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PHARMACEUTICAL TECHNOLOGY

FORMUALTION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM CONTAINING CLARITHROMYCIN FOR *HELICOBACTER PYLORI*

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Abstract: Floating matrix tablets are designed to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. With this objective, floating dosage form containing clarithromycin as drug was designed for the treatment of *Helicobacter pylori*. Tablets containing hydroxypropylmethylcellulose (HPMC), drug and different additives were compressed using wet granulation and D-optimal design technique. The study shows that tablet composition and mechanical strength have great influence on the floating properties and drug release. Incorporation of gas-generating agent together with polymer improved drug release, besides optimal floating (floating lag time <30 s; total floating time >10 h). The drug release was sufficiently sustained (more than 8 h) and anomalous diffusion as well as zero-order was confirmed. Optimization of the evaluating parameters with 'design expert' software was employed to get final optimized formulation. The optimized formulation was obtained using 62.5% clarithromycin, 4.95% HPMC K15M, 18.09% HPMC K4M, 12.96% sodium bicarbonate which gave floating lag time < 30 s with a total floating time > 10 h, *in vitro* release profile very near to the target *in vitro* release profile and follows anomalous diffusion as well as zero order pattern of release.

Keywords: floating tablets; D-optimal design; optimization

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route of administration has received the more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other routes. Development of a successful oral controlled release drug delivery dosage form requires an understanding of three aspects: (1) gastrointestinal (GI) physiology (2) physiochemical properties of the drug and (3) dosage form characteristics (1,2).

Novel oral controlled dosage form that is retained in the stomach for prolonged and predictable period is of major interest among academic and industrial research groups. One of the most feasible approaches for achieving prolonged and predictable drug delivery profile in the GI tract is to control gastric residence time (GRT). Dosage form with prolonged GRT or gastro-retentive dosage form (GRDF) provides an important therapeutic option (3).

Various approaches for preparation of gastro-retentive drug delivery system include floating systems, swellable and expandable systems, high density systems, bioadhesive systems, altered shape systems, gel forming solution or suspension system and sachet systems. Among these, the floating dosage form has been used most commonly. The floating systems include gas-generating systems, non-effervescent systems and raft forming systems (4-5).

Helicobacter pylori is a prevalent human-specific pathogen, which is now believed to be the causative bacterium for chronic gastritis, peptic ulcer and adenocarcinoma, one of the most common forms of cancer in humans (6) and its eradication requires high concentration of drug within the gastric mucosa for long duration. Thus, floating oral delivery system is expected to remain buoyant in a lasting way upon the gastric contents and enhance bioavailability of all drugs which are well absorbed from the GI tract.

Clarithromycin is an advanced generation macrolide antibiotic used in treatment of *H. pylori* and respiratory infection. In controlled release formulation, if the concentration of antibiotic is maintained above MIC, drug resistance can be reduced. Clarithromycin exhibits concentration dependent pharmacodynamics, where peak concentration/MIC ratio of approximately 10 has clinical

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success. Therefore, high drug level should be the goal of the therapy. This is best achieved by using gastric floating drug delivery system. Short elimination half-life of clarithromycin (3-6 h), makes it a useful candidate for controlled release dosage form and stability in the acidic environment is useful for gastro-retentive drug delivery system (7,8).

The objective of this study include (1) developing floating drug delivery system containing drug and polymer filler by using D-optimal design, (2) study on the effect of polymer filler and processing parameter on floating and drug release behavior of the system and (3) selection of the best formulation based on optimization techniques using evaluation parameters like floating lag time, total floating time and release profile.

EXPERIMENTAL

Materials

Clarithromycin donated by Cipla Pharma Private Ltd., Vapi, India. HPMC K4M (nominal viscosity of 2% aqueous solution 4000 cP) and HPMC K15M (nominal viscosity of 2% aqueous solution 15000 cP) were obtained from Zydus Cadila, Ahmedabad. Sodium bicarbonate was procured from Loba Chemie Private Ltd., Mumbai. Folin-Ciocalteu's phenol reagent was procured from

Table 1. Formulations of D-optimal design

FORMULATION CODE	DRUG (%)	HPMC K4M (%)	HPMC K15M (%)	$NaHCO_3$ (%)	Mg stearate (%)	TALC (%)
DF – 1	62.5	23.00	01.50	11.50	0.5	1
DF – 2	62.5	11.50	11.50	13.00	0.5	1
DF – 3	62.5	23.00	00.00	13.00	0.5	1
DF – 4	62.5	00.00	23.00	13.00	0.5	1
DF – 5	62.5	13.00	13.00	10.00	0.5	1
DF – 6	62.5	00.00	23.00	10.00	0.5	1
DF – 7	62.5	03.00	23.00	10.00	0.5	1
DF – 8	62.5	23.00	00.00	13.00	0.5	1
DF – 9	62.5	23.00	03.00	10.00	0.5	1
DF – 10	62.5	06.12	17.63	12.25	0.5	1
DF – 11	62.5	17.62	07.63	10.75	0.5	1
DF – 12	62.5	07.63	17.63	10.75	0.5	1
DF – 13	62.5	23.00	03.00	10.00	0.5	1
DF – 14	62.5	03.00	23.00	10.00	0.5	1

Table 2. Optimized Formulations

FORMULATION CODE	DRUG (%)	HPMC K4M (%)	HPMC K15M (%)	$NaHCO_3$ (%)	Mg stearate (%)	TALC (%)
OF – 1	62.5	9.73	13.28	12.98	0.5	1
OF – 2	62.5	4.95	18.09	12.96	0.5	1
OF – 3	62.5	11.37	11.70	12.93	0.5	1
OF – 4	62.5	4.66	18.44	12.90	0.5	1
OF – 5	62.5	8.28	14.88	12.84	0.5	1
OF – 6	62.5	5.63	17.45	12.92	0.5	1
OF – 7	62.5	4.90	18.19	12.90	0.5	1
OF – 8	62.5	2.63	20.47	12.90	0.5	1
OF – 9	62.5	3.06	20.12	12.82	0.5	1

Spectrochem Pvt. Ltd., Mumbai. All other chemicals used were of analytical reagent grade, available commercially and used as such without further processing.

Methods

Formulations were developed following a 'D-optimal design' after setting the individual excipient ranges obtained through preformulation

Table 3. Model statistics.

Response*	Model equation	F-value	P<F	LOF	R^2	Predicted R^2	PRESS
f_2	f_2 = +9.84241*K15 + 8.27736 * K4 +35.91900 * SB -0.30751 * K15 *K4 -2.16607 * K15 *SB -1.99641 * K4* SB+0.031493* K15 *K4*SB	22.94	0.0001	11.31	0.9101	0.7124	125.55
CDR1	CDR1 = +4.78413 * K15 +4.92589 * K4 +17.05815 * SB -0.23599* K15 * K4 -1.06631 * K15* SB -1.07467 * K4 * SB +0.020428 * K15 * K4 * SB	9.71	0.0042	4.17	0.8008	0.4607	20.22
CDR2	CDR2 = +9.56427 * K15 +7.84355 * K4 +33.7007 * SB -0.14534* K15* K4 -2.13702* K15 * SB -1.98264 * K4 * SB +0.012285* K15* K4 * SB -1.33812E-003 * K15 * K4 * (K15-K4)	95.26	0.0001	4.55	0.9807	0.9385	5.96
CDR3	CDR3 = +5.82267 * K15 +1.88438 * K4 +7.98100 * SB -0.097146 * K15 * K4 -0.60115* K15 * SB -0.38241* K4 * SB -9.74154E-004 * K15 * K4 * (K15-K4)-0.010183* K15 * SB * (K15-SB)	318.88	0.0001	1.50	0.9942	0.9695	1.78
CDR5	CDR5 = +127.60808 * K15 +133.31939* K4 – 1328.67626 * SB +0.089179 * K15 * K4 +64.11500 * K15 * SB +63.90181 * K4*SB -3.22817 * K15 * K4 * SB +2.06490E-003* K15 * K4 * (K15-K4) -1.60225* K15 * SB * (K15-SB) -1.62244 * K4 * SB * (K4-SB)	78.44	0.0004	N/A	0.9817	N/A	N/A
CDR8	CDR8 = +7.44218 * K15 +4.41474 * K4 +21.2600 * SB -0.12677* K15 * K4 -1.26491 * K15 * SB -1.00371 * K4 * SB +0.013589* K15 * K4 * SB -3.45549E-003 * K15 * K4 * (K15-K4)	20.48	0.0009	4.47	0.9129	0.7351	53.98
DLE	DLE = +4.95035 * K15 +5.82019 * K4 +11.93082 * SB +0.11498 * K15 * K4 -0.55677* K15 * SB -0.64143* K4 * SB -0.012373 * K15 * K4 * SB	20.64	0.0004	2.78	0.9006	0.7805	31.86
WV	WV = -21.21323 * K15 -21.20503 * K4+224.7311 SB -0.012767 * K15 * K4-10.83175 * K15 * SB-10.83019 * K4* SB+0.54001 * K15 * K4 * SB -1.79986E-004 * K15 * K4 * (K15-K4) +0.26962 * K15 * SB * (K15-SB) +0.26949* K4 * SB * (K4-SB)	1.32	0.4221	N/A	0.1812	N/A	N/A
FLT	FLT = +62.45293 * K15 +48.88813* K4 – 465.930 * SB +0.20617 * K15 * K4 +21.82028 * K15 * SB +22.36018 * K4 * SB -1.2235 * K15 * K4 * SB -0.62911* K15 * SB * (K15-SB) -0.57842* K4 * SB * (K4-SB)	5.32	0.0410	3.99	0.7268	-2.4689	131.82

* f_2 = FDA similarity factor; CDRx = Cumulative % drug released at 'x'th hour; DLE = Drug loading efficieny; WV= weight variation; FLT = Floatation lag time

Table 4. Predicted, target and obtained values of the response parameters of the optimized formulations

Response parameter	Optimized Formulation Code					
	OF – 2			OF -7		
	Predicted	Target	Obtained	Predicted	Target	Obtained
CDR 1 h (%)	17.22	20	17.74333	17.22	20	17.58
CDR 2 h (%)	26.68	30	28.76667	26.68	30	28.52
CDR 3 h (%)	34.71	42.5	38.66	34.71	42.5	38.79333
CDR 5 h (%)	54.06	57.5	56.69667	54.06	57.5	56.75333
CDR 8 h (%)	80.36	80	81.59	80.36	80	81.37333
FLT (s)	24	<30	23	24	<30	25
TFT (h)	>10	>10	>10	>10	>10	>10

studies (9,10). By using this design and taking three formulation variables viz. percentage of HPMC K4M, percentage of HPMC K15M and percentage of $NaHCO_3$ as factors of the design, we developed a series of formulations (DF=Designed formulation) mentioned in Table 1.

Table 2 contains optimized formulations (OF). They were obtained by subjecting the response parameters to the statistical analysis like ANOVA mentioned in Table 3, 4 and numerical optimization using the software 'Design Expert' (10).

Tablet preparation

Floating matrix tablets containing clarithromycin were prepared by wet granulation technique using varying concentrations of different grades of polymers with sodium bicarbonate.

Polymers and clarithromycin were mixed homogeneously using glass mortar and pestle. Isopropyl alcohol was used as granulating agent. Granules were prepared by passing the wet coherent mass through a BSS # 16 sieve. The granules were dried in hot air oven at a temperature of 60°C. Dried granules were sieved through BSS # 20/44 sieves and mixed with sodium bicarbonate used as gas generating agent and lubricated with magnesium stearate and talc just 4-5 min before compression.

Lubricated granules were compressed into tablets using Rimek Minipress-I rotary tablet machine to obtain tablets of desired specifications.

Weight variation and hardness

Weight variation test was done according to USP and hardness was measured with Monsanto hardness tester.

Buoyancy / Floating test

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remained buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of floatation i.e. as long the dosage form remains buoyant is called Total Floating Time (TFT).

Tablet density

Tablet density is an important parameter for floating tablets. The tablet will float only if its density is less than that of gastric fluid (1.004). Density (d) was determined using the relationship $d = m/v$ where $v = \pi r^2 h$.

***In vitro* release study**

The *in vitro* release study for all the formulations were carried out by USP Dissolution Test Apparatus Type-II. The temperature of the dissolution medium (0.1 M HCl, 900 mL) was maintained at 37°C ± 1°C with a stirring rate of 50 rpm. This study was done for 8 h. The tablet was placed inside the dissolution vessel. At time of 15, 30, 60, 120 and 180 min 6 mL of samples were

withdrawn, at time of 240, 300 and 360 min 3.5 mL whereas after 420 and 480 min 2.5 ml of samples were withdrawn, respectively. The volume of dissolution fluid was adjusted every time to 900 mL.

Samples were suitably diluted with 2 mL Folin-Ciocalteu's phenol reagent (diluted to 1:2 with distilled water) and 2 mL of 20% sodium carbonate solution and 0.1 M HCl up to 10 mL and assayed spectrophotometrically at λ=760 nm in a double beam UV and visible spectrophotometer (Shimadzu UV 1700) against reagent blank. The drug concentration was calculated using standard calibration curve (11).

Mechanism of release

The mechanism of release was determined by fitting the release data to the various kinetic equations such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas and finding the R^2 values of the release profile corresponding to each model (12,13).

Optimization of the final formula:

The final optimized formula was found after analyzing the response variables (f_2, CDR1, CDR2, CDR3, CDR5, CDR8 corresponding to the cumulative % drug released at the specified time, DLE, FLT) using Design-Expert software following the D-optimal experimental design. The ANOVA study of each of the response variables yielded the best fitting polynomial model for that variable (Table 3, 4). Only those models were considered which had a high F-value corresponding to $p < 0.05$. Repeating this procedure for all the variables yielded 9 polynomial models which were solved simultaneously by numerical methods keeping the target values as given in Table 5. The target for f_2 and DLE were set at maximum, CDR values as per the dissolution points obtained for the marketed sustained release product (URCLAR), which is in consonance with the profile desirable for the pharmacokinetics of the drug, and FLT was set at minimum for optimization. The predicted, target and observed values for the predicted formulations are also shown in Table 5. Calculating % error in observed values w.r.t predicted and target values assessed the robustness of the predictions (data not shown). The closest matches were selected as the final optimized products (Table 5).

RESULTS AND DISCUSSIONS

The tablets were prepared by wet granulation method following extensive preformulation studies to select the appropriate formulation components (mainly the polymers) and processing factors. The optimization study was conducted following the D-optimal design (Table 1) after fixing the processing parameters and finally selecting two grades of HPMC (K4M and K15M) to provide sufficient swelling as well as drug release retardation and sodium bicarbonate was selected as the suitable gas generating agent to reduce floating lag time and to provide sufficient buoyancy to the tablets.

Weight variation and assay

The percentage weight variation of each tablet from average weight was less than 5%, which proved good uniformity. The assays for drug content were found uniform among different batches of floating tablets and ranged between 90% and 110%.

Weight variation was studied as a function of polymer fillers and sodium bicarbonate quantity (%) in the tablet formula. The statistical model generated for weight variation study (WV; Table 4) indicated that uniform tablets could be obtained at relatively lower levels of HPMC K4M and K15M and at higher levels of sodium bicarbonate, presumably due to the better flow properties of the mix at higher bicarbonate levels (negative coefficients for K4 and K15 and comparatively higher positive coefficients of SB; Table 4). However, the variation in bicarbonate level was too narrow (10-13%, w/w) and so was the overall variation in weight among the formulations. This further explains the reason for not getting a highly validated model for WV in Table 4.

Hardness

The hardness of all formulas was kept at 4 – 6 Kg/cm^2.

Buoyancy / Floating test

The tablet floating lag time (FLT) was found to be less than 30 s and total floating time more than 10 h.

The floating lag time may be explained as a result of the time required for dissolution medium to penetrate the tablet matrix and develop the swollen layer for entrapment of CO_2 generated in situ. The tablet mass decreased progressively due to liberation of CO_2 and release of drug from the matrix. On the other hand, as solvent front penetrated the glassy polymer layer, the swelling of HPMC K4M and K15M caused an increase in volume of the tablet. The combined effect is a net reduction in density of the tablets, which prolongs the duration of floatation beyond 10 h.

The relative influence of tablet excipients on floating lag time may be explained in the light of FLT model in Table 4. Both the swelling polymers

(HPMC K4M and K15M) appeared to prolong the lag time (positive coefficients of K4 and K15 in FLT model equation), while sodium bicarbonate appeared to reduce the lag time (negative coefficient of SB in FLT model) as expected. However, the influence of sodium bicarbonate was found to be more important which is evident from higher coefficient value for SB (approx. 466) compared to K4 and K15 (approx. 62 and 49, respectively). This is in perfect agreement with release rate and mechanism observed (discussed later), since the polymers did not swell initially, but helped in keeping the tablet afloat during the late hours of dissolution.

Tablet density

The tablet density was found to be uniform among different batches of floating tablets and ranged from 0.93 to 0.96 g/cm^3.

The tablet density is less than gastric fluid both before and after ingestion so the tablets float on the surface of the gastric fluid for as long as 10-12 h.

***In vitro* release profile**

The primary objective of the study was to design a floating tablet of the high drug dose of clarithromycin with a release profile sufficient to maintain adequately high local/systemic concentration. Preliminary formulations with various polymers, either alone or in combination, yielded a wide variety of release profiles (data not shown) to obtain an idea of the range and type of polymers to be used in the final formulation design. Based on such studies, HPMC K4M and HPMC K15M were selected as release modifier polymeric fillers and sodium bicarbonate as the float accelerator. Maximum and minimum levels of each ingredient were thus fixed as follows to set-up a D-optimal mixture design for optimization of release profile and other tablet characteristics. The drug was kept fixed at its dose level (62.5% w/w).

Ingredient	Level	
	Max.	Min.
HPMC K4M	23	0
HPMC K15M	23	0
Sodium bicarbonate	13	10

A rigorous study of their dissolution profile yielded some insight into the effect of polymeric fillers and gas generating agent on release profile of the formulations.

From the release profiles (Figures 1 – 6), it could be easily visualized that the variation of polymers from 0 – 23% of the formula weight varied drug release approx. 5 – 15%. From Figure 1, the effects of HPMC K4M and K15M could be observed at constant sodium bicarbonate level. The presence of HPMC K15M increased the release rate and extent slightly compared to HPMC K4M (DF3 vs. DF4, Figure 1, Table 1). This may be further inferred from the model equations for release parameters (CDR1 – CDR8; Table 3, 4), where the coefficients of HPMC K15M term are almost equal or greater than those of HPMC K4M term (at 1st, 2nd, 3rd and 8th hour release models). The same trend is observable from Figure 2 between DF6 and DF8. In general, this release promoting effect of HPMC K15M is observable for all the formulations, though the concurrent presence of HPMC K4M reduces the effect to variable extent depending on its level. Thus, in all the formulations containing relatively higher % of HPMC K15M, the release was higher, viz., DF4>DF1>DF3 (Figure 1), DF6>DF7>DF5> DF8 (Figure 2), DF10>DF12>DF11 (Figure 3) and DF14>DF13 (Figure 4). Similar profiles are observed, though in a much smaller extent (due to closeness of the formulations) in case of the optimized formulations OF1 – OF9 (Figure 5, 6). These findings might be explained in the light of the difference in molecular weight of the two varieties of HPMC. HPMC K15M, being of higher molecular weight, forms gel of higher viscosity (ca. 15000 cP) compared to HPMC K4M (nominal viscosity ca. 4000 cP). However, due to higher molecular weight, the polymer chains are bulkier in K15M leading to less flexibility and hence more time is required for polymer-solvent interaction and polymer chain relaxation. Consequently, the polymer chain unwinding is delayed in case of HPMC K15M compared to HPMC K4M, thereby leading to reduced gelling rate for the former variety, as a result of which the effective diffusion rate of the drug through the matrix containing higher % of HPMC K15M is more prone to higher drug release.

Further, no characteristic trend can be mentioned for dissolution up to 1 h (CDR1 model; Table 3, Figures 1 – 6). This may be due to the time taken for both the polymers in tablet matrix to get hydrated before changing from glassy to rubbery state. Thus, during the first hour of dissolution, there was no significant polymer chain relaxation due to which a rate controlling gel barrier could not be formed. Most of the sodium bicarbonate present on the outer layer of the tablet was involved in reaction with acidic medium. Thus, during this period channels for later absorption of solvent were being formed along with liberation of CO_2 that imparted initial buoyancy to the tablets. This also explains the absence of any lag phase in the release profile. Had

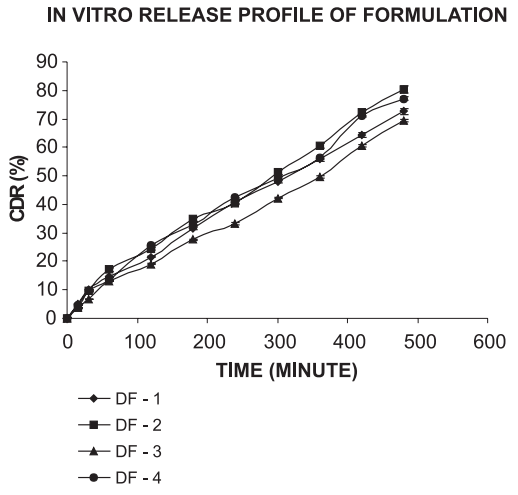

Figure 1. In vitro release profile of designed formulations DF1–DF 4.

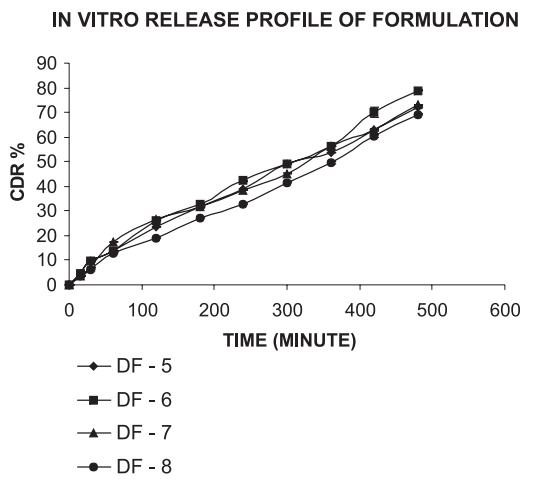

Figure 2. In vitro release profile of designed formulations DF5–DF8.

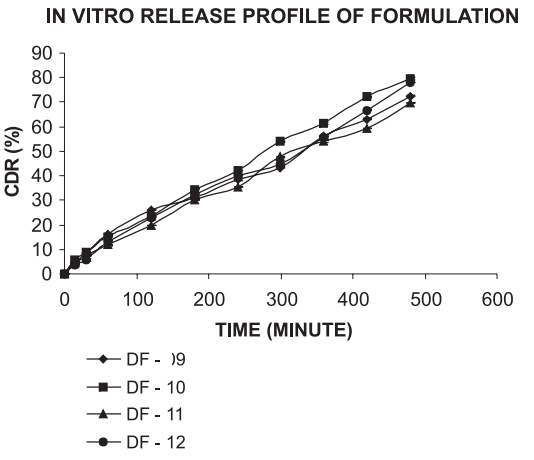

Figure 3. In vitro release profile of designed formulations DF9–DF12.

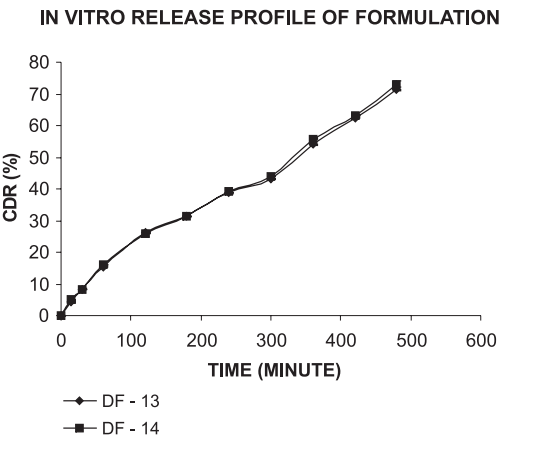

Figure 4. In vitro release profile of designed formulations DF13–DF14.

there been any immediate gel formation, there would have been a distinct lag-time in release.

Mechanism of release

The R^2 values of Korsmeyer-Peppas release as well as R^2 values of zero order release pattern for all formulations were near one. The n value of Korsmeyer-Peppas model of all formulations was between 0.70 and 0.85. Therefore, the most probable mechanism that the release patterns of all formulations followed was non-fickian diffusion or anomalous diffusion (5) wherein the drug release mechanism is controlled by both diffusion as well as polymer relaxation process. Since no lag-time was observed in the dissolution of any of the developed formulations, it may be inferred that the swellable polymers could not turn into gel immediately in contact with dissolution fluid, thereby giving an initial higher release rate from the tablets. However, once the gel barrier is established around the tablet, the rate of gel barrier progression became the rate-limiting factor by modulating the drug diffusibility. The rate of drug permeation out of the matrix is supposed to be proportional to the rate of solvent entry and broadening of the diffusion path length due to swelling of the matrix as a result of polymer

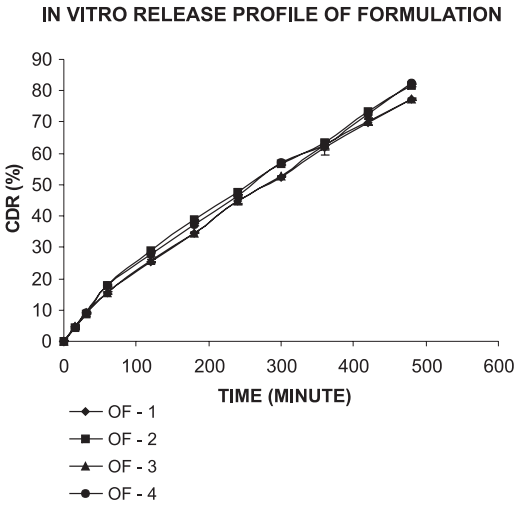

Figure 5. In vitro release profile of optimized formulations OF1-OF4.

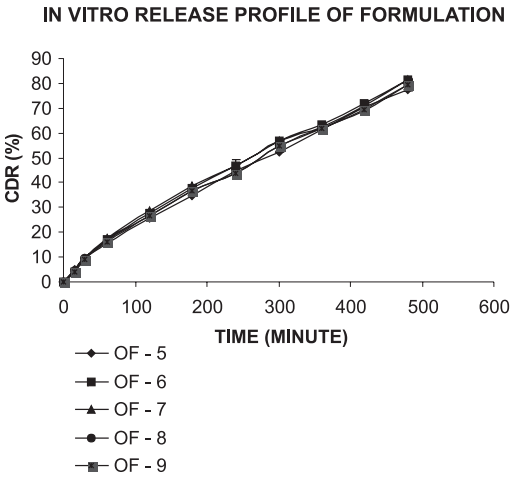

Figure 6. In vitro release profile of optimized formulations OF5-OF9.

hydration and subsequent strand relaxation. That this mechanism was operative throughout the dissolution period for all the formulations is evident from the closeness of R^2 values to 1, as also from the straightness of the dissolution curves (Figures 1 – 6). These findings are in line with other authors (16) who used HPMC based matrices.

Final formula optimization

Having investigated the tablet characteristics statistically by generating suitable regression models for all the quantified tablet parameters, the next logical step followed was to utilize this information to develop the final optimized tablet

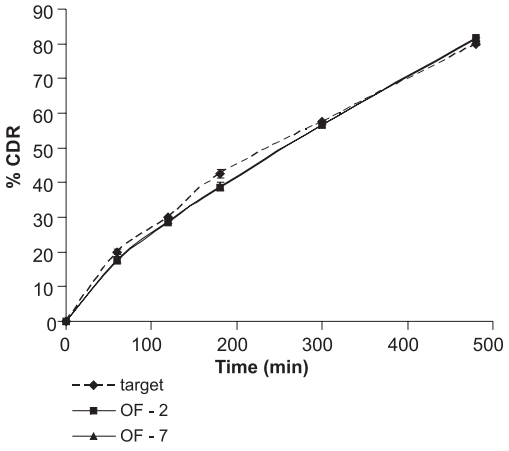

Figure 7. Deviation of Optimized formulation from target release profile.

with desired release profile and prolonged floatation capability. Since all the investigated tablets had a total floating time of >10 h, this property was already optimized and was not studied further. However, release profile needed to be fine-tuned to achieve a uniformly prolonged release pattern. In the absence of any pharmacopoeial guideline for extended release clarithromycin, we choose the release profile of a market leader brand (URCLAR*OD) as the target profile (dashed line in Figure 7, Table 5). The closeness of release profiles can be judged by FDA recommended f_2 (similarity factor) (17) that should lie between 50-100 for adequate similarity of profile. We also compared the % CDR at predetermined time points extending over the entire dissolution period up to approx. 80% of drug release. A further objective of optimization was to minimize the floating lag time (FLT) to less than 30 s. Simultaneous numerical solution of all the model equations (Table 3, 4), setting the target objectives as per Table 5 predicted the final optimized formulations (OF1 – OF9; Table 2).

The optimization process (18-20) also predicted corresponding values for the other tablet parameters modeled. The release profiles of the optimized formulations were experimentally verified. It was found that out of the nine formulations predicted and experimentally studied, OF2 and OF7 (Table 2) demonstrated the closest release profile and minimum floating lag times compared to the target and predicted values of the tablet characteristics (Table 5, Figure 7). Thus, the optimized tablet could be formulated with 62.5% drug, 4.95% HPMC K15M, 18.09% HPMC K4M

and 12.96% sodium bicarbonate which gave a floating time of >10 h, floating lag time of <30 s and release profile equivalent to the market leader brand.

Hence a very robust formulation could be developed from scratch having desired characteristics where multiple targets could be optimized using only 23 (14 + 9) formulations. Further, the developed models might be reused without going for a new F&D endeavor to optimize the product to any desired release profile (whether OD or BD tablets). Additionally, the empirical models generated also helps in explaining the influence of excipients on tablet parameters without the need of extensive "change one-factor at-a-time" approach.

CONCLUSION

From the data obtained, it can be concluded that:

- Hydrodynamically Balanced Tablet of an antibacterial drug clarithromycin can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability.
- Among the polymers used to improve the gastric residence, cellulose polymers (HPMC K4M, HPMC K15M) showed better control over drug release.
- Formulated tablets gave satisfactory results for various physicochemical evaluation for tablets like tablet dimensions, hardness, weight variation, tablet density, floating lag time, content uniformity and *in vitro* drug release.
- Formulation OF-2 and OF-7 gave better-controlled drug release in comparison to other prepared formulation.
- Formulated floating tablets best fitted to Korsmeyer-Peppas model and zero order kinetics.
- Further it is concluded that, by the application of optimization technique, optimized formulation can be obtained with minimum expenditure of time and money.
- Thus the objective of formulating a floating dosage form of clarithromycin by using optimization technique has been achieved.

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