Carbohydrate Polymers 102 (2014) 360–368

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Optimization of HPMC and carbopol concentrations in non-effervescent floating tablet through factorial design

Sujata Acharya [a], Sradhanjali Patra [a], Nihar Ranjan Pani [b,*]

[a] Department of Pharmaceutical Sciences, Utkal University, Bhubaneswar, Odisha, India
[b] Department of Pharmaceutics, Gayatri College of Pharmacy, Sambalpur, Odisha, India

ARTICLE INFO

Article history:
Received 28 October 2013
Received in revised form
12 November 2013
Accepted 27 November 2013
Available online 6 December 2013

Keywords:
Optimization
Response surface methodology
Non-effervescent floating tablet
Glipizide

ABSTRACT

This study was to optimize HPMC K4M and carbopol 934 concentration in the development of non-effervescent floating tablets (NEFTs) of glipizide as model drug using 3^2 factorial design. The time required for releasing drug of 50% and 80% and similarity factor were the target responses. HPMC K4M and carbopol 934 concentrations were the variables. The response surface methodology and optimized polynomial equations were used to select the optimal formulation with desired responses. The excipients used in tablets were compatible with glipizide as per the results of isothermal stress testing and DSC study. The drug release of entire NEFTs followed zero order kinetics and non-Fickian diffusion mechanism. Validation of the optimization technique demonstrated the reliability of the model. The optimized formulation containing 124.33 mg HPMC K4M and 25.76 mg carbopol 934 was prepared according to the software determined levels. The stability study of the optimized formulation proved the integrity of the developed formulation.

1. Introduction

The real challenge in the development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time (Prajapati, Patel, & Patel, 2008). Drug absorption from GIT is a complex process influenced by many variables. It has been reported that the extent of drug absorption from the GIT is related to contact time with the small intestinal mucosa. Gastroretentive drug delivery systems are designed to retain drug in the gastric region for several hours and assist in improving sustained delivery of orally administered drugs those have an absorption window in a particular region of the GIT (Hirtz, 1985).

Gastroretentive drug delivery systems can be formulated using many techniques including floating drug delivery systems. Floating drug delivery systems are of two types: (A) effervescent drug delivery systems, depending on the generation of carbon dioxide gas upon contact with gastric fluids and (B) non-effervescent drug delivery systems (NEFDDS). NEFDDS has many advantages over effervescent floating drug delivery system. NEFDDS are prepared using a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and gel-forming hydrocolloid. After oral administration, the dosage form will swell in contact with gastric fluids and attain a bulk density of <1 mg/mL. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel like structures act as a reservoir and allow sustained release of drug through the gelatin mass.

The combined/only usage of hydroxy propyl methyl cellulose (HPMC) and carbopol as mucoadhessive polymers is already reported (Khanna et al., 1997). The residual floating force values of the different grades of HPMC were in the order HPMC K4M ~ HPMC E4M ~ HPMC K100 LV > HPMC E5 LV. HPMC K4M and HPMC E4M do not have significant floating properties. Better floating was achieved at a higher HPMC/carbopol ratio (Li, Lin, Chien, & Daggy, 2001; Li, Lin, Daggy, Mirchandani, & Chien, 2002).

Pharmaceutical formulators often face the challenge of finding the appropriate combination of independent process variables (factors) that will produce the product with optimum properties (Malakar & Nayak, 2012; Nayak & Pal, 2011; Pani, Nath, & Bhunia, 2010). However, this can be easily analyzed and understood using established statistical design of experiment tools such as factorial designs. They are considered most effectively in estimating the influence of individual process variables with minimum experimentation and time, where all factors are studied in all possible combinations (Bhunia, Dutta, & Chaudhuri, 2011; Joshi, Chavan, &

* Corresponding author. Tel.: +91 8018544142.
E-mail address: niharpani@gmail.com (N.R. Pani).

0144-8617/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.carbpol.2013.11.060

Table 1
Results of isothermal stress testing study of glipizide after 3 weeks of storage at stressed conditions.

Sample	Ratio (drug:excipient)	Quantity unchanged[a] (%, w/w)	
		Control samples	Stressed samples
GPZ	–	100.81 ± 0.72	99.74 ± 2.53
GPZ + mannitol	1:2	101.42 ± 1.34	100.27 ± 1.65
GPZ + HPMC	1:1	100.46 ± 0.86	100.32 ± 1.78
GPZ + Povidone	2:1	101.8 ± 1.48	99.34 ± 1.86
GPZ + talc	3:1	100.62 ± 2.68	99.27 ± 2.04
GPZ + carbopol	1:1	99.84 ± 1.72	100.27 ± 1.32
GPZ + Aerosil	3:1	100.72 ± 2.17	99.24 ± 2.14

[a] Values expressed as average ± standard deviation. $n = 3$.

Sawant, 2010; Pani et al., 2010). Based on the factorial design of experiment, the optimization technique encompasses the generation of model equations for the investigated responses over the experimental design to determine the optimum formulation(s).

Glipizide (GPZ) is a second-generation sulfonylurea that can acutely lower the blood glucose level in humans by stimulating the release of insulin from the pancreas and is typically prescribed to treat type II diabetes (non-insulin-dependent diabetes mellitus). Its short biological half-life (3.4 ± 0.7 h) necessitates that it is administered in 2 or 3 doses of 2.5–10 mg per day (Foster & Plosker, 2000). Thus, the development of controlled-release dosage forms would clearly be advantageous. Researchers have formulated oral controlled release products of GPZ by various techniques (Chowdary and Rao, 2003a, 2003b; Thombre et al., 1999). Moreover, the site of absorption of GPZ is in stomach. Dosage forms that are retained in the stomach would increase the absorption, improve drug efficiency, and decrease drug requirement. Thus, GPZ was selected as a model drug to develop the non-effervescent floating tablet (NEFT) in this study.

The objective of the present investigation was to develop NEFT of GPZ using 3^2 factorial design. The 3^2 factorial design-based optimization was employed to investigate the effect of two independent process variables (factors), i.e., amount of HPMC K4M and carbopol 934 on the dependent variables like time required to release 50% of drug (t_{50}), 80% of drug (t_{80}) and similarity factor (f_2). In this study, Design Expert software was used to give information not only on the critical values required to achieve the desired response but also the possible interactions of the selected independent variables on the dependent variables.

2. Materials and methods

2.1. Materials

Methocel K4M was kindly supplied by Colorcon Asia Pvt. Ltd. (Goa, India) and carbopol 934 and mannitol were procured from Central drug house Pvt. Ltd. (New Delhi, India) and Thomas baker chemicals Pvt. Ltd. (Mumbai, India) respectively. Glipizide was the kind gift from Macleod Pharmaceuticals (Mumbai, India). Talc, and magnesium stearate were purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). All other ingredients were of analytical grade.

2.2. Differential scanning calorimetry (DSC)

A differential scanning calorimeter (JADE DSC, PerkinElmer, Waltham, MA, USA) was used for thermal analysis of drug and drug–excipients mixtures (Pani, Nath, & Acharya, 2011; Pani, Nath, & Bhunia, 2012). Excipients that were used in the development of formulation and their maximum ratio with drug used in a tablet were selected for the present study (Table 1). Individual samples (drug and excipients) as well as physical mixtures of drug and selected excipients (all passed through 80-mesh sieve) were weighed directly in the DSC aluminum pan and scanned in the temperature range of 50–300 °C under nitrogen atmosphere. Heating rate of 20 °C/min was used and thermograms obtained were observed for any interaction.

2.3. Isothermal stress testing

For isothermal stress testing (Pani et al., 2011, 2012), drug and different excipients were weighed (Table 1) directly in to 4 mL-glass vials ($n = 2$) and mixed on a vortex mixer for 2 min. In each of the vials, 10% (w/w) water was added and the drug–excipients blend was further mixed with a glass capillary (both the ends of which were heat sealed). To prevent any loss of material, capillary was broken and left inside the vial. Each vial was sealed using a Teflon-lined screw cap and stored at 50 °C using a hot air oven (Narang Scientific Industries, Haryana, India). These samples were periodically examined for any unusual color change. After 3 weeks of storage at the above conditions, samples were quantitatively analyzed using a UV–visible spectrophotometer. Drug–excipients blends without added water and stored in a refrigerator served as controls.

2.4. Preparation of glipizide non-effervescent floating tablets

Tablets containing 10 mg GPZ were prepared according to the design depicted in Table 2 by wet granulation technique. For each formulation (Table 2), GPZ, HPMC K 4M and Mannitol were manually blended homogeneously. Ethanol (95%) was added to the mixture in a quantity just enough to bind the mass. The wet mass was screened in sieve No. 20 and kept for drying in a tray dryer at 45 °C overnight. The dried granules were collected and blended with carbopol 934, aerosol and talc for 5 min. The homogeneous lubricated blend was compressed in single station tablet punching machine (Hardik, Ahmedabad, India) by using flat face, round tooling, 10 mm punches. The compression force was adjusted to obtain tablets with hardness in range of 4–5 kg/cm^2.

2.5. In vitro evaluation of the prepared tablets

2.5.1. Tablet weight variation

Twenty tablets were randomly selected and accurately weighed. Results are expressed as mean values ± SD.

2.5.2. Tablet thickness

A vernier caliper (For-bro Engineers, Mumbai, India) was used to determine thickness of 10 randomly selected tablets. Results are expressed as mean values ± SD.

2.5.3. Drug content uniformity

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (200 mg) was extracted in 100 mL of Phosphate buffer, pH 6.8. The solution was filtered through a cellulose acetate membrane (0.45 μm). The drug content was determined by UV spectroscopy (Shimadzu UV-1601 UV/Vis double beam spectrophotometer, Kyoto, Japan) at a wavelength of 276 nm (USP, 2003) after a suitable dilution with Phosphate buffer, pH 6.8 (Sankalia, Sankalia, & Mashru, 2008).

2.5.4. Tablet friability

According to the BP specifications (The British Pharmacopoeia, 2007), 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus (FAB-2, Logan Instruments Corp., NJ, USA). The drum was adjusted to rotate 100 times in 4 min. The tablets were removed, dedusted and accurately weighed. The percent weight loss was calculated.

Table 2
3^2 full factorial design and formulae with observed response value of glipizide non-effervescent generating floating tablets.

Ingredients	Amount in mg								
	NEFT-1	NEFT-2	NEFT-3	NEFT-4	NEFT-5	NEFT-6	NEFT-7	NEFT-8	NEFT-9
Glipizide	10	10	10	10	10	10	10	10	10
HPMC K4M (X_1)	110 (−1)	120 (0)	130 (+1)	110 (−1)	120 (0)	130 (+1)	110 (−1)	120 (0)	130 (+1)
Carbopol 934 (X_2)	25 (−1)	25 (−1)	25 (−1)	30 (0)	30 (0)	30 (0)	35 (+1)	35 (+1)	35 (+1)
Mannitol	50	40	30	45	35	25	40	30	20
Aerosil	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
t_{50}	5.5	6.6	7.8	8.3	9.1	10.3	10.1	13.6	15.6
t_{80}	11.3	12.5	14.2	13.9	14.5	15.8	15.6	21.5	23.9
f_2	40.48	49.77	58.06	64.80	75.54	66.28	47.03	43.88	41.11

Coded values are in bracket; (X_1) and (X_2) are independent factors; (+1) = higher values; (0) = medium value and (−1) = lower values.
t_{50}, time required for 50% of drug release; t_{80}, time required for 80% of drug release; f_2, Similarity factor.

2.5.5. Tablet swelling ability

The swelling behavior of the tablets was determined, in triplicate, according to the method described by Dorozynski et al. (2004). Briefly, a tablet was weighed (W_1) and placed in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 °C. At regular time intervals, the tablet was removed and the excess surface liquid was carefully removed by a filter paper (Patel, Modasiya, Shah, & Patel, 2009). The swollen tablet was then reweighed (W_2). The swelling index (SI) was calculated using the formula (1):

$$\mathrm{SI} = \frac{W_2 - W_1}{W_1} \quad (1)$$

2.5.6. Tablet floating behavior

The floating behavior of the tablets was visually determined, in triplicate, according to the floating lag time method described by Rosa, Zia, and Rhodes (1994). Briefly, a tablet was placed in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 °C. The floating lag time (the time between tablet introduction and its buoyancy) and total floating duration (the time during which tablet remains buoyant) were recorded.

2.5.7. Tablet adhesion retention period

The adhesion retention period of the tablets was evaluated in triplicate by an in vitro method reported by Nakamura, Ohta, Machida, and Nagai (1996) for measuring the nasal mucoadhesion of some water-soluble polymers. Briefly, an agar plate (1%, w/v) was prepared in 0.1 N HCl (pH 1.2). A side of the tablet was wetted with 50 μL of 0.1 N HCl and attached to the center of agar plate by applying a light force with a fingertip for 20 s (Perioli, Ambrogi, Paganoa, Scuota, & Rossi, 2009). Five minutes later, the agar plate was attached to a USP disintegration test apparatus (DST-3, Logan Instruments Corp., NJ, USA) and moved up and down in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C. The adhering tablet on the plate was immersed into the solution at the lowest point and got out of the solution at the highest point. The retention period of the tablet on the plate was noted.

2.6. Drug release study

The drug release study of NEFTs as well as the commercially available extended release tablets of GPZ (Glucotrol XL) was performed using USP XXIV basket apparatus (Electrolab, TDT-06T, Mumbai, India) at 37 ± 0.5 °C and at 50 rpm using 900 mL of phosphate buffer (pH 6.8) as a dissolution medium (n = 3) as per USP XXVI dissolution test prescribed for GPZ extended release tablets (USP, 2003). Aliquots of 5 mL were withdrawn from the dissolution apparatus at different time intervals and filtered through a cellulose acetate membrane (0.45 μm). The drug content was determined spectrophotometrically at a wavelength of 276 nm (USP, 2003), as mentioned before. At each time of withdrawal, 5 mL of fresh medium was replaced into the dissolution flask. The time required for 50% of drug release (t_{50}) and 80% of drug release (t_{80}) was calculated.

2.7. Determination of difference and similarity factors

The in vitro drug release profile of the NEFT (test) was compared with the release profile of commercial tablet (reference) determining the 'difference factor', f_1 and 'similarity factor', f_2 (Geoffroy, Fredrickson, & Shelton, 1998; Hamed & Sakr, 2001). The difference factor (f_1) measures the percent error between the two curves over all time points and was calculated by using Eq. (2).

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100 \quad (2)$$

where 'n' is the number of sampling points, R_j and T_j are the percent dissolved of the reference and test products at each time point j respectively.

The similarity factor (f_2) is a logarithmic transformation of the sum of squared error of differences between the test T_j and the reference products R_j over all time points. It was calculated as Eq. (3).

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{j=1}^{n} w_j |R_j - T_j|^2 \right]^{-0.5} \times 100 \right\} \quad (3)$$

where w_j is an optional weight factor and other terms are as defined earlier.

2.8. Kinetics of drug release

The kinetics of drug release is important because they are useful tools to correlate the in vitro and in vivo drug responses by comparing the results of pharmacokinetics with dissolution profiles of the formulations. Different mathematical models i.e., zero order, first order and Higuchi equations were applied for describing the kinetics of the GPZ release process from NEFT, and the most suited being the one which fitted best the experimental results. The data obtained from in vitro drug release studies were used to calculate the correlation coefficient (R) value between 'cumulative amount of drug released and time' for zero order (Eq. (5)), 'log cumulative percentage of drug remaining and time' for first order (Eq. (6)) and 'cumulative percentage of drug released and square root of time'

for Higuchi's model (Eq. (7)). The best fit model was considered to that one which had maximum '*R*' value (~1).

2.8.1. Zero-order kinetics of drug release

The zero-order kinetic model signifies that the rate of dissolution remains constant with time and independent of absolute ambient of substance (Higuchi, 1963; Wai-Yip Lee and Robinson, 2000). Indeed, this is valid only for very dilute solutions, hence under sink conditions. If the concentration comes close to the saturation limit, the dissolution proceeds in a pseudo-first order process.

$$Q_t = K_0 t \tag{4}$$

where Q_t is the amount of drug release, K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours.

2.8.2. First-order kinetics of drug release

The rate of drug release is proportional to the concentration of the drug remaining to be release at any time period in the first-order kinetics of drug release (Higuchi, 1963; Wai-Yip Lee and Robinson, 2000). In the case of drug release from reservoir devices as well as multi particulate systems the first order kinetics is followed.

$$\text{Log } C = \text{Log } C_0 - \frac{K_1 t}{2.303} \tag{5}$$

where C is the amount of drug remaining to be release at time 't' in hour, C_0 is the initial amount of drug, K_1 is the first order rate constant expressed in units of concentration/time.

2.8.3. Higuchi kinetics of drug release

Higuchi developed several theoretical models to study the release of high and low water-soluble drugs incorporated in semisolid and/or solid matrices. According to this model, drug release was described as a square-root of time. This process of drug release by diffusion is based on Fick's law (Wai-Yip Lee and Robinson, 2000; Higuchi, 1963). This relation can be used to describe drug dissolution from several types of modified-release dosage forms by the following equation:

$$Q_t = K_H (t)^{1/2} \tag{6}$$

where K_H is the Higuchi's rate constant, and Q_t is the amount of drug released at time t.

2.9. Mechanism of drug release

The commonly adopted model for understanding release of drug from hydrophilic matrix is a simple exponential equation known as Korsmeyer–Peppas equation.

$$\frac{M_t}{M_\infty} = K_p t^n \tag{7}$$

where M_t corresponds to amount of drug release at time t, M_∞ is the total amount of drug release after an infinite time, K_p is constant related to the structural and geometric properties of the drug delivery system (tablets) and n is the release exponent related to the mechanism of release. Peppas used this n value in order to characterize different release mechanisms. The n value was obtained from the slope of a plot of $\log M_t/M_\infty$ versus log time. If the n value is 0.5 or less, the release mechanism follows Fickian diffusion, and higher values $0.5 < n < 1$ for mass transfer follow a non-Fickian model (anomalous transport). The model follows zero-order drug release and case-II transport if the n value is equal to 1. For the values of n higher than 1, the mechanism of drug release is regarded as super case-II transport (Korsmeyer, Gurny, Doelker, Buri, & Peppas, 1983; Narasimhan, 2001; Takahara, Takayama, & Nagai, 1997).

2.10. Experimental design, statistical analysis and optimization

A 3^2 randomized full factorial design was used to optimize the variables in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations (Bolton, 1990; Franz, Browne, & Lewis, 1988; Mendenhall & Sincich, 1989). The percentage (55%, 60% and 65%) of HPMC K4M (X_1), and cabopol 934 (12.5%, 15% and 17.5%) of tablets (X_2), were selected as independent variables. The times required for 50% of drug release (t_{50}), 80% of drug release (t_{80}) and similarity factor (f_2) were selected as dependent variables. Data obtained from all NEFT formulations were analyzed using Design Expert software and used to generate the study design and the response surface plots. The matrix of the design including investigated factors and responses are shown in Table 2. Polynomial models, including linear, interaction and quadratic terms were generated for all the response variables using the software. The best fitting model was selected based on comparisons of several statistical parameters, including the coefficient of variation (CV), regression coefficient (R^2) and adjusted regression coefficient (adjusted R^2) provided by Design Expert software. In addition, analysis of variance (ANOVA) was used to identify significant effects of factors on response regression coefficients. The F test and P values were also calculated using the software. For optimization, effects of various independent variables upon measured responses were modeled using following mathematical model equation involving independent variables and their interactions for various measured responses generated by 3^2 factorial design is following:

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2 \tag{8}$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) showed how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. The relationship between the dependent and independent variables was further elucidated using response surface plots. These plots are useful to study the effects of various factors on the response at a given time and to predict the responses of dependent variables at intermediate levels of independent variables. Subsequently, a numerical optimization technique using the desirability approach and a graphical optimization technique using overlay plots were used to generate new formulations with the desired responses.

2.11. Validation of the experimental design

To validate the chosen experimental design, the experimental values of the responses were quantitatively compared with predicted values and, the relative error (%) was calculated using the following equation (Eq. (9)):

$$\text{Relative error}\,(\%) = \frac{\text{Predicted value} - \text{Experiment value}}{\text{Predicted value}} \times 100 \tag{9}$$

2.12. Physical stability studies

Physical stability studies of optimized NEFT formulation were conducted according to International Conference on Harmonization (ICH) guidelines (Mathews, 1999). The formulation was enclosed in polyethylene bottles and loaded in a desiccator containing a saturated solution of sodium chloride (75% RH) (O'Neil, Smith, & Heckelman, 1989). The desiccator was kept in an oven at 40 °C for 3 months (Patel et al., 2009). At specified time intervals, the tablets were examined for any statistical difference in their

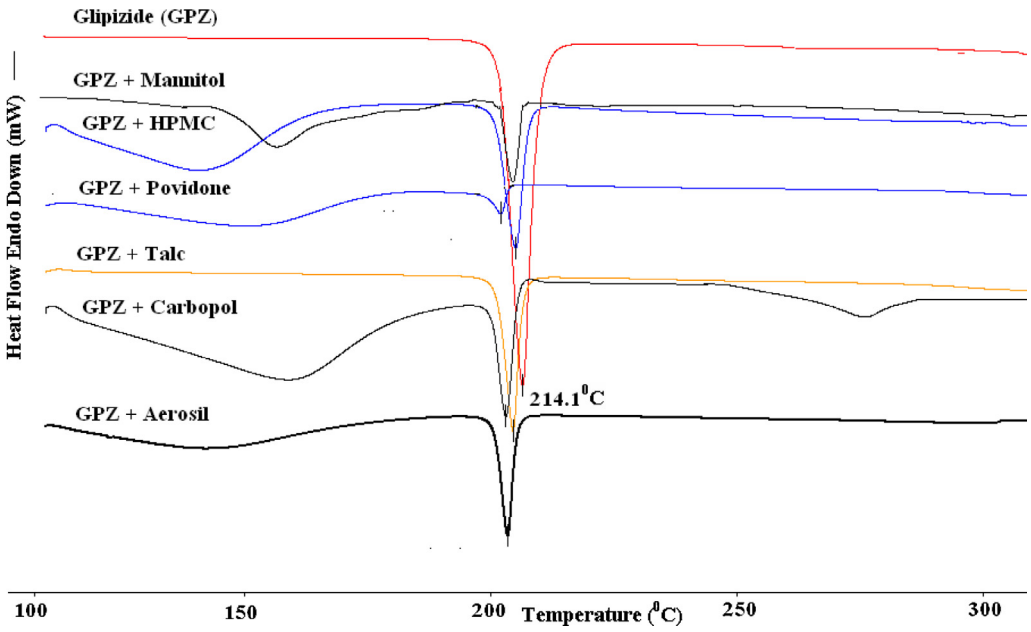

Fig. 1. Comparison of DSC thermogram of glipizide with drug–excipients mixture.

hardness values, matrix integrity, adhesion retention periods and floating characteristics using a paired Student's *t*-test. Differences were considered to be significant at $p < 0.05$.

2.13. Statistical analysis

Statistical optimization was performed using Design-Expert software (Stat-Ease Inc., USA). All measured data are expressed as mean ± standard deviation (S.D.). Each measurement was done in triplicate ($n = 3$).

3. Result and discussion

3.1. Drug–excipient interaction study

Drug–excipient interaction study at an early stage of product development is an important exercise in the development of a stable dosage form. As shown in Fig. 1, a sharp endothermic peak was observed at 214 °C in DSC thermogram of GPZ. However, the endothermic peak of GPZ was well preserved at 214 ± 2 °C in the DSC thermogram of GPZ-excipients mixtures (Fig. 1). This result inferred that there was no interaction between drug and excipients.

In isothermal stress testing, it was observed that there was no physical change (color and appearance) as well as drug content after storage of drug–excipient blends under stressed conditions (Table 1), which supported a previously reported result of DSC study on drug–excipient compatibility testing (Pani et al., 2011).

3.2. Physicochemical characteristics of tablets

Controlled-release non-effervescent floating tablets of GPZ were developed using release-retarding gel-forming polymer(s) like HPMC K4M and carbopol 934. Mannitol was used as water soluble diluent which helps in the water uptake capacity, porosity of the tablet matrix in gastric fluid and consequently would enhance floating abilities. In a previous work, Gambhire, Ambade, Kurmi, Kadam, and Jadhav (2007) studied the influence of the tablet hardness on the floating lag time and the release of diltiazem hydrochloride and concluded that tablet hardness had no (or little) effect on the drug release profile but was a determining factor with regard to buoyancy of the tablets. Increasing the hardness (>5–6 kg/cm^2) would possibly lead to prolongation of the floating lag time by affecting the rate of the tablet penetration by the dissolution medium. Based on these conclusions, the hardness of the floating tablets was adjusted, in the current work, to 4.5 kg/cm^2. The thickness of all tablet batches ranged from 2.76 ± 0.05 to 2.84 ± 0.07 mm. All the tablet formulae showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability. The weight of the tablets ranged from 197.39 ± 1.62 to 199.87 ± 2.4 mg. Drug uniformity results were found to be good among different batches; the percentage of drug content ranged from 98.80 ± 1.77% to 102.22 ± 1.27%. The percentage friability for all formulae was less than 1%, indicating good mechanical resistance.

3.3. Analysis of swelling indices

The hydration ability of the formula is important because it influences: (i) tablet buoyancy, (ii) adhesion ability of swellable polymers as HPMC K4M and carbopol 934 in contact with the test fluid and (iii) drug release kinetics. It could be concluded that the test medium uptake of the prepared matrices depends on the type and ratio of polymers. Formula NEFT-9 showed the highest swelling indices (3.98) throughout the study period. This may be related to the high affinity of carbopol 934-containing matrices to the test medium. On the other hand, significant reductions ($p < 0.05$) in the swelling indices were observed with the formulae NEFT-1 to 8 (2.72–3.71) containing higher HPMC K4M/carbopol 934 ratios. As reported by Bertram and Bodmeier (2006), the ability of hydrogels to absorb water is due to the presence of hydrophilic groups. The hydration of these functional groups results in water entry into the polymer network leading to expansion and consequently an ordering of the polymer chains. Peppas and Khare (1993) suggested that the swelling equilibrium (maximum swelling index) is reached when the osmotic forces of the functional groups are balanced by the restrictive forces of the higher ordering of the polymer chains.

Table 3
Analysis of in vitro dissolution data of factorial batch tablets.

	NEFT-1	NEFT-2	NEFT-3	NEFT-4	NEFT-5	NEFT-6	NEFT-7	NEFT-8	NEFT-9	Glucotrol XL
Zero order (R_0)	0.998	0.996	0.995	0.998	0.998	0.994	0.999	0.997	0.997	0.993
First order (R_1)	0.980	0.969	0.960	0.966	0.963	0.973	0.941	0.968	0.967	0.930
Higuchi (R_H)	0.987	0.988	0.992	0.981	0.980	0.968	0.988	0.975	0.974	0.971
K–Peppas (R_p)	0.986	0.988	0.992	0.997	0.994	0.993	0.999	0.997	0.996	0.976
n_p	0.655	0.746	0.787	0.901	0.862	0.749	0.628	0.961	0.708	0.984
K_p	0.163	0.122	0.099	0.075	0.055	0.039	0.040	0.035	0.024	0.021
Disimilarity factor (f_1)	46.38	28.55	19.43	13.91	6.63	11.25	25.24	32.07	37.71	
Similarity factor (f_2)	40.48	49.77	58.06	64.80	75.54	66.28	47.03	43.88	41.11	

R_0, R_1, R_H and R_p are the correlation coefficient of zero order, first order, Higuchi and K–Peppas equations; n_p, diffusion exponent.

3.4. In vitro buoyancy lag time and buoyancy

On immersion in 0.1 N HCl solution (pH 1.2) at 37 °C, tablets float immediately and remain buoyant more than 24 hr without disintegration. In fact, buoyancy of the tablet is governed by both the swelling (hydration) of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids, which in turn results in an increase in the bulk volume, and the presence of internal voids in the dry center of the tablet (porosity). These two factors are essential for the tablet to acquire bulk density less than 1 and so remain buoyant on the gastric fluid.

3.5. Adhesion retention periods

Like mucin covering the mucus membranes, agar gels contain large numbers of negatively charged carboxyl and sulfate groups; therefore, they have a high negative charge. The adhesion retention period of Glucotrol XL tablets was 27.50 ± 2.4 min where it was higher in prepared NEFT formulations (64.54 ± 3.45 to 05.48 ± 3.24). The adhesion retention period of the NEFT formulations were inversely proportional to the concentration of both HPMC K4M and carbopol. This may be due to the ability of HPMC K4M and carbopol to interact with agar by entanglements.

3.6. Analysis of model independent and dependent factors of drug release study

The amount of drug release from the tablets of all factorial batch tablets and commercially available Glucotrol XL tablet was determined at predetermined time points (Fig. 2a and b) and time required for 50% of drug release (t_{50}) and 80% of drug release (t_{80}) calculated (Table 3). The results of dissolution model independent factors (f_1 and f_2), calculated using drug release profile of Glucotrol XL as a reference and, model dependent factors (release rate kinetics) are depicted in Table 3. The values of t_{50} (8.5 h) and t_{80} (11.7 h) of Glucotrol XL shows that commercial tablet succeeded in controlling the rate of drug release for more than 12 h. The drug release profile of NEFT-4 (f_1 = 13.91 and f_2 = 64.80), NEFT-5 (f_1 = 6.63

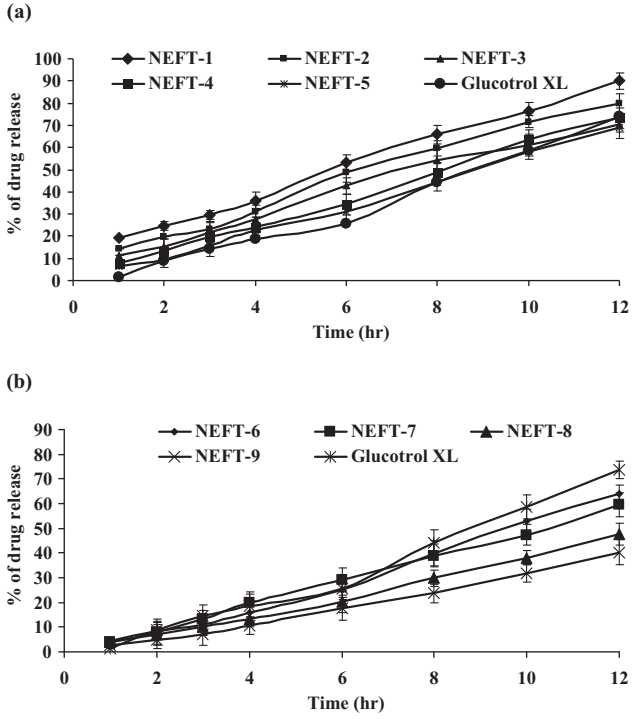

Fig. 2. Comparison of dissolution profiles of non-effervescent floating tablets (a) NEFT-1 to NEFT-5 with Glucotrol XL; (b) NEFT-6 to NEFT-9 with Glucotrol XL.

Table 4
Analysis of variance table for dependent variables from full factorial design.

Source	df	Sum square	Mean square	*F*-value	Prob > *F*
Time required for 50% of glipizide release (t_{50})					
Model	3	80.39	26.80	57.38	0.0003
X_1	1	15.94	15.94	34.13	0.0021
X_2	1	62.00	62.00	132.75	<0.0001
X_1X_2	1	2.45	2.45	5.25	0.0405
Time required for 80% of glipizide release (t_{80})					
Model	3	123.75	41.25	16.23	0.0052
X_1	1	28.41	28.41	11.18	0.0205
X_2	1	88.20	88.20	34.71	0.0020
X_1X_2	1	7.14	7.14	2.81	0.0346
Similarity factor (f_2) of dissolution study					
Model	4	192.46	98.11	16.30	0.0096
X_1	1	28.78	28.78	14.57	0.0078
X_2	1	44.23	44.23	52.42	0.0095
X_1X_2	1	138.06	138.06	7.55	0.0415
$(X_2)^2$	1	981.39	981.39	53.65	0.0018

and $f_2 = 75.54$) and NEFT-6 ($f_1 = 11.25$ and $f_2 = 66.28$) are best fitted to reference release profile. If the similarity factor (f_2) value is nearer to 100 and difference factor (f_1) value is nearer to 0, the drug release profile of test tablets can be considered as superior fit to the reference drug release profile (Higuchi, 1963; Takahara et al., 1997). Hence, the drug release profile of NEFT-5 was showed superior fit to the theoretical drug release profile among other tablets.

The correlation coefficients of zero order (R_0), First order (R_1) and Higuchi (R_H) kinetics of all formulations was determined (Table 3). The in vitro drug release from all formulations including glucotrol XL was best explained by zero order equation with highest linearity, followed by Higuchi's equation, and first order except NEFT-6. This explains that the concentration was nearly independent of drug release and drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics (or Higuchi's kinetics). The n_p value of K–Peppas equation indicates the mechanism of drug release. The n_p value of entire formulations was within the limit of 0.628–0.961 which indicates that the drug release followed anomalous diffusion ($0.5 < n_p < 1$) mechanism. Anomalous diffusion of drug release mechanism signifies a coupling of both diffusion and erosion mechanism which indicate that the drug release is controlled by more than one process during the entire period of drug release.

3.7. Analysis of data and optimization of design

The results obtained from the experiment were statistically analyzed for response variables by using Design Expert (Stat-Ease Inc., Minneapolis, Minnesota). A total nine formulations were proposed by the 3^2 factorial design for two independent variables: amount of HPMC K4M and (X_1) and amount of carbopol 934 (X_2), which were varied at two different levels (high and low). The effects of these independent variables on t_{50}, t_{80} and f_2 were investigated as optimization response parameters in the current investigation. Overview of the experimental trial and observed responses is presented in Table 2. The software provided suitable polynomial model equations involving individual main factors and interaction factors after fitting these data. The optimized model equations relating $Y_1(t_{50})$, $Y_2(t_{80})$ and $Y_3(f_2)$ as responses are given in Eqs. (10), (11) and (12) respectively.

$$Y_1(t_{50}) = 9.66 + 1.63X_1 + 3.21X_2 + 0.78X_1X_2 \quad (10)$$

$$Y_2(t_{80}) = 15.92 + 2.18X_1 + 3.83X_2 + 1.34X_1X_2 \quad (11)$$

$$Y_3(f_2) = 68.87 + 2.19X_1 - 2.72X_2 - 5.87X_1X_2 - 22.15(X_2)^2 \quad (12)$$

In the case of Y_1 (t_{50}) and Y_2 (t_{80}), coefficients b_1 and b_2 were found to be significant, with an interaction of b_{12}. It is observed from Eqs. (10) and (11) that all the coefficients are positive. It signifies dependent variable, t_{50} (Y_1) increases on increasing the value of independent variables, amount of HPMC K4M (X_1) or/and carbopol 934. In Eq. (12), the coefficient of X_1 is positive and the coefficient of X_2, X_1X_2 and $(X_2)^2$ are negative. It indicates that dependent variable, Y_3 (f_2) is directly proportional with amount of HPMC K4M (X_1) and inversely proportional to the amount of carbopol 934.

The results of ANOVA, as shown in Table 4, indicated all models were significant ($p < 0.05$) for all response parameters investigated. Model simplification was carried out by eliminating non-significant terms ($p > 0.05$) in polynomial equations (Nayak and Pal, 2011). In addition, Design-Expert software generated three-dimensional response surface plots are presented in Fig. 3a for $Y_1(t_{50})$, Fig. 3b for $Y_2(t_{80})$ and Fig. 3c for $Y_3(f_2)$. Fig. 3a and b shows that a downward trend of the wire mesh was at lower level (−1) and the upward trend was at higher level (+1) of both HPMC K4M and carbopol 934 concentration. It is predicted that the dependent variables (t_{50} and t_{80}) was inversely proportional to both the dependent variables (concentration of both HPMC K4M and carbopol 934). In Fig. 3c, the peak of folded wire mesh was at maximum point of dependent (f_2) variable when both the independent variables were at middle level (0) and signifies, f_2 value is maximum at middle point of entire concentration range (−1 to +1) treated for both HPMC K4M and carbopol 934.

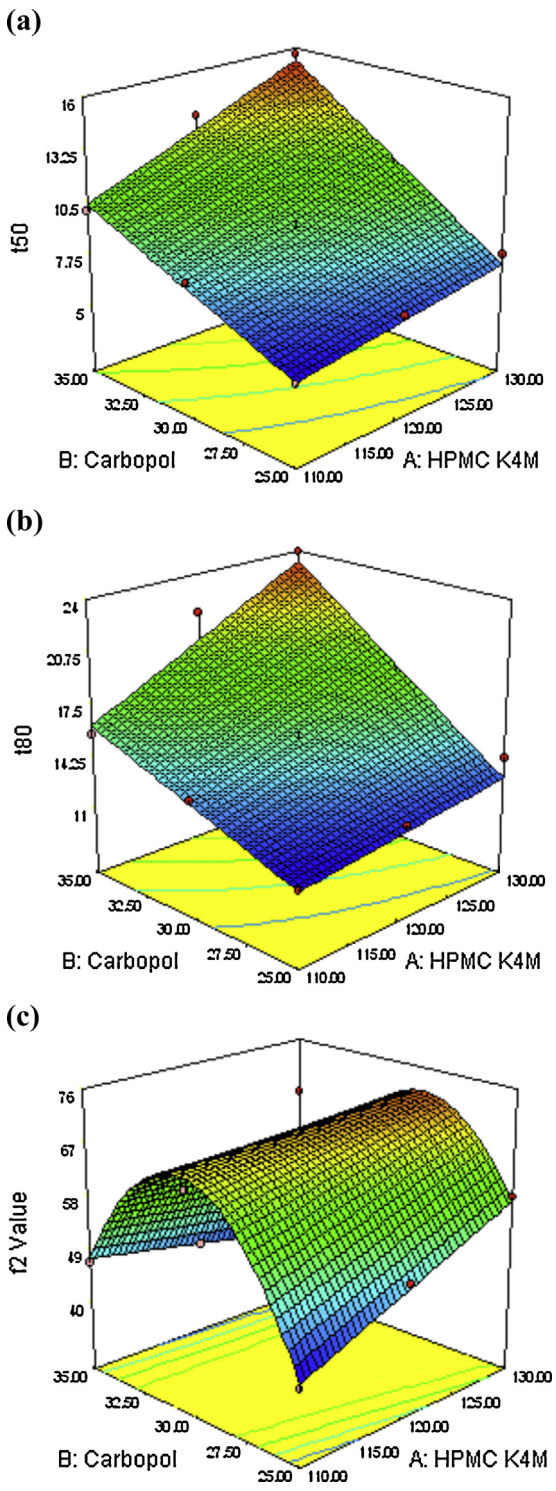

Fig. 3. Three-dimensional response curve of (A) t_{50}; (B) t_{80}; (C) f_2.

To optimize all the responses with different targets, a multi-criteria decision approach (a numerical optimization technique by the desirability function and a graphical optimization technique by

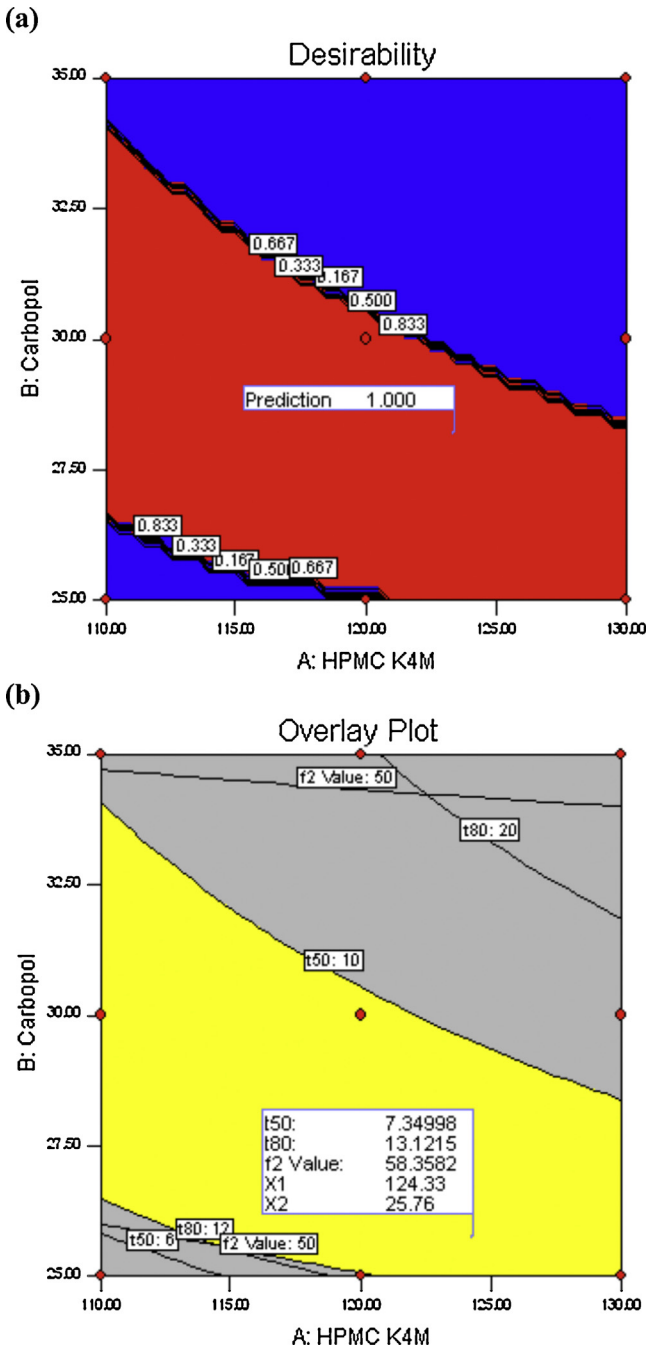

Fig. 4. Optimization of non-effervescent floating tablets (a) desirability plot; (b) overlay plot.

the overlay plot) was used (Fig. 4a and b). The optimized formulation was obtained by applying constraints on dependent variable responses and independent variables. The constraints were: t_{50}, 6–10 h; t_{80}, 12–24 h and f_2, 50–100. These constrains were common for all the formulations. The recommended concentrations of the independent variables were calculated by the Design Expert software from the above plots which has the highest desirability near to 1.0.

The optimum values of selected variables obtained using Design Expert software were 124.33 mg of X_1 and 25.76 mg of X_2. The final composition of NEFT-O comprised 10 mg GPZ, 124.33 mg HPMC K4 M, 25.76 mg carbopol 934, 33.91 mg mannitol, 2 mg Aerosil and 3 mg talc.

3.8. Evaluation and validation of the optimized formulation

The statistically optimized formulation (NEFT-O) fulfilled all the physicochemical criteria. In vitro dissolution studies were carried out on the prepared optimized formulation and t_{50}, t_{80} and f_2 were calculated to verify the theoretical prediction. The observed value of t_{50} (7.54 h), t_{80} (13.73 h) and f_2 (60.02) were in close agreement with the model predictions of t_{50} (7.35 h), t_{80} (13.12 h) and f_2 (58.36). The relative errors (%) between the predicted and experimental values for each response were calculated and the values found to be within 5%. The experimental values were in agreement with the predicted values confirming the predictability and validity of the model.

The experimental values of NEFT-O were 7.54 h for t_{50}, 13.73 h for t_{80} and 60.02 for f_2. Drug release from the optimized formulation followed zero order kinetics with a non-Fickian diffusion mechanism.

3.9. Stability study

The optimized formulation (NEFT-O) was evaluated after 3 months of storage at accelerated stability condition (40 °C ± 2 °C and 75% ± 5% RH). Stability studies indicate no significant change in appearance of the tablets, assay ($p < 0.05$), floating characteristics, t_{50} and t_{80} ($p < 0.05$).

4. Conclusion

This study discussed a positive application of a computer optimization technique for the development of controlled-release non-effervescent floating tablets of GPZ. A systematic study using a 3^2 factorial design revealed the most suitable content of HPMC K4M and carbopol 934 in the NEFT. The optimized formulation fulfilled all the requirements of the target set and exhibited suitable values of t_{50}, t_{80} and f_2. The present study clearly indicates the applicability of statistical optimization techniques to predict the composition of a formulation that gives optimum product parameters. The dosage form can control the release, avoid dose dumping, and extend the duration of action of a drug with prolonged floating time. This dosage form holds promise for further in vivo studies, which can be extrapolated for the development of other delivery systems.

References

Bertram, U., & Bodmeier, R. (2006). In situ gelling, bioadhesive nasal inserts for extended drug delivery: In vitro characterization of a new nasal dosage form. *European Journal of Pharmaceutical Sciences*, *27*, 62–71.

Bhunia, B., Dutta, D., & Chaudhuri, S. (2011). Optimization of enzyme activity determination and partial characterization of extracellular alkaline protease from *Bacillus licheniformis* NC IM-2042. *Engineering in Life Sciences*, *11*, 207–215.

Bolton, S. (1990). *Pharmaceutical statistics* (2nd ed.). NY, USA: Marcel Decker Inc.

Chowdary, K. P. R., & Rao, Y. S. (2003a). Design and in vitro and in vivo evaluation of mucoadhesive microcapsule of glipizide for oral controlled release: A technical note. *AAPS PharmSciTech*, *4*, E39.

Chowdary, K. P. R., & Rao, Y. S. (2003b). Design and in vitro evaluation of mucoadhesive controlled release oral tablets of glipizide. *Indian Journal of Pharmaceutical Sciences*, *65*, 591–594.

Dorozynski, P., Jachowicz, R., Kulinowski, P., Kwiecinski, S., Szybinski, K., Skorka, T., et al. (2004). The polymers for the preparation of hydrodynamically balanced systems – Methods of evaluation. *Drug Development and Industrial Pharmacy*, *30*, 947–957.

Foster, R. H., & Plosker, G. L. (2000). Glipizide: A review of the pharmacoeconomic implications of the extended-release formulation in type 2 diabetes mellitus. *Pharmacoeconomics*, *18*, 289–306.

Franz, R. M., Browne, J. E., & Lewis, A. R. (1988). *Experiment design, modeling and optimization strategies for product and process development* (1st ed.). *Pharmaceutical dosage forms: Disperse systems* (Vol. 1) NY, USA: Marcel Decker Inc.

Gambhire, M. N., Ambade, K. W., Kurmi, S. D., Kadam, V. J., & Jadhav, K. R. (2007). Development and in vitro evaluation of an oral floating matrix tablet formulation of diltiazem hydrochloride. *AAPS PharmSciTech*, *8*, E1–E9.

Geoffroy, J. M., Fredrickson, J. K., & Shelton, J. T. (1998). A mixture experiment approach for controlling the dissolution rate of a sustained-release tablet. *Drug Development and Industrial Pharmacy*, *24*, 799–806.
Hamed, E., & Sakr, A. (2001). Application of multiple response optimization technique to extended release formulation design. *Journal of Controlled Release*, *73*, 329–338.
Higuchi, T. (1963). Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *Journal of Pharmaceutical Sciences*, *52*, 1145–1149.
Hirtz, J. (1985). The GIT absorption of drugs in man: A review of current concepts and methods of investigation. *British Journal of Clinical Pharmacology*, *19*, 77S–83S.
Joshi, S. A., Chavan, S. S., & Sawant, K. K. (2010). Rivastigmine-loaded PLGA and PBCA nanoparticles: Preparation, optimization, characterization, *in vitro* and pharmacodynamic studies. *European Journal of Pharmaceutics and Biopharmaceutics*, *76*, 189–199.
Khanna, R., Agarwal, S. P., & Ahuja, A. (1997). Mucoadhesive buccal tablets of clotrimazole for oral candidiasis. *Drug Development and Industrial Pharmacy*, *23*, 831–837.
Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P., & Peppas, N. A. (1983). Mechanisms of solute release from porous hydrophilic polymers. *International Journal of Pharmaceutics*, *15*, 25–35.
Li, S., Lin, S., Chien, Y. W., Daggy, B. P., & Mirchandani, H. L. (2001). Statistical optimization of gastric floating system for oral controlled delivery of calcium. *AAPS PharmSciTech*, *2*, E1.
Li, S., Lin, S., Daggy, B. P., Mirchandani, H. L., & Chien, Y. W. (2002). Effect of formulation variables on the floating properties of gastric floating drug delivery system. *Drug Development and Industrial Pharmacy*, *28*, 783–793.
Malakar, J., & Nayak, A. K. (2012). Formulation and statistical optimization of multiple-unit ibuprofen-loaded buoyant system using 2^3-factorial design. *Chemical Engineering Research and Design*, *90*, 1834–1846.
Mathews, B. R. (1999). Regulatory aspects of stability testing in Europe. *Drug Development and Industrial Pharmacy*, *25*, 831–856.
Mendenhall, W., & Sincich, T. (1989). *Multiple regression* (3rd ed.). USA: Dellen Publishing Co.
Nakamura, F., Ohta, R., Machida, Y., & Nagai, T. (1996). In vitro and in vivo nasal mucoadhesion of some water-soluble polymers. *International Journal of Pharmaceutics*, *134*, 173–181.
Narasimhan, B. (2001). Mathematical models describing polymer dissolution: Consequences for drug delivery. *Advanced Drug Delivery Reviews*, *48*, 195–210.
Nayak, A. K., & Pal, D. (2011). Development of pH-sensitive tamarind seed polysaccharide–alginate composite beads for controlled diclofenac sodium delivery using response surface methodology. *International Journal of Biological Macromolecules*, *49*, 784–793.
O'Neil, M. J., Smith, A., & Heckelman, P. E. (1989). *The Merck index* (11th ed.). Whitehouse Station, NJ, USA: Merck & Co., Inc.
Pani, N. R., Nath, L. K., & Acharya, S. (2011). Compatibility studies of nateglinide with the excipients of immediate release tablets. *Acta Pharmaceutica*, *61*, 237–247.
Pani, N. R., Nath, L. K., & Bhunia, B. (2010). Formulation, development and optimization of immediate release tablet of nateglinide by factorial designs. *Drug Discoveries & Therapeutics*, *4*, 453–458.
Pani, N. R., Nath, L. K., & Bhunia, B. (2012). Application of DSC IST and FTIR study in the compatibility testing of nateglinide with different pharmaceutical excipients. *Journal of Thermal Analysis and Calorimetry*, *108*, 219–226.
Patel, A., Modasiya, M., Shah, D., & Patel, V. (2009). Development and in vivo floating behavior of verapamil HCl intragastric floating tablets. *AAPS PharmSciTech*, *10*, 310–315.
Peppas, N. A., & Khare, A. R. (1993). Preparation, structure and diffusional behavior of hydrogel in controlled release. *Advanced Drug Delivery Reviews*, *11*, 1–35.
Perioli, L., Ambrogi, V., Paganoa, C., Scuota, S., & Rossi, C. (2009). FG90 chitosan as a new polymer for metronidazole mucoadhesive tablets for vaginal administration. *International Journal of Pharmaceutics*, *377*, 120–127.
Prajapati, S. T., Patel, L. D., & Patel, D. M. (2008). Gastric floating matrix tablets: Design and optimization using combination of polymers. *Acta Pharmaceutica*, *58*, 221–229.
Rosa, M., Zia, H., & Rhodes, T. (1994). Dosing and testing in-vitro of a bioadhesive and floating drug delivery system for oral application. *International Journal of Pharmaceutics*, *105*, 65–70.
Sankalia, J. M., Sankalia, M. G., & Mashru, R. C. (2008). Drug release and swelling kinetics of directly compressed glipizide sustained-release matrices: Establishment of level A IVIVC. *Journal of Controlled Release*, *129*, 49–58.
Takahara, J., Takayama, K., & Nagai, T. (1997). Multiobjective simultaneous optimization technique based on an artificial neural network in sustained release formulations. *Journal of Controlled Release*, *49*, 11–20.
(2007). *The British Pharmacopoeia*. London: British Pharmacopoeia Commission, HMSO (electronic version).
(2003). *The United States Pharmacopeia*. Rockville, MD: United States Pharmacopeial Convention.
Thombre, A. G., DeNoto, A. R., & Gibbes, D. C. (1999). Delivery of glipizide from asymmetric membrane capsules using encapsulated excipients. *Journal of Controlled Release*, *60*, 333–341.
Wai-Yip Lee, T., & Robinson, R. J. (2000). Controlled drug delivery systems. In A. R. Gennaro (Ed.), *Remington: The science and practice of pharmacy* (pp. 903–929). Philadelphia: University of Sciences.