. Infrared spectroscopic studies

Levofloxacin and the formulations were subjected to FT-IR analysis in order to evaluate possible interactions between the drug and the polymers. The FT-IR spectra of pure levofloxacin, drug loaded capsules are shown in Figs. 6–8. The levofloxacin FT-IR spectra obtained were similar to that of Alex et al. (2010). The data were compared with the standard spectrum for levofloxacin, and characteristic peaks associated with specific structural characteristics of the molecule and their presence/absence in the polymeric carrier were noted. The peaks at 3268 and 1048 cm^{-1} indicate the –COOH monomeric stretching and bonding. Two peaks at 2848 and 1620 cm^{-1} designate for alkanes $–CH_3$ and aromatic rings, respectively. Other characteristic bands are shown at 1725 cm^{-1} for C═O stretching vibration of the COOH group, at 839 cm^{-1} for C–F peak. The spectrum of levofloxacin with SA shows the peak shift to lower frequencies for –COOH monomeric from 3268 to 3264 cm^{-1}. This peak shift could be attributed to opaque nature, i.e., presence of moisture within the sample. All the above peaks are present in drug-loaded formulations that confirm the presence of drug in the polymer without any interaction.

4.3. In vitro drug release

Results of an *in vitro* drug release of levofloxacin loaded capsules prepared using various polymers concentrations were shown in Figs. 3 and 4. The difference in the rate and extent of drug release was observed in formulation F3 and F4. The F3 formulation was characterized by a burst release, this could be because carboxylate groups on the carbopol polymer backbone rapidly ionize, resulting in repulsion between the negative particles, which adds to the swelling of the polymer and the osmotic pressure from within which may break up the structure (Jian, 2003), while F4 formulation showed slight delay in complete drug release. This could be attributed to an increase in tendency towards gel formation by carbopol when used in high concentration. This suggests burst release can be reduced by increasing the polymer concentration (Ziyaur et al., 2006). Formulation prepared with HMPC showed better release, F6 formulation showed release upto 8 h. The photograph of HPMC capsules suggests steady slow gel formation, which could be the reason for prolonged release. The next best result observed was for sodium alginate based formulations F1 and F2. The F2 formulations showed prolonged release upto 7 h while the F1 formulations showed release for a period of 4 h. It has been suggested that the stability of an alginate molecule is strongly dependent on the conditions to which it is subjected, i.e., temperature, pH, and presence of contaminants. The glycosidic linkages between the sugar monomers of the polysaccharide are susceptible to cleavage in acidic media. If the pH of the alginate-containing solution is lowered below the pK_a of the constituting acids, phase separation or hydrogel formation occurs (Ivan and Sergio, 2009). Further becomes soluble owing to favorable entropic contribution from the free (non-condensed) counterions, which might result in F1 formulations to be released with few hours, while higher concentration could take longer bit of time for glycosidic cleavage. The shape of F2 formulation remains intact after 7 h (Fig. 5). The release profile was similar to some extent for F2 and F6 formulations might be due to more air entrapment in HPMC formulation due to its low density, while SA formulations were compactly packed during filling operation. It is postulated by Paolo et al. (2000) that HPMC do not form the gel layer quickly, well because in dry systems the diffusion coefficient is very low. In such systems water acts as a plasticizer and reduces the glass transition temperature (T_g) of the system. Once the T_g equals the temperature of the system, the polymer chains undergo transition from the glassy to the rubbery state (Chambina et al., 2004). This might lead to sustained release of HPMC formulations F5 and F6. With sodium CMC formulations, the release was biphasic: a first phase at the beginning of the experiment with a slower slope and a second phase constant until the end of the dissolution process. In comparison to HPMC formulation, the sodium CMC formulation releases faster, would be due to disintegrating property of sodium

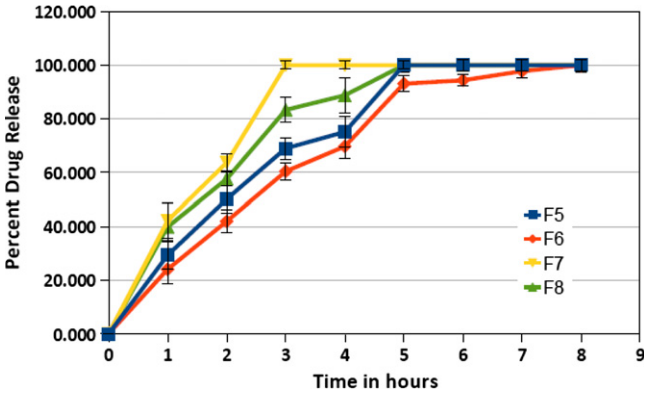

Figure 4 Comparison of influence of formulation variables on *in vitro* drug release from new levofloxacin floating ring capsules.

Figure 5 The F2 formulation containing sodium alginate after 7 h of drug release.

CMC (Raymond et al., 2009). Generally drug release was observed to be slower with increased polymer concentrations in most of the formulations.

4.4. Mathematical drug release

In order to develop an ideal kinetic model to interpret *in vitro* drug dissolution rate data in terms of meaningful parameters, various kinetic models were applied to obtain the best fit of the data. It has been found that the release have been realized in accordance with zero order for F7 formulation only. Besides the fact that it is emitted in accordance with zero order, the levofloxacin is distributed homogenously in the formulations. The best fit model for F1 formulation showed Peppas order release, '*r*' values equal to 0.9825 (Table 3). The formulations F4 and F5 showed release mechanism corresponding to Peppas model

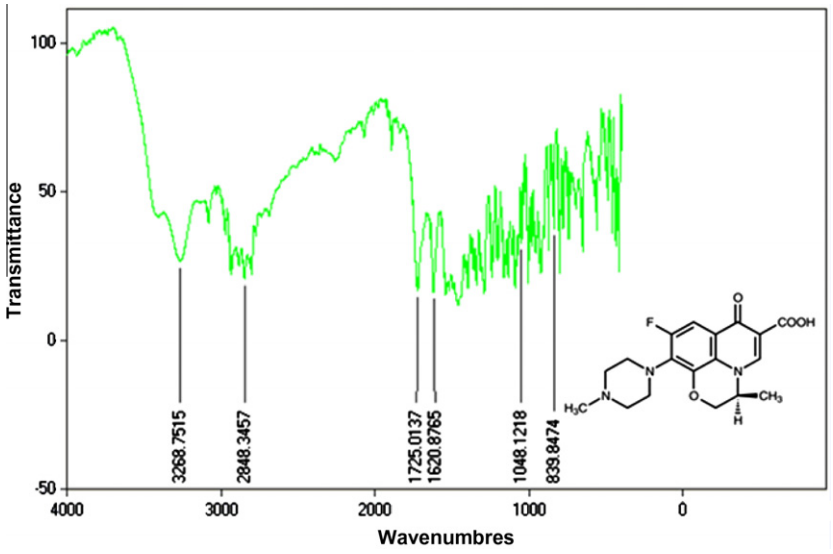

Figure 6 The structural formula and the FT-IR spectra of levofloxacin.

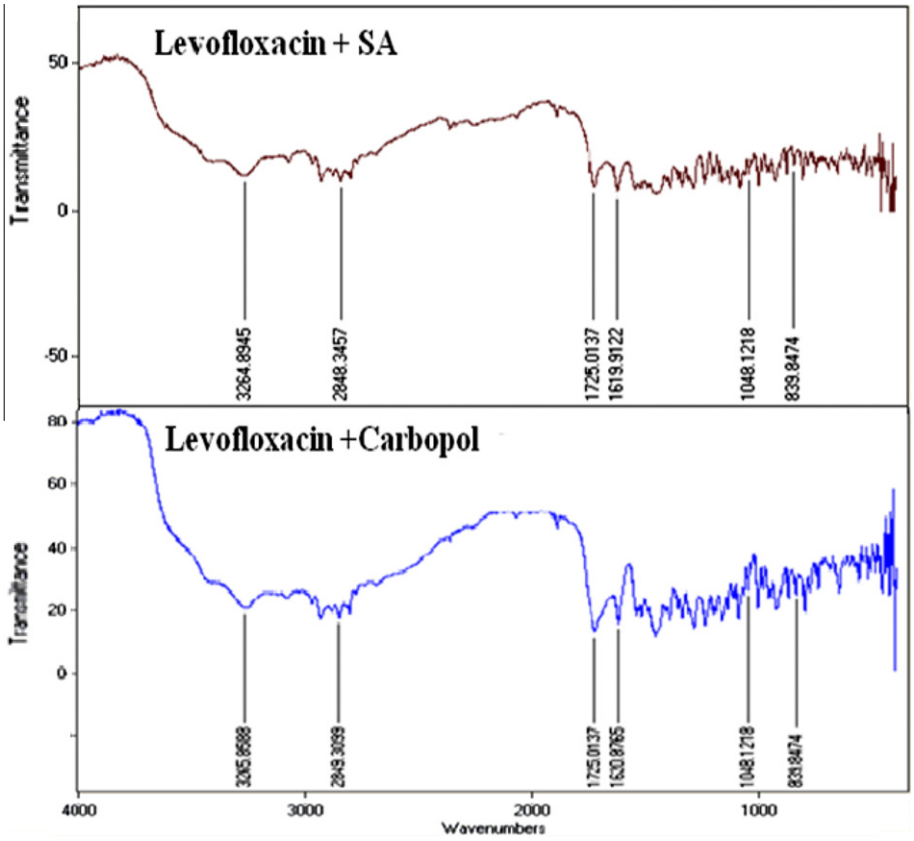

Figure 7 FT-IR spectra of altered levofloxacin in SA and carbopol.

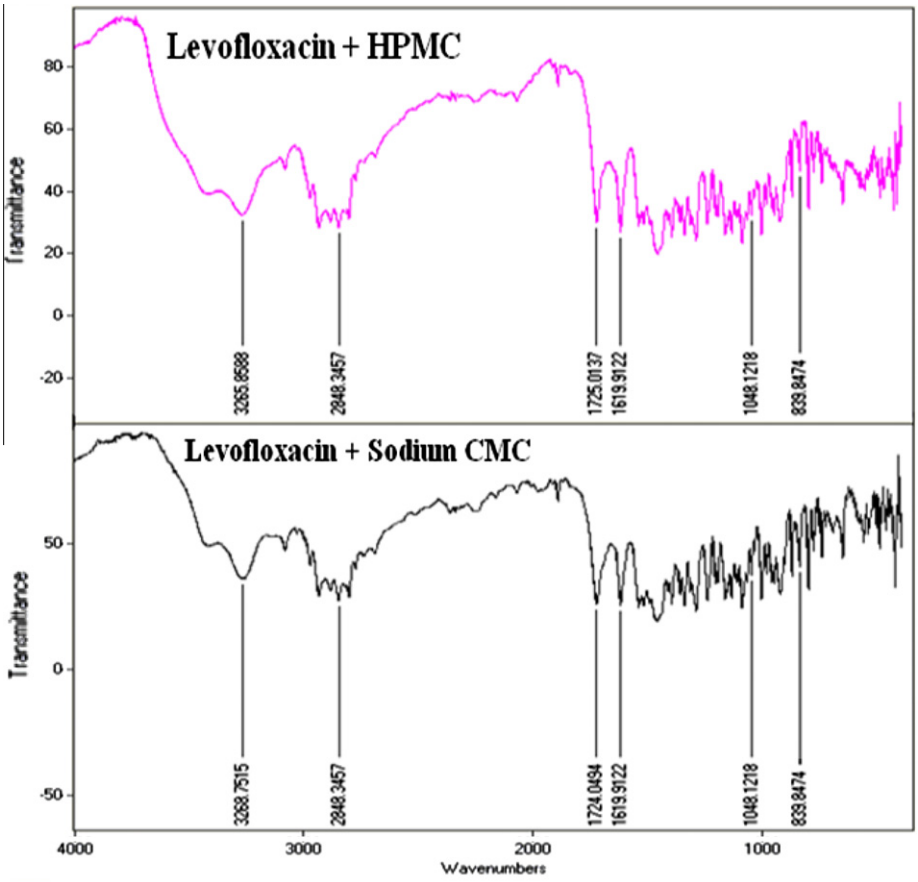

Figure 8 FT-IR spectra of altered levofloxacin in HPMC and sodium CMC.

Table 3 Some *in vitro* kinetic data models of prepared formulations.

Code of formulation	Zero order		First order		Korsmeyer–Peppas			Best fit model
	r	*k*	*r*	*k*	*r*	*k*	*n*	
F1	0.9424	29.3616	0.8330	1.9898	0.9825	44.7911	0.6384	Peppas
F2	0.9328	11.53	0.9835	15.52	0.9548	13.47	0.96	First order
F3	0.9818	3.7739	0.9584	0.460	0.9979	0.6659	0.97	Peppas
F4	0.7112	41.9714	0.9457	2.6951	0.9982	93.2712	0.0620	Peppas
F5	0.9785	20.6659	0.6825	1.3341	0.9938	29.6334	0.7320	Peppas
F6	0.9805	9.30	0.9055	14.59	0.9836	9.35	0.99	Peppas
F7	0.9918	33.5284	0.7951	2.1658	0.9846	40.8015	0.7663	Zero order
F8	0.9833	11.43	0.9824	15.43	0.9528	13.27	0.97	Zero order

r, Correlation coefficient; *n*, release exponent; *k*, kinetic constant.

with '*r*' values equal to 0.9982 and 0.9938, respectively. The value of the exponent *n* was calculated as an indicator of the drug transport mechanism. Formulation F8 having '*n*' values 0.97 indicates a case-II transport drug release mechanism (Siepmanna and Peppas, 2001). The increase in carbopol loading in formulation F4 decreased the *n* value from 0.97 to 0.062. Similar results were obtained by Aleksandra et al. (2009) for formulations containing carbopol. The '*n*' values between 0.5 and 1 have been observed for most of the formulations. This indicates that the drug release depends on swelling, erosion, and diffusion. The *n* value from the Korsmeyer–Peppas model for most of the formulations were between 0.6384 and 0.99 which confirms the non-Fickian/anomalous type of diffusion (Kandasamy and Veintramuthu, 2010), however, the formulation containing higher concentration of carbopol followed Fickian diffusion (Sam et al., 2007).

5. Conclusion

There were two principle objectives to this study. Firstly, to the develop NFRCDS by crosslinking gelatin shell. The data presented here have established that these prepared formulations

were highly effective by floating phenomena in order to target drugs to the stomach region, and to treat such *H. pylori* infections.

The second objective was to assess the effects of formulation variables. Such a new design may provide extended release to improve therapeutic efficacy and to provide extended residence time by floating behavior. Optimization of the floating phenomena for such porous filled capsules can be achieved either by slowing water penetration inside the formulation, or by improving the swelling properties of the dosage form. Further, these formulations were shown to be free from any chemical interaction. The results of *in vitro* experiment study demonstrated that such a new concept can be successfully applied for site specific drug delivery in the GI tract. In spite of such a new concept, challenges will remain as there is still scope for further optimization.

Acknowledgments

The authors would like to thank Chairperson, Padmashree Mrs. Fatma Rafiq Zakaria, Maulana Azad Education Trust, Aurangabad for providing research facilities. We are also thankful to Wockhardt Research Labs for providing gift sample of drug.

References

Aleksandra, P., Nebojsa, C., Svetlana, I., Svetlana, T., Zorica, D., Dragica, P., Radmila, P., 2009. Application of mixture experimental design in the formulation and optimization of matrix tablets containing carbomer and hydroxypropyl methylcellulose. Arch. Pharm. Res. 32, 1767–1774.

Alex, Kugel, Bret, Chisholm, Scott, Ebert, Michael, Jepperson, Laura, Jarabek, Shane, Stafslien, 2010. Antimicrobial polysiloxane polymers and coatings containing pendant levofloxacin. Polym. Chem. 1, 442–452.

Brahma, S.N., Kwon, Kim, H., 2000. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Rel. 63, 235–259.

Cavallaro, L.G., Egan, B., O'Morain, C., Di Mario, F., 2005. Treatment of *Helicobacter pylori* infection. Eur. Gastroenterol. Rev. 1, 56–59.

Chambina, O., Championb, D., Debraya, C., Rochat, G.M.H., Mesteb, M.Le., Pourcelota, Y., 2004. Effects of different cellulose derivatives on drug release mechanism studied at a preformulation stage. J. Control. Rel. 95, 101–108.

Chien, Y.W., 1992. Novel Drug Delivery Systems. Marcel Dekker, New York.

Davis, S.S., Stockwell, A.F., Taylor, M.J., Hardy, J.G., Whalley, D.R., Wilson, C.G., Bechgaard, H., Christensen, F.N., 1986. The effect of density on the gastric emptying of single and multiple-unit dosage forms. Pharm. Res. 3, 208–213.

Enrico, C.N., Marcello, C., Maria, A.Z., Filippo, C., Veronica, O., Rosalba, F., Spada, C., Cammarota, G., Gasbarrini, G., Gasbarrini, A., 2006. Levofloxacin-based triple therapy in first-line treatment for *Helicobacter pylori* eradication. Am. J. Gastroenterol. 9, 1985–1990.

Forman, D., Webb, P., Parsonnet, J., 1994. *Helicobacter pylori* and gastric cancer. Lancet 343, 243–244.

Gibaldi, M., Feldman, S., 1967. Establishment of sink conditions in dissolution rate determinations – theoretical considerations and application to non disintegrating dosage forms. J. Pharm. Sci. 56, 1238–1242.

Higuchi, T., 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. J. Pharm. Sci. 50, 874–875.

Higuchi, T., 1963. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145–1149.

Ivan, Donati, Sergio, Paolett, 2009. Material properties of alginates. In: Rehm, Bernd H.A. (Ed.), Alginates Biology and Applications. Springer-Verlag, Berlin/Heidelberg, pp. 2–53.

Jian, H.G., 2003. Carbopol Polymers for Pharmaceutical Drug Delivery Applications 3(6). <http://www.drugdeliverytech.com>.

Kandasamy, R., Veintramuthu, S., 2010. Formulation and optimization of zidovudine niosomes. AAPS Pharm. Sci. Tech. 11, 1119–1127.

Korsmeyer, R.W., Gurny, R., Doelker, E.M., Buri, P., Peppas, N.A., 1983. Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm. 15, 25–35.

Megraud, F., Lamouliatte, H., 1992. *Helicobacter pylori* and duodenal ulcers. Dig. Dis. Sci. 37, 769–772.

Muller-Lissner, S.A., Will, N., Muller-Duysing, W., Heinzel, F., Blum, A.L., 1981. A floating capsule with slow release of drugs: a new method of oral drug medication. Dtsch. Med. Wochenschr. 106, 1143–1147 (article in German).

Mulye, N.V., Turco, S.J., 1995. A simple model based on first order kinetics to explain release of highly water soluble drugs from porous dicalcium phosphate dihydrate matrices. Drug Dev. Ind. Pharm. 21, 943–953.

Nathalie, Rouge, Jean-Christophe, L., Ewart, C.T., Eric, Doelker, Pierre, Buri, 1997. Prevention of the sticking tendency of floating minitablets filled into hard gelatin capsules. Eur. J. Pharm. Biopharm. 43, 165–171.

Paolo, Colombo, Ruggero, Bettini, Patrizia, Santi, Peppas, N.A., 2000. Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. PSTT 3 (6), 198–204.

Peppas, N.A., 1985. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. 60, 110–111.

Pina, M.E., Sousa, A.T., 2002. Application of hydroalcoholic solutions of formaldehyde in preparation of acetylsalicylic acid gastro-resistant capsules. Drug Dev. Ind. Pharm. 28, 443–449.

Raymond, C.R., Paul, J.S., Marian, E.Q., 2009. Carboxymethylcellulose sodium. Handbook of Pharmaceutical Excipients, sixth ed. Pharmaceutical Press, UK, pp. 118–121.

Rosa, M., Zia, H., Rhodes, T., 1994. Design and testing *in vitro* of a bioadhesive and floating drug delivery system for oral application. Int. J. Pharm. 105, 65–70.

Sam, T., Mathew, S., Gayathri, Devi, Sandhya, K.V., 2007. Formulation and evaluation of ketorolac tromethamine-loaded albumin microspheres for potential intramuscular administration. AAPS Pharm. Sci. Tech. 8 (1), E1–E9 (Article 14).

Sarah, A., Molokhia, A., Himanshu, Sant, Jacquelyn, Simonis, Bishop, C.J., Burr, R.M., Bruce Gale, K., Balamurali, A.K., 2010. The capsule drug device: novel approach for drug delivery to the eye. Vis. Res. 50, 680–685.

Shan-Yang, Lin, Pei-Chin, Lin, 1992. Effect of acid type, acetic acid and sodium carboxymethylcellulose concentrations on the formulation, micromeritic, dissolution and floating properties of theophylline chitosan microcapsules. Chem. Pharm. Bull. 40, 2491–2497.

Sheth, P.R., Tossounian, J., 1984. The hydrodynamically balanced system (HBSE): a novel drug delivery system for oral use. Drug Dev. Ind. Pharm. 10, 313–339.

Shoufeng, Li, Senshang, Lin, Bruce, D.P., Haresh, M.L., Chien, Y.W., 2003. Effect of HPMC and carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int. J. Pharm. 253, 13–22.

Siepmanna, Peppas, N.A., 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose. Adv. Drug Del. Rev. 48, 139–157.

Takashi, I., Harumi, H., Masao, K., Masakazu, M., Hiroyuki, Y., 1998. Design and evaluation of a new capsule-type dosage form for colon-targeted delivery of drugs. Int. J. Pharm. 168, 31–40.

Thakkar, V.T., Shah, P.A., Soni, T.G., Parmar, M.Y., Gohel, M.C., Gandhi, T.R., 2008. Fabrication and evaluation of levofloxacin hemihydrate floating tablet. Res. Pharm. Sci. 3, 1–8.

Timmermans, J., Moes, A.J., 1990. How well do floating dosage forms float. Int. J. Pharm. 62, 207–216.

Washington, N., Washington, C., Wilson, C.G., Davis, S.S., 1986. What is liquid gaviscon? A comparison of four international formulations. Int. J. Pharm. 34, 105–109.

Wong, P.S.L., Edgren, D.E., Dong, L.C., Ferrari, V.J., 1996. Active agent dosage form comprising a matrix and at least two insoluble bands. US Patent 5,534,263.

Wong, P.S.L., Edgren, D.E., Dong, L.C., Ferrari, V.J., 1997. Banded prolonged release active agent dosage form. US Patent 5,667,804.

Ziyaur, Rahman, Kanchan, Kohli, Roop, K.K., Mushir, Ali, Naseem, A.C., Areeg, S.A.A., 2006. Characterization of 5-fluorouracil microspheres for colonic delivery. AAPS Pharm. Sci. Tech. 7 (Article 47).