Formulation and optimization of floating matrix tablets of clarithromycin using simplex lattice design

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Abstract: The purpose of the present study was to prepare floating matrix tablets of clarithromycin employing simplex lattice design. Hydroxypropyl methylcellulose (HPMC) and Ethyl Cellulose (EC) were used as matrix forming agents; sodium bicarbonate and citric acid as effervescence producing agents. Simplex lattice design was used as optimization technique employing three independent formulation variables viz. concentration of HPMC (X_1), Citric Acid (X_2), EC (X_3) whereas floating lag time, $t_{50\%}$, $t_{90\%}$, and MDT (Mean Dissolution Time) were the response (dependent) variables. Seven formulations (F1-F7) were prepared and evaluated for dissolution studies, floating characteristics, weight variation, hardness, thickness, friability.$t_{50\%}$ of the formulations was found to be ranging from 317±2.54 to 522±2.39 minutes. The $t_{90\%}$ and MDT of the tablets were found to be ranging between 659.65±1.89 to 967.35±1.67 minutes and 527.20±1.22 to 846.78±2.61 minutes respectively. Total floating time of the formulations was more than 12 hours and the drug content was in the range of 98.54±0.46 to 99.92±0.32. The amount of both HPMC and EC were found to play a dominating role in controlling the release of the drug from the formulation whereas ratios of sodium bicarbonate and citric acid were showing significant effect on the floating lag time. The release exponent (n) from Korsmeyer-Peppas model was found to be between 0.62 and 0.75 indicating non-Fickian or anomalous drug release behavior from the formulated floating matrix tablets. Simplex lattice design was reported to be an effective optimization technique for optimizing pharmaceutical formulations against desired responses.

Keywords: Floating matrix tablets. Clarithromycin. Simplex lattice design. Hydroxypropyl methyl cellulose. Ethyl cellulose.

INTRODUCTION

Administration of drugs via oral route has been the most versatile, convenient and hence the preferred route of drug delivery. However, drug absorption could be inadequate and variable in individuals due to physiological variability such as gastrointestinal transit as well as the gastric residence time of the dosage forms. The residence time of a drug delivery system in the stomach is dependent upon physiological pH, size of the dosage form, food intake, and biological factors which include age, body mass index, gender, posture, and diseased states like hepatic failure, diabetes, Chron's disease e.t.c (Streubel *et al.,* 2007). Various approaches for enhancing the gastric residence time of a dosage form in the stomach includes bioadhesive system (Santus *et al.,* 1997), swelling and expanding systems (Deshpande *et al.,* 1997), floating systems (Whitehead *et al.,* 1998) and other delayed gastric emptying devices (Chawla and Bansal 2003). The floating approach has some advantages likes less irritation, random gastric emptying, better bioavailability, site specific drug delivery, fewer side effects e.t.c. (Moes 1993). Floating systems can be developed by effervescent or non-effervescent approaches. The effervescent system requires a gas generating agent that makes the system buoyant and also alkalizes the microenvironment of the stomach. Non effervescent floating formulations include hydrodynamic ally balanced systems, micro porous systems, alginate beads, and hallow microsphere-micro balloons (Tavakoli *et al.,* 2012).

Clarithromycin is a broad spectrum macrolide antibiotic, used in the treatment of respiratory, skin and otolaryngology infections as well as *Helicobacter pylori* infections. Short elimination half life (3-4 h), stability in acidic medium and highest rate of eradication of *H. pylori* for the treatment of peptic ulcers makes the drug a suitable candidate for the development of floating matrix tablets (Labenz *et al.,* 2001; Rajinikanth *et al.,* 2008).

Simplex lattice design has been widely used as an optimization technique in pharmaceutical field and is an effective tool to study the effect of formulation variables on the response variables. Aatish et evaluated foalting tablets of acyclovir using HPMC K100 LV and Psyllium Husk with Sodium Bicarbonate as variables for simples lattice design (Aatish *et al.,* 2014). Vaghani *et al* employed simplex lattice design for optimizing mucoadhesive tablets of repaglinide (Vaghani *et al.,* 2012). Patel *et al* optimized floating tablets of carbamazepine using simplex lattice design (Patel *et al.,* 2007).

The present study was designed to develop floating matrix tablets of clarithromycin, using HPMC as a matrix

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forming agent, EC as release retardant polymer and citric acid/ sodium bicarbonate as gas generating agents employing simplex lattice matrix design as an optimization technique. Seven formulations, containing a fixed amount of drug and lubrication and different combinations of HPMC, citric acid and EC, were prepared as per simplex lattice design. The formulated floating matrix tablets were evaluated for various tablet quality control tests. The effect of three independent variables (factors) i.e. the concentration of HPMC (X_1), Citric acid (X_2) and EC (X_3) was studied on various dependent variables (responses/response variables) like floating lag time, $t_{50\%}$, $t_{90\%}$, MDT and tablet tensile strength.

MATERIALS AND METHODS

Materials

Clarithromycin was provided as gift sample by Ind-Swift Laboratories Ltd**,** Punjab, India. Hydroxypropyl methyl cellulose (HPMC K 15M), ethyl cellulose and microcrystalline cellulose (Avicel PH 102) kindly gifted by Park Pharma, Baddi, India**.** Magnesium stearate, citric acid, talc were procured from Loba Chemie, Mumbai, India. Sodium bicarbonate was purchased from Qualigens fine chemicals, Mumbai, India. All excipients and chemicals used in the study were of analytical grade.

Simplex lattice design

A simplex lattice design (Moore and Flanner 1996) was adopted for optimizing the formulation variables. Seven formulation batches (F1-F7) were prepared. The amounts of matrix forming agent (HPMC, X_1), gas generating agent (Citric acid, X_2) and release retardant (EC, X_3) were selected as independent variables. The floating lag time (FLT), time required for 50% ($t_{50\%}$) and 90% ($t_{90\%}$) drug release and mean dissolution time (MDT) were taken as responses. Design-Expert® software (version 8.0.6, Stat-Ease Inc., Minneapolis, MN, USA) was employed for generating multiple linear regression analysis (MLRA) equations and response surface plots for the selected.

Preparation of Clarithromycin floating matrix tablets

Different batches of floating matrix tablets of clarithromycin were prepared according to formulations designed as per simplex lattice matrix design. For preparing floating matrix tablets 250mg drug was selected. Amounts of HPMC, citric acid and EC were added as per calculations according to simplex lattice design. Avicel PH 102 (qs), PVP K 30 (5.5%w/w) and Talc (1%w/w) and Magnesium stearate (1%w/w) were taken as diluents, binder and flow modulators respectively. Tablets with constant theoretical weight of 550mg were obtained using mulitpunch tableting machine (AK Industries, Nakodar, India) fitted with 12.95 mm flat round die-punch tooling. Compaction was accomplished by direct compression of drug excipient blends previously mixed for 15 minutes in a polybag.

Evaluation

Pre-compression evaluation of powder mixtures

The pre-compression powder blends were evaluated for bulk density, tapped density, compressibility index, hausner's ratio (Rockvilled 2000) and angle of repose.

Tablet assay and evaluation

Ten tablets were pulverized. Powder equivalent to 250mg of Clarithromycin was shaken with 100ml of 0.1N HCL for 30 minutes. The contents were filtered through a 0.45 µm membrane filter, diluted and analyzed at 254nm by UV/VIS double beam spectrophotometer (2202, systronics, India).

The formulated tablets were evaluated for hardness using hardness tester (n=10), friability using Roche friabilator (n=10), thickness and diameter using digital vernier calliper (M/s Mitutoyo Corp., Japan n=10). Tensile strength (T) of tablets was calculated from the equation:

$T=2P/\pi Dt$

Where, P denotes the crushing load and D and t represent diameter and thickness of the tablet, respectively.

Floating lag time

Floating lag time was determined as per the method described by Rosa *et al.,* 1994. Test tablet was placed in 100ml beaker containing 0.1N HCl as medium. Time required by the to float continuously was determined as the floating lag time (FLT) and the total time for which the tablet remained buoyant was determined as total floating time (TFT).

In vitro dissolution studies

In vitro dissolution studies were carried out in paddle type six station dissolution apparatus (DS8000, Lab India, Mumbai, India) employing paddle stirring speed of 50 rpm, 37°C±0.5°C temperature and 0.1N HCl (pH 1.2) as dissolution medium. 5ml samples were withdrawn at predetermined time intervals. The samples were filtered through a 0.45µm membrane filter, diluted suitable and were analyzed at 254 nm using UV/VIS double beam spectrophotometer (2202 Systronics, India). Cumulative percentage drug release was calculated from equation obtained from the calibration curve of drug. The time required for 50% ($t_{50\%}$) and 90% ($t_{90\%}$) drug release from the tablets was computed from the best-fit order equation. Mean dissolution time was calculated from the dissolution data of different floating tablet batches. Mean dissolution time was calculated from the following equation (Costa and Lobo 2001):

$$MDT_{in\ vitro} = \frac{\sum_{i=1}^{n} T_{mid} \Delta M}{\sum_{i=1}^{n} \Delta M}$$

Here, '*i*' is the dissolution sample number, *n* is the number of dissolution sampling times; T_{mid} is the midpoint between times T_i and T_{i-1}, and ΔM is the amount of drug dissolved between times T_i and T_{i-1}.

Kinetic modelling of drug release

The dissolution profile data of all the batches of floating matrix tablets was fitted to various models like zero-order (*cumulative % drug release vs. time*), first order (*log cumulative % drug remaining vs. time*), Higuchi (*cumulative % drug release vs. square root of time*) (Higuchi 1963), Hixson-Crowell (*cube root of cumulative % drug remaining vs. time*) (Hixson and Crowell 1931), Korsmeyer and Peppas (*log cumulative % drug remaining vs. log time*) for understanding the mechanism drug release from the formulation (Korsmeyer *et al.,* 1983).

Fourier transform infrared-attenuated total reflectance (FTIR-ATR) spectroscopy

FTIR-ATR spectral analysis of the samples was performed for studying interactions between drug and selected polymers. The FTIR-ATR spectra of samples were obtained using FTIR-ATR spectrophotometer (IFS 66/S, Alpha Bruker, Germany). Samples of the pure drug, polymer and physical mixture of drug and polymer were scanned in the spectral region of 4000 cm^{-1} to 400 cm^{-1}.

Scanning electron microscopy

SEM photographs were taken for studying surface morphology of the optimized formulation of floating matrix tablet before and after subjecting to dissolution studies employing scanning electron microscope (Hitachi S 4300 SE/N model) equipped with secondary electron at an accelerating voltage of 10 kV. Samples were mounted on sample stub using double sided sticking carbon tape (thickness, 200nm) under reduced pressure (0.001 mmHg).

RESULTS

The present investigation was designed to develop floating matrix tablets of clarithromycin employing simplex lattice design as an optimization technique. Simplex lattice design was effective to determine the effect of the three factors on the dependent variables. The effect of three independent formulation variables i.e. the concentration of HPMC (X_1), Citric acid (X_2) and EC (X_3) was studied on various dependent variables like floating lag time, $t_{50\%}$, $t_{90\%}$, mean dissolution time studies. It is reported that formulation variables such as type of matrix-forming polymer, amount of effervescent agent and compression force significantly influenced floating properties and drug release from floating tablets (Soungthongjeen *et al.,* 2011).

Drug□polymer interactions studies were carried out using FTIR-ATR analysis. FTIR-ATR spectra of drug, polymers and physical mixtures (drug and polymers) are given in (fig. 1). Presence of characteristic peaks of drug in the spectra of drug/polymer physical mixtures indicates the absence of chemical interaction between drug and polymers used in the preparation of floating matrix tablets. The values of powder flow properties (bulk density, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose) as shown in table 1 indicated toward the good flow behavior of the precompression powder blend. Appropriate specifications of properties of powders for different characterization parameters must be established to ensure reproducible powder quality.

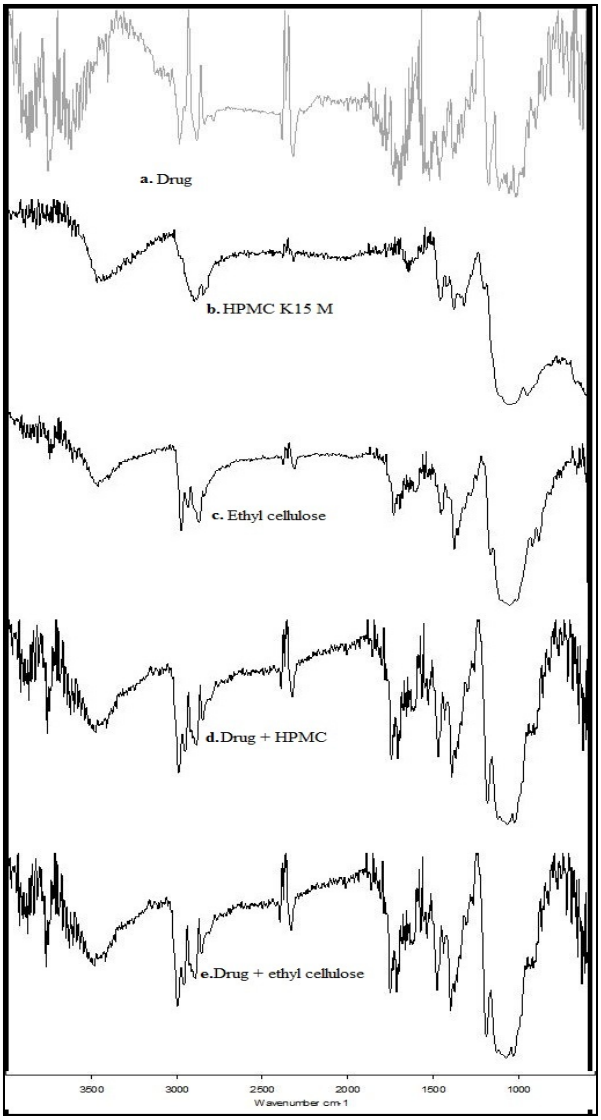


Fig. 1: FTIR-ATR spectra of: (a) Clarithromycin; (b) Hydroxypropyl methyl cellulose; (c) Ethyl cellulose; (d) Physical mixture of drug and HPMC; (e) Physical mixture of drug and ethyl cellulose.

The drug content of the formulated tablets varied between 98.54±0.46% and 99.92±0.32%. The tablet thickness varied between 3.81±0.042 mm and 4.04±0.012 mm and diameter varied between 12.89±0.05 mm and 12.97±0.03 mm. Tablets must have sufficient strength and resistance to friability for withstanding mechanical shocks during manufacturing, shipping and packaging. Tablet friability and hardness was found to be ranging between 0.29±0.10

% and 0.90±0.03% and 3.0±0.35Kg/cm^2 and 5.1±0.27 Kg/cm^2 respectively (table 2). Tensile strength, a measure of inherent strength of the compacted material, characterizes the ability of a formulation to undergo good particle bending, producing good tablet with optimal disintegration and dissolution. The tensile strength was found to be ranging between 0.377±0.06mN/m^2 and 0.650±0.02mN/m^2.

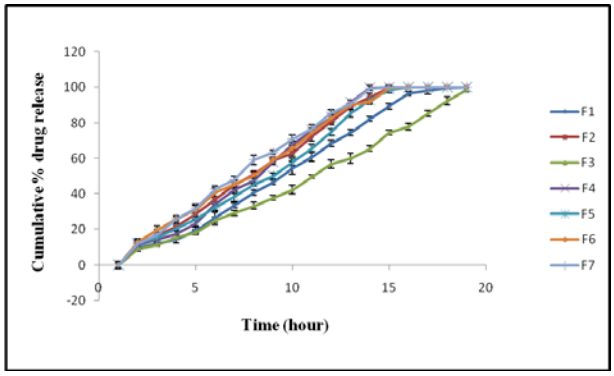


Fig. 2: *In vitro* drug release profile of all the seven formulations.

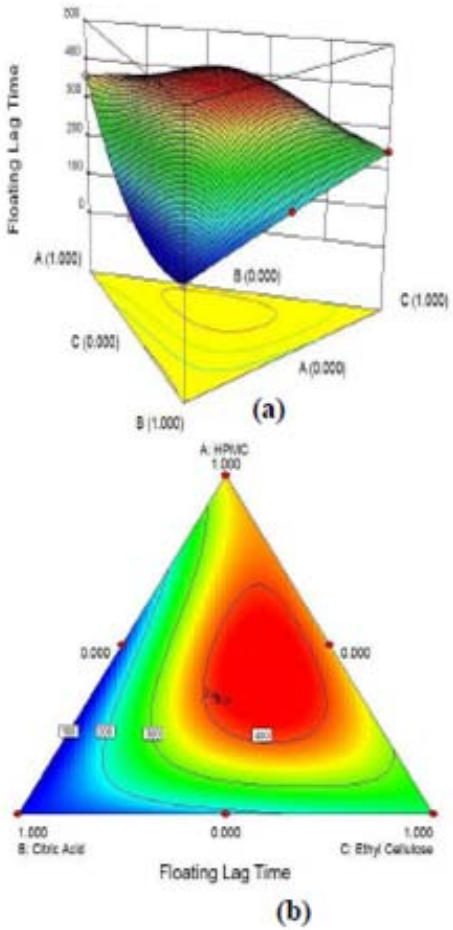


Fig. 3: (a) Response surface plot showing the influence of HPMC K15M (X1), Citric acid (X2) and Ethyl cellulose (X3) on floating lag time (FLT) of the formulated tablets. (b) The corresponding contour plot.

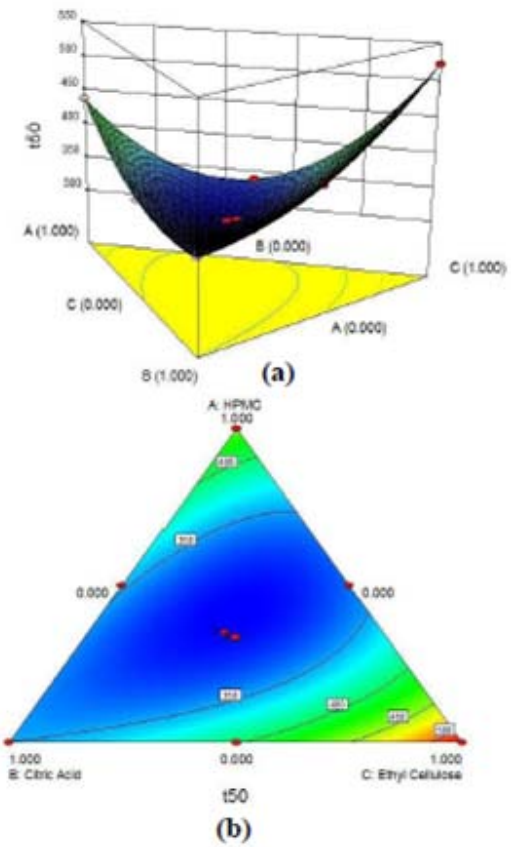


Fig. 4: (a) Response surface plot showing the influence of HPMC K15M (X_1), citric acid (X_2) and ethyl cellulose (X_3) on $t_{50\%}$ of the formulated tablets, (b) the corresponding contour plot.

The floating lag time (FLT) was found to be ranging between 110±10 to 420±6 seconds. The total floating time (TFT) for all formulation batches was found to be more than 12 hours with F3 formulation showing maximum floating lag time 17 hrs.

In vitro dissolution studies

Dissolution studies were carried out using USP type II apparatus employing 0.1N HCl (pH 1.2) as dissolution medium. It is evident from the *in vitro* studies that increase in EC concentration in the formulation showed decreased effect on release rate of drug and increased effect on floating time (fig. 2). Depending upon the concentration of EC and HPMC K15 M F3, F5, F6 and F7 formulations showed a total floating time of 17, 14, 13, 12 hours respectively and the drug release was found to be ranging between 65.45% to 99.33% up to 12 hour time period which was indeed sufficient to control the release of drug from the tablets. Depending upon concentration of HPMC K15M, F1, F2 and F4 formulations showed a total floating time of 16, 13, 12 hours respectively and drug release up to 12 hours was 82.24% to 99.52% which shows that HPMC K15 M has a promising effect on controlling the release of drug from the tablets.

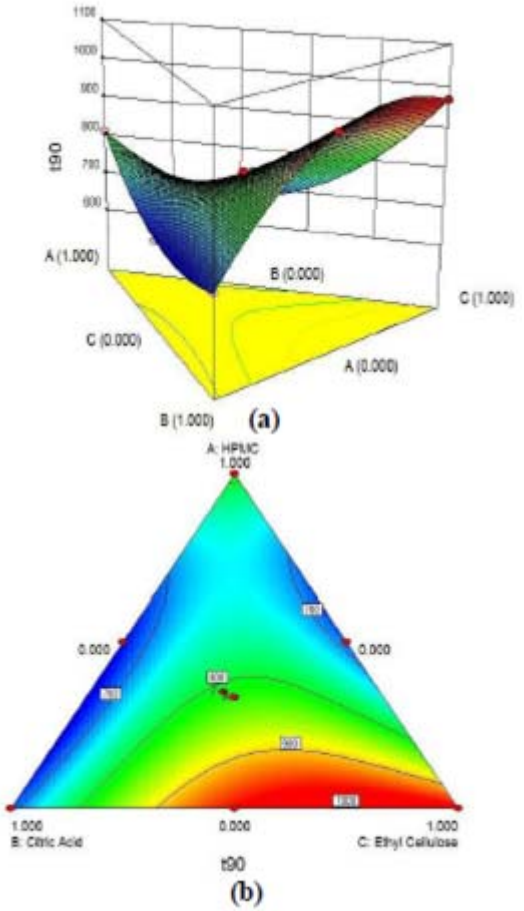


Fig. 5: (a) Response surface plot showing the influence of HPMC K15M (X_1), citric acid (X_2) and ethyl cellulose (X_3) on $t_{90\%}$ of the formulated tablets, (b) the corresponding contour plot.

Kinetic analysis and mechanism of drug release data

From the kinetic analysis of the *in vitro* drug release data (table 4) it was found that the r^2 value of all the batches was maximum in case of zero order, thus it can be said that the drug release from the formulation follows zero-order model. The n values of Korsmeyer-Peppas model of all the formulations were ranging between 0.62 and 0.75. Most probable mechanism that could explain the release pattern of drug from the formulations was non-Fickian or anomalous, indicating that the drug release from the floating tablets could be due to diffusion and/or relaxation of the polymeric chains. The rate of drug release from the formulation is governed by rate of entry of the solvent and creation of channel due to swelling of the polymer caused by polymer relaxation and subsequent polymeric chain relaxation (Patel *et al.,* 2006). According to another theory, the solvent induced glass-rubbery transition of the polymer with in the dosage form leads increase in polymeric chain mobility such that the network mesh of the polymer enlarges/erodes thereby leading to dissolution and diffusion of drug molecules through the gel layer (Ammar *et al.,* 2009; Singh and Rana 2013).

Simplex lattice design

Simplex lattice design was constructed as shown in (table 2). All the formulation batches were prepared within the factor space. The best-fit model for all the responses was found to be a special cubic model in the following form:

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3 \quad (1)$$

Where Y is the dependent variable (response parameter) and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1, X_2 and X_3) represent the average result of changing one factor at a time from its low and high value. The interaction terms (X_1X_2, X_1X_3 and X_2X_3) show how the response changes when two or more factors are changed simultaneously.

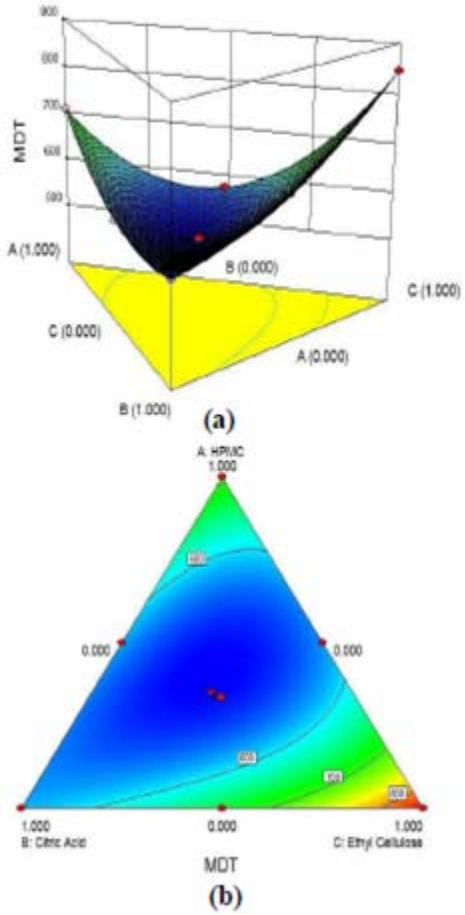


Fig. 6: (a) Response surface plot showing the influence of HPMC K15M (X_1), citric acid (X_2) and ethyl cellulose (X_3) on mean dissolution time (MDT) of the formulated tablets, (b) the corresponding contour plot.

Mathematical relationships generated by multiple linear regression analysis (MLRA) using Stat Ease, Inc. (Minneapolis, MN) Design Expert 8.0.6 software for the studied response variables are expressed in Eqs. (2)-(5) in terms of coded factors.

$$\text{Floating Lag Time (FLT)} = 360.05\,X_1 + 110.05\,X_2 + 239.90\,X_3 - 458.28\,X_1X_2 + 239.26\,X_1X_3 + 19.26\,X_2X_3 + 5645.15\,X_1X_2X_3 \quad (2)$$

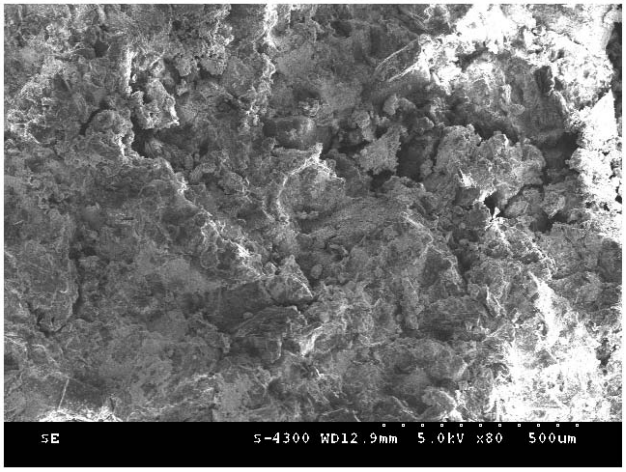
$t_{50\%} = 438.42X_1 + 350.10X_2 + 521.98X_3 - 159.54X_1X_2 - 564.16X_1X_3 - 156.32\ X_2X_3 - 578.33X_1X_2X_3$ (3)

$t_{90\%} = 814.06X_1 + 685.06X_2 + 966.87X_3 - 359.77X_1X_2 - 822.94X_1X_3 + 563.05X_2X_3 + 1839.74X_1X_2X_3$ (4)

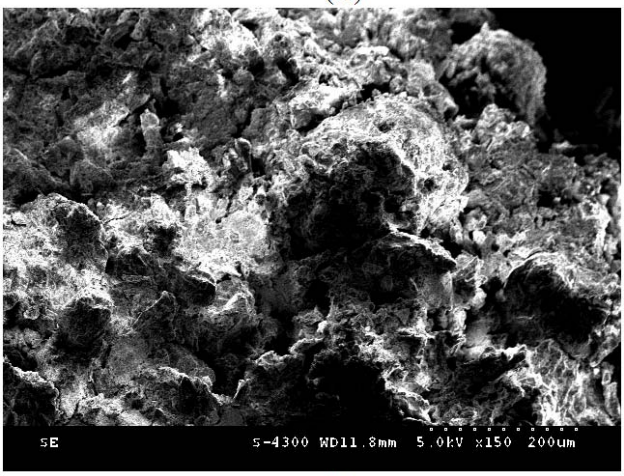
Mean Dissolution Time (MDT) = $711.03X_1 + 580.03X_2 + 845.93X_3 - 268.82X_1X_3 - 188.50X_2X_3 - 1151.22X_1X_2X_3$ (5)

After considering the magnitude of coefficient, the polynomial equations can be used to draw conclusions regarding the effect of selected variable on a particular response. The equation of FLT suggests that X_1 (concentration of HPMC) has more dominant effect than X_3 (EC) and X_2 (Citric acid) on the floating lag time. Therefore, a high level of factor X_1 should be selected for enhanced floating lag time. The effect of different independent variables on floating lag time is demonstrated in response surface plot (fig. 3a) and the respective contour plot (fig. 3b). HPMC being a gelling and matrix forming agent tends to form strong mesh like structure after contact with the dissolution media. The presence of gel layer is responsible for the retardation of drug release from the polymer matrix. Similarly, high concentration of HPMC will form more matrixed structure and thus slower down the release of CO_2 (formed by reaction between $NaHCO_3$ and citric acid) from the formulation leading to increase in floating lag time. Rani *et al* reported that the use of HPMC K15 M along with psyllium husk enhanced the floating duration and help to maintain the dimensional stability of the formulation (Rani *et al.,* 2014). Ethyl cellulose being water insoluble is used as release retardant in drug delivery formulations. As the concentration of EC is increased more complex structure is formed due to the entrapment of EC chains in the gelled matrix layers of HPMC. This complex structure might be responsible for the enhancement of floating lag time. Higher concentration of citric acid leads to enhanced rate of reaction between citric acid and $NaHCO_3$ leading to increased effervescence caused by higher production of carbon dioxide which might be the probable cause of decreased FLT with increase in concentration of citric acid in the formulation.

From the equations 3 and 4, it can be concluded that factor X_3 has a more important role in prolonging both the $t_{50\%}$ and $t_{90\%}$. The $t_{50\%}$ and $t_{90\%}$ of formulated batches of floating matrix tablets were found in the range of 317.00 ±2.54 to 522.00±2.39 minutes and 659.65±1.89 to 967.35±1.67 minutes (table 3) respectively. The equations depict the prevailing effect of X_3 (EC) on $t_{50\%}$ and $t_{90\%}$ as compared to X_1 (HPMC) and X_2 (citric acid). EC being a water insoluble polymer and HPMC a matrix-forming agent plays an important role in retarding the drug release from the formulation. Swelling of HPMC polymer after contact with the dissolution media and formation of viscous gel layers of the polymer are responsible for slow drug release from the formulation. Addition of EC further adds to the release retardant behavior ur of the polymer. EC chains gets entangled in HPMC matrix which leads to the formation of more complexed mesh like arrangement which is responsible for the increase in $t_{50\%}$ and $t_{90\%}$ with increase in EC concentration. The response surface plots and the corresponding contour plots for $t_{50\%}$ and $t_{90\%}$ are depicted in fig. 4 and 5 respectively.



(A)



(B)

Fig. 7: SEM image of the optimized tablet (a) before dissolution studies; (b) after dissolution studies.

Mean dissolution time (MDT) of floating matrix tablets was in the range of 527.20±1.22 to 846.78±2.61 (table 3) minutes. The equation 5 of mean dissolution time (MDT) suggests that X_3 has more considerable effect on MDT as compared to X_1. The high values of X_1 and X_3 coefficient also suggests that the interaction between X_1 and X_3 has a significant effect on MDT due to matrix forming properties of X_1 (HPMC K15M) and release retardant effect of X_3 (ethyl cellulose) which causes decrease in release rate of drug from the dosage form. Response surface plot and corresponding contour plots for effect of formulation variables on MDT are shown in fig. 6. MDT was found to increase with the increase in concentration of HPMC. Similarly increase in the concentration of EC was found to have a synergistic effect on drug release

Table 1: Preformulation study parameters of physical mixtures.

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index	Hausner's ratio	Angle of repose (θ)
F1	0.446±0.013	0.526±0.016	20.64±0.23	1.26±0.004	24.56±0.52
F2	0.450±0.043	0.568±0.025	20.64±0.12	1.26±0.006	24.19±0.60
F3	0.463±0.027	0.595±0.032	22.18±0.16	1.29±0.005	25.08±0.41
F4	0.510±0.034	0.625±0.022	18.40±0.19	1.23±0.003	26.05±0.42
F5	0.543±0.037	0.735±0.031	26.12±0.22	1.35±0.006	22.73±0.11
F6	0.515±0.022	0.632±0.025	18.52± 0.20	1.23±0.003	25.94±0.31
F7	0.538±0.034	0.694±0.036	22.48± 0.18	1.29±0.005	26.68±0.32

Table 2: Assessment of various physical parameters of prepared tablet batches.

Formulation code	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Diameter (mm)	Tensile Strength (mN/m^2)
F1	4.0±0.41	0.29±0.05	4.00±0.06	12.97±0.03	0.491±0.06
F2	5.1±0.27	0.75±0.08	3.84±0.08	12.89±0.05	0.650±0.02
F3	5.0±0.31	0.61±0.05	4.02±0.05	12.98±0.03	0.613±0.02
F4	3.0±0.35	0.90±0.03	3.92±0.04	12.97±0.02	0.377±0.06
F5	3.0±0.42	0.29±0.10	3.81±0.04	12.9±0.06	0.382±0.08
F6	5.0±0.48	0.69±0.07	4.04±0.01	12.92±0.04	0.615±0.04
F7	3.0±0.38	0.86±0.03	3.98±0.02	12.94±0.04	0.378±0.05

Table 3: Formulation and evaluation parameters of simplex lattice designed formulation batches of floating matrix tablets of clarithromycin.

Formulation Code	Transformed fractions of variables			Floating lag time (seconds)	Total floating time (hours)	$t_{50\%}$ (minutes)	$t_{90\%}$ (minutes)	MDT (minutes)
	X_1	X_2	X_3					
F1	1	0	0	360±8	16	438.42±1.48	814.72±1.56	711.32±1.74
F2	0	1	0	110±10	13	350.10±2.52	685.00±2.53	580.32±1.92
F3	0	0	1	240±6	17	522.00±2.39	967.35±1.67	846.78±2.61
F4	0.5	0.5	0	120±15	12	354.30±1.66	659.65±1.89	580.88±2.86
F5	0	0.5	0.5	180±12	14	397.00±1.78	967.00±1.45	666.47±1.96
F6	0.5	0	0.5	360±4	13	339.20±2.86	685.00±2.77	575.26±2.05
F7	0.33	0.33	0.33	420±6	12	317.00±2.54	817.00±1.97	527.20±1.22

Values are mean ± SD (n = 3)

retardation from the formulation. The increased amount of ethyl cellulose leads to increase in mean dissolution time of tablets as ethyl cellulose (due to its hydrophobic character) forms more complex barrier between the drug and the matrix and thus allows slow dissolution of drug (Murtaza *et al.,* 2015).

Code Values	Actual Values*		
	X_1	X_2	X_3
0	15	2	0
1	25	6	10

***** X_1 is the amount of HPMC (%w/w); X_2 is the amount of citric acid (%w/w); X_3 is the amount of EC (%w/w).

The SEM image (fig. 7) of the optimized formulation batch of floating tablets of clarithromycin was taken to study the morphology of the tablets before and after dissolution studies. SEM images of the intact tablet shows the absence of pores and channels on the surface whereas the SEM image of the tablet sample taken midway of conducting dissolution studies clearly indicates the presence of sufficient pores/channels formed due to polymer disentanglement and polymer erosion that are responsible the release of the drug from the formulation (Singh and Rana 2013).

Numerical optimization

Numerical optimization technique using the desirability approach was employed for developing new formulation having desired responses. Upon comprehensive evaluation and exhaustive grid searches, the formulation composition with 14.56% w/w HPMC, 1.85% w/w citric acid and 9.23% w/w ethyl cellulose, fulfilled maximum requirements of an optimum formulation because of better regulation of floating lag time, $t_{50\%}$, $t_{90\%}$ and mean dissolution time alongside drug dissolution parameters. The predicted desirability of the optimized formulation was found to be 0.872. The optimized formulation was

Table 4: *In vitro* drug release (kinetic modelling) data of the formulated floating tablet batches.

Batch	Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
	K_0	r^2	K_1	r^2	K_H	r^2	K_{HC}	r^2	K_{KP}	r^2	n value
F1	3.395	0.994	2.47	0.660	-27.16	0.951	5.21	0.884	1.05	0.952	0.757
F2	8.303	0.998	2.31	0.653	-20.37	0.964	4.93	0.882	1.15	0.982	0.740
F3	2.938	0.992	2.25	0.605	-23.75	0.920	4.95	0.836	1.03	0.954	0.714
F4	3.585	0.994	2.27	0.693	-25.14	0.941	4.97	0.878	1.14	0.947	0.730
F5	7.022	0.996	2.35	0.539	-20.29	0.945	4.95	0.832	1.17	0.961	0.658
F6	11.67	0.997	2.27	0.625	-15.75	0.968	4.84	0.872	1.25	0.983	0.627
F7	10.60	0.996	2.22	0.709	-17.82	0.978	4.83	0.898	1.23	0.990	0.676

Table 5: Comparison of experimentally observed responses of the optimized formulation with the predicted responses.

Response parameters	Constraint sets	Observed values*	Predicted values	Error (%)
Floating Lag Time (minutes)	Minimize	225.45±6.81	239.91	6.41
$t_{50\%}$ (minutes)	Maximize	498.94±5.40	521.98	4.62
$t_{90\%}$ (minutes)	Maximize	910.53±4.29	966.87	6.18
MDT (minutes)	Maximize	802.44±3.82	845.93	5.42

* Values are mean ± SD (*n*=3)

evaluated for various dependent variables. The response values were calculated and compared to the corresponding predicted values. The values of the observed and predicted responses along with the percentage prediction errors are depicted in table 5. The prediction error for the response parameters was found to be ranging between 4.62% and 6.41%. Drug release from the optimized formulation was found to follow non-Fickian drug diffusion model.

CONCLUSIONS

In the present study floating drug delivery system of clarithromycin was developed using HPMC K15M as matrix forming agent, citric acid to produce effervescence and ethyl cellulose as release retardant. Simplex lattice design was used as optimization tool so as to investigate the effect of independent variables X_1 (HPMC K15M), X_2 (citric acid) and X_3 (ethyl cellulose) on the dependent variables viz. floating lag time, t_{50}, t_{90} and mean dissolution time. The release rate of the drug from the floating tablets was significantly influenced by the proportion of HPMC K15M and ethyl cellulose either individually or in combination with each other. Higher amount of polymer decreased the drug release rate and increased the floating time. The n values of Korsmeyer-Peppas model of all the formulations are in between 0.62 and 0.75. Therefore, the most probable mechanism that the release patterns of the formulations followed was non-Fickian diffusion or anomalous drug release mechanism which is controlled by both diffusion as well as polymer relaxation process. The dependent variables viz. $t_{50\%}$, $t_{90\%}$, mean dissolution time (MDT) and floating lag time (FLT) could be modulated by varying the critical formulation variables, namely the amount of HPMC, citric acid and ethyl cellulose. The statistical model generated using the multiple linear regression and global desirability function showed good predictive power for the experimental value. Based on the results, it may be concluded that desirability and simplex lattice design are quite helpful in understanding the interaction (s) between different independent variables and for rapid formulation development. High degree of prognosis obtained using simplex lattice design indicates that simplex lattice design is quite efficient in optimizing drug delivery systems.

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