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Der Pharmacia Lettre, 2010, 2(4): 384-392
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Formulation and development of gastroretentive multi-layer coated tablets containing Gatifloxacin against H.pylori infection

Shreeraj H. Shah[a]*, Jayvadan K. Patel[b], Nirav V. Patel[c]

[a*]*L.J. Institute of Pharmacy, Gujarat University, Ahmedabad- 382 210, Gujarat, India.*
[b] *Nootan Pharmacy College, North Gujarat Hemchandracharya University, Visnagar- North Gujarat, India.*
[c]*Anand College of Pharmacy, S.P. University, Anand- 388 001, Gujarat, India.*

ABSTRACT

Floating multi-layer coated tablets were formulated based on gas formation. The system consists of a drug containing core tablet coated with a protective layer (Hydroxy Propyl Methyl Cellulose-HPMC), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane, respectively. Eudragit RL 30D was chosen as a gas-entrapped membrane due high water permeability and low CO_2 permeability. The obtained tablets showed the buoyancy due to the CO_2 gas formation and the gas entrapment by polymeric membrane of Eudragit RL 30D. The effect of formulation variables on floating properties and drug release was investigated. The floating tablets using direct-compressed cores had shorter time to float and faster drug release than those using wet-granulated cores. The increased ratio of sodium bicarbonate to HPMC increased the drug release from the floating tablets while increasing coating level of gas-entrapped membrane increased floating lag time. Good floating properties and sustained drug release were achieved. These floating tablets seem to be a promising floating gastroretentive drug delivery system which can be targeted in stomach to eradicate H.pylori infection.

Keywords: Gatifloxacin, floating, multi-layer coated tablets, sodium bicarbonate, Eudragit RL 30D, floating lag time

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INTRODUCTION

The real challenge in the development of a controlled drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper

small intestine until all the drug is completely released in the desired period of time [1–2]. The residence of a drug delivery system in the upper part of the gastrointestinal tract (GIT) can be accomplished by several types of gastroretentive drug delivery systems, such as intragastric floating systems [3-5], swelling and expandable systems [6], bioadhesive systems [7], modified shape systems [8], high density systems [9], delayed gastric emptying systems [10] and low density super porous systems [11]. FDDS, also called hydrodynamically balanced system, is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. This technology is suitable for drugs with an absorption window in the stomach or in the upper part of the small intestine, drugs acting locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid. FDDS have a bulk density lower than the gastric fluid and thus remain buoyant in the stomach, without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly [12]. Gatifloxacin, the model drug for this study, is an 8-methoxyfluoroquinolone with *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The antibacterial action of Gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV, essential enzymes that are involved in the replication, transcription, and repair of bacterial DNA. The recommended adult oral dosage of Gatifloxacin is 200mg twice daily or 400mg daily. The solubility of the compound is pH dependent. The maximum aqueous solubility (40-60 mg/ml) occurs at a pH range of 2 to 5 [13, 14]. The bioavailability of Gatifloxacin is 96%. It is one of the drugs with absorption window, so its primary site of absorption is the stomach region. Research is also going on the various delivery approaches for Gatifloxacin. Motwani *et al* [15] has reported nanoparticles for ophthalmic delivery containing Gatifloxacin. Amal *et al* [16] has also reported Gatifloxacin biodegradable implant for treatment of experimental osteomyelitis. Recently, Gatifloxacin is proved to be one of the potential drugs against H.pylori infection, responsible for duodenal ulcers and various cytotoxic complications. H.pylori resides mainly in stomach region, specifically in the sub-region of the mucous layer in stomach [17]. So it demands prolonged and constant drug conc. at that particular site to eradicate the infection. This leads to the formulation of clinically acceptable sustained-release dosage forms of Gatifloxacin. The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. The local delivery of Gatifloxacin by this approach will also promote a fast and effective eradication of H.pylori rather than a conventional tablet containing Gatifloxacin.

In this study, a new reservoir-type, multi-layer coated tablet was formulated as a FDDS based on gas formation. The drug-loaded core tablets were prepared by direct compression or wet granulation method and consecutively coated with a protective layer of HPMC, a gas forming layer of sodium bicarbonate using HPMC as binder and a gas-entrapped membrane. The effect of the preparative parameters, e.g., core tablet preparation methods, amount of the gas forming agent layered onto the core tablets, and coating level of the gas-entrapped membrane, on the floating properties and drug release of the floating tablets were evaluated.

MATERIALS AND METHODS

Materials

Gatifloxacin was purchased from West-Coast Pharmaceuticals Ltd. (Ahmedabad, India), HPMC (Methocel K4M) was gifted by Colorcon Asia Pvt. Ltd. (Goa, India), aqueous colloidal

polymethacrylate dispersion Eudragit RL 30D was a gift sample from Roehm Pharma Polymers-Evonik Industries (Germany). All other ingredients were of analytical grade and kindly supplied by Purvi Chemicals (Ahmedabad, India).

Methods:

Formulation of Gatifloxacin floating tablets

The core tablets were prepared by a direct compression or a conventional wet granulation method. The core components consist of a drug (Gatifloxacin 200 mg per tablet), spray dried lactose (140 mg per tablet) and microcrystalline cellulose (140 mg per tablet). For direct compression, the core tablet excipients were mixed in a cube mixer for 10 min, followed by the addition of magnesium stearate (1% w/w) and Aerosil (1% w/w). The powder mixture was further mixed for 5 min and was compressed into tablets (diameter, 12.7 mm; biconvex; hardness, 5 kg/cm^2; average tablet weight, 500 mg) using an 8-station rotary tablet machine (Make: Pharmatech, Ahmedabad).

For wet granulation, the core tablet excipients were sieved and mixed in a mortar by geometric dilution technique. The mixtures were mixed with PVP K30 solution as a binder (10% w/w in distilled water) to obtain damp mass. The damp mass was granulated through sieve No. 14 (mesh size 1.41 mm) and dried at 60^{0}C in trey drier for 6 h. The dried granules were passed through sieve No. 18 (mesh size 1.00 mm) again and mixed with magnesium stearate (1% w/w) and Aerosil 200 (1% w/w) in the cube mixer for 5 min. The core tablets (diameter, 12.7 mm; biconvex; hardness, 5 kg/cm^2; average tablet weight, 500 mg) were compressed using an 8-station rotary tablet machine.

Coating of the core tablets

The core tablets were coated with three successive layers; an inner protective layer (HPMC), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane layer (aqueous colloidal polymethacrylate dispersion, Eudragit RL 30D), respectively. The protective layer was 5% w/w HPMC solution plasticized with PEG 6000 (10% w/w based on the solid content of HPMC). The coating level of protective layer was 2% w/w. For gas forming layer, sodium bicarbonate was incorporated into HPMC solution plasticized with PEG 6000 (10% w/w based on the solid content of HPMC) and then layered onto the core tablets. On a dry solid basis, the ratios of sodium bicarbonate to HPMC were 2.5:10, 5:5 and 10:2.5 w/w. The coating level of gas forming layer was 12% weight gain and the solid content of coating solution was kept constant at 10% w/w. The coating solution was sprayed onto the core tablets in a pan coater (Make: Riddhi, Ahmedabad). The conditions for layering protective and gas forming layers were given as follows: Batch size, 1 kg; preheating temperature, 50^{0}C; preheating time, 30 min; inlet temperature, 48^{0}C to 50^{0}C; outlet temperature, 38^{0}C to 40^{0}C; spray rate, 5 ml/min to 10 ml/min. The layered tablets were further dried in the coating chamber for additional 30 min at 50^{0}C. The prepared tablets were then removed from the coating chamber and stored in a closed container for further experiments. The two-layer coated tablets were subsequently coated with aqueous colloidal polymethacrylate dispersion (Eudragit RL 30D) to achieve a weight gain of 5% and 10% w/w to obtain the complete floating tablets. A plasticizer (Diethyl phthalate-DEP; 20% w/w based on polymer solids) was added into the colloidal polymer dispersions and the dispersions were gently stirred for at least 30 min prior to an appropriate dilution with purified water and

subsequent coating. The solid content of the coating dispersions was 15% w/ w. The coating conditions were as follows: batch size, 1 kg; preheating temperature, 50^0C; preheating time, 30 min; inlet temperature, 48^0C to 50^0C; outlet temperature, 39^0C to 41^0C; spray rate, 5 ml/min to 8 ml/min. The floating tablets were further dried in the coating chamber for 30 min after the coating was finished in order to evaporate the residual moisture in the polymeric coatings prior to storage.

In vitro evaluation of floating ability

6 tablets each containing 200 mg of Gatifloxacin were placed in 900 ml of 0.1 N HCl in vessels maintained at 37°C ± 0.5°C and stirred at 50 r/min in a US Pharmacopeia (USP) 24 type II dissolution test apparatus (Make: ELECTRO-DBK, Ahmedabad, India). The floating times were measured by visual observation.

In vitro drug release studies

The release of drug from the tablets was investigated. Studies were performed in triplicate using a USP 24 type II dissolution test apparatus with an agitation speed of 50 r/min in 0.1 N HCl maintained at 37°C ± 0.5°C. At appropriate time intervals, the samples were withdrawn and assayed spectrophotometrically at 292 nm wavelength (λmax) after filtration through Whatman filter paper and suitable dilutions. The methodology for *in vitro* dissolution was kept the same for all the batches prepared.

RESULTS AND DISCUSSION

Floating mechanism of floating tablets

Fig. 1 shows floating mechanism of the floating multilayer coated tablets. Upon contact with the acidic medium (i.e. 0.1 N HCl), the fluid permeated into the gas forming layer through the outer gas-entrapped membrane. Carbon dioxide was liberated via neutralization reaction and was entrapped in the polymeric membrane. Eudragit RL 30D is a highly water permeable polymer according to its hydrophilic content and quaternary ammonium groups in the structure [18]. It therefore hydrated faster and resulted in a faster gas generation. Consequently, the swollen tablets with a density less than 1.0 g/ml floated and maintained the buoyancy; therefore, the drug was released from the system. The floating sequence of the floating tablet at different times is shown in Fig. 2.

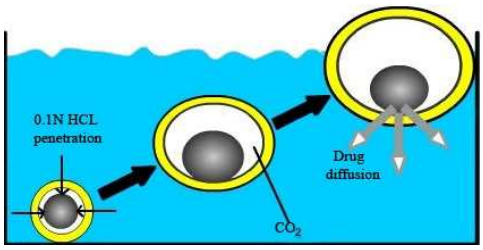
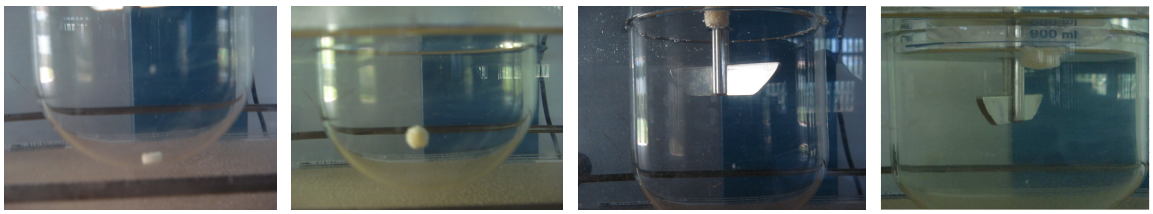


Fig. 1 Floating mechanism of a floating multi-layer coated tablet



A B C D

Fig. 2 Floating sequence in 0.1 N HCl of a floating multi-layer coated tablet using direct compressed core, $NaHCO_3$:HPMC; 10:2.5 w/w and 5% Eudragit RL 30D. (A: 0 min, B: 2 min, C: 3.5 min, D: after 10 hrs.).

Effect of formulation variables on floating properties and drug release

To obtain the floating tablets which can float in a few minutes after contact with gastric fluid and maintain the buoyancy for a long period with sustained release action, effect of formulation variables on the floating properties and the drug release such as a core preparation method, an amount of gas forming agent and a level of gas entrapped polymeric coating was investigated in this study.

Core preparation method

The floating tablets using direct-compressed cores significantly showed shorter time to float (floating lag time-Table 1) and faster drug release (Fig. 3). It might be explained by the different properties of the cores. The direct-compressed cores had very short disintegration time (less than 1 min) whereas the wet-granulated cores had long disintegration time (about 85 min). The rapid disintegration of the direct-compressed cores was due to the presence of disintegrating direct compression filler, microcrystalline cellulose. The slow disintegration of the wet-granulated cores was attributable to the presence of binder (PVP K30).

Table: 1 Floating properties of floating multi-layer coated tablets with diff. Cores and levels of gas forming agent with gas entrapped coating in 0.1 N HCL (n = 10)

Formulation batches	Floating lag time (Min ± SD)	Total floating time (h)
Direct compressed core		
$NaHCO_3$:HPMC; 10:2.5		
• 5% w/w Eudragit RL 30D	4.714 ± 0.180	8.3
• 10% w/w Eudragit RL 30D	7.217 ± 0177	8.8
$NaHCO_3$:HPMC; 5:5		
• 5% w/w Eudragit RL 30D	4.698 ± 0.442	9.1
• 10% w/w Eudragit RL 30D	7.561 ± 0.413	9.5
$NaHCO_3$:HPMC; 2.5:10		
• 5% w/w Eudragit RL 30D	4.840 ± 0.443	10.1
• 10% w/w Eudragit RL 30D	7.881 ± 0.295	10.4
Wet granulation core		
$NaHCO_3$:HPMC; 10:2.5		

• 5% w/w Eudragit RL 30D	4.854 ± 0.365	9.4
• 10% w/w Eudragit RL 30D	7.952 ± 0.611	9.8

Table 2 % Drug release of various types of core preparation containing $NaHCO_3$: HPMC; 10:2.5 with 5% w/w Eudragit RL 30D

Method of formulation	% Drug release at every hr												
	0	1	2	3	4	5	6	7	8	9	10	11	12
Direct compression	0	26.6	5701	82.0	84.2	86.4	90.5	91.8	92.7	93.4	96.6	99.4	102.2
Wet granulation	0	12.0	22.3	30.0	41.0	53.4	60.8	68.7	75.1	81.1	84.5	89.5	91.0

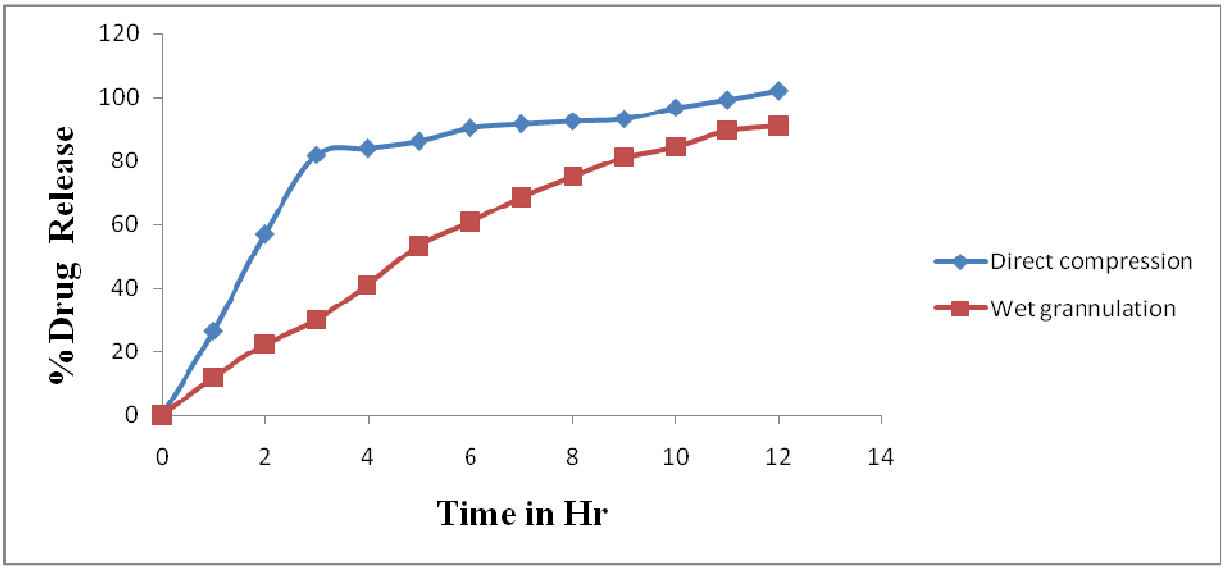


Figure: 3 Effect of the core preparation method of drug release of floating tablets ($NaHCO_3$: HPMC; 10:2.5 with 5% w/w Eudragit RL 30D)

Amount of gas forming agent

Here the drug release decreased with decreasing ratio of gas forming agent to HPMC (Fig. 4). HPMC seemed to play an important role to retard drug release. A faster and higher CO_2 generation caused by increasing of the level of effervescent agent [19] resulted in higher swelling of polymeric membrane according to a higher gas pressure and subsequent faster drug release. Additionally, the faster drug release from the floating tablets with higher amount of gas forming agent is probably explained by their higher porosity or volume inside the polymeric membrane. This may allow the liquid to dissolve the drug more easily, compared to the lower porosity generated from the tablets with low amount of a gas forming agent.

Table: 3 % Drug Release of Direct compression batch containing various proportions of $NaHCO_3$ and HPMC (Direct compressed core, 5% Eudragit RL 30D)

Proportion of $NaHCO_3$ and HPMC	% Drug Release at every hr												
	0	1	2	3	4	5	6	7	8	9	10	11	12
$NaHCO_3$:HPMC;10:2.5	0	28.3	57.4	85.0	88.4	92.5	95.0	96.2	97.4	98.0	99.1	99.9	101.8
$NaHCO_3$:HPMC;5:5	0	14.7	29.1	43.0	57.2	71.1	81.5	84.7	87.9	90.4	94.1	98.8	101.4
$NaHCO_3$:HPMC;2.5:10	0	8.5	16.8	25.0	40.2	58.9	70.0	73.7	78.1	82.0	88.6	95.4	100.7

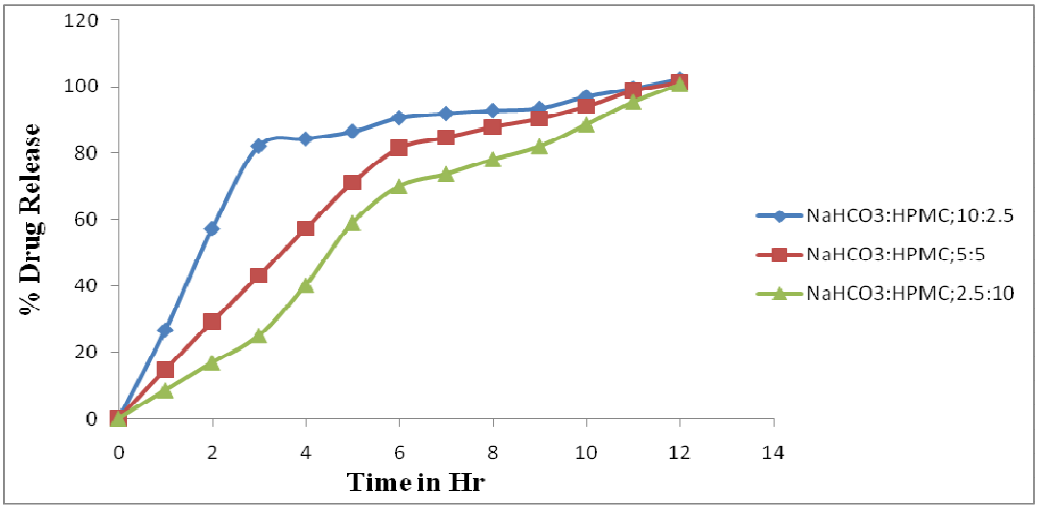


Fig: 4 Effect of $NaHCO_3$ layered onto the core tablets on drug release from floating tablets in 0.1 N HCl (Direct compressed core, 5% Eudragit RL 30D)

Level of gas-entrapped membrane coating

As expected, the floating lag time was longer with increased coating level of gas-entrapped membrane (Table 2) and was coated tablets in the different extent. The obtained results suggested that Eudragit RL 30D has a major influence on the floating properties of the coated tablets and indicated the low CO_2 permeability as gas could be entrapped for longer than 8 h, in all cases. However, the influence of the coating level on the drug release was less than the amount of gas forming agent but the floating lag time depended significantly on the coating level.

Table: 4 % Drug Release of Direct compression batch containing various proportions of $NaHCO_3$ and HPMC (Direct compressed core, 10% Eudragit RL 30D)

Proportion of $NaHCO_3$ and HPMC	% Drug Release at every hr												
	0	1	2	3	4	5	6	7	8	9	10	11	12
$NaHCO_3$:HPMC;10:2.5	0	18.8	38.8	55	67.1	79.8	90.0	92.3	94.1	95.0	97.3	98.9	101.8
$NaHCO_3$:HPMC;5:5	0	13.1	24.8	35	49.2	58.9	72	76.9	84.9	88	92.6	96.1	99.8

Fig: 5 a)

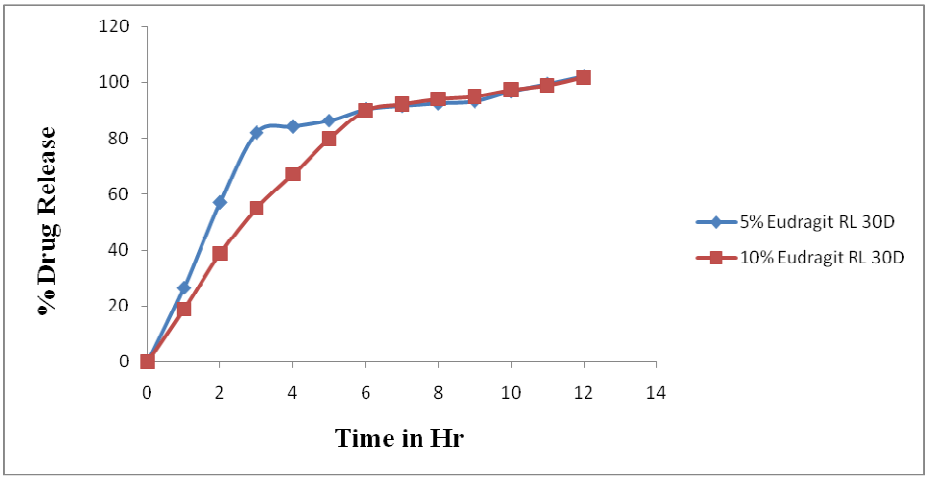


Fig: 5 b)

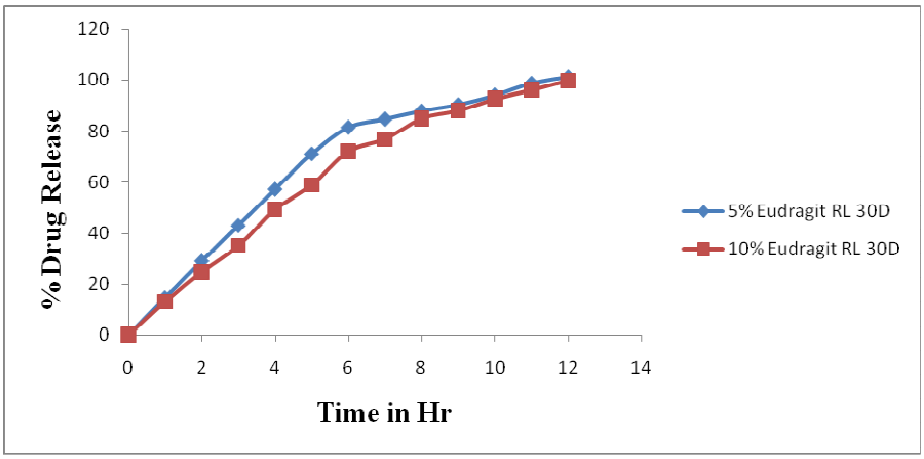


Fig: 5 Effect of Gas-entrapped membrane coating level on drug release (Direct compression core), a) $NaHCO_3$: HPMC; 10:2.5 w/w, b) $NaHCO_3$: HPMC; 5:5 w/w

CONCLUSION

The system consists of drug-containing core tablets coated with a protective layer, a gas forming layer and a polymeric membrane, respectively. The floating tablets using direct-compressed cores had shorter floating lag time and faster drug release than those using wet-granulated cores. Good floating properties and sustained drug release were obtained. The increased amount of a gas forming agent did not affect floating lag time but increased the drug release from the floating tablets while increasing coating level of gas-entrapped membrane increased floating lag time. The floating properties and the drug release from the floating tablets were dependent on the core preparation method, the amount of a gas forming agent (ratio of $NaHCO_3$ to HPMC) and the level of gas-entrapped membrane. The tablets with good floating properties (floating lag time

less than 8 min, floating time more than 8 h) and sustained drug release were obtained. These gastroretentive floating multi-layer coated tablets can be targeted in stomach in order to eradicate H.pylori infection to treat gastric ulcers.

Acknowlegement
The authors sincerely thank Colorcon Asia Pvt. Ltd. (Goa, India) for providing HPMC K4M, and Roehm Pharma Polymers-Evonik Industries (Germany) for providing Eudragit RL 30D sample. The authors are sincerly thankful to Dr.K.Pundarikakshudu (Director, L.J.Institute of Pharmacy and The L.J.Trust (Ahmedabad, India) for providing the laboratory facilities for the present work.

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