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Development of controlled release tablet by optimizing HPMC: Consideration of theoretical release and RSM

Nihar R. Pani[a,*], Lila K. Nath[b]

[a] Department of Pharmaceutics, Gayatri College of Pharmacy, Sambalpur, Orissa, India
[b] Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam, India

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ABSTRACT

The objective of the study was to develop controlled release tablets of nateglinide, a meglitinide derivative anti-diabetic drug, considering theoretical release profile and response surface methodology (RSM). 3^2 factorial design was utilized to optimize concentration of hydroxylpropylmethylcellulose (HPMC) K15M and K100M to obtain the desired responses (drug release at one and six hours). Theoretical release profile of drug for controlled release formulation was calculated and considered as reference for the determination of similarity factor (f_2) and desimilarity factor (f_1). RSM, f_2 and f_1 were used to select the optimum formulation. Formulation containing HPMC K15M (5%) and HPMC K100M (15%) was found optimum with desired responses with $f_2 = 86.05$ and drug release profile followed zero order kinetics. Excipients used were compatible with drug, confirmed initially through DSC and IST study. The optimization of experiments was validated and optimum formulation was passed the stability study.

1. Introduction

Regardless of the delivery type of controlled release formulations, the main mechanisms associated with drug transport include diffusion, swelling, erosion, ion exchange, and osmotic effect which have been investigated in several studies (Das & Das, 2003). Hydrophilic matrix systems are the most popular among different technologies used in controlled drug delivery because of the simplicity of formulation, ease of manufacturing, low cost, FDA acceptance, and applicability to drugs with wide range of solubility (Jamzad & Fassihi, 2006; Sako, Sawada, Nakashima, Yokohama, & Sonobe, 2002; Turner, Federici, Hite, & Fassihi, 2004). Drug release from these systems is the consequence of controlled matrix hydration, followed by gel formation, change of textural/rheological behavior, matrix erosion, and/or drug dissolution and diffusion, the significance of which depends on drug solubility, concentration and changes in matrix characteristics (Korsmeyer, Gurny, Doelker, Buri, & Peppas, 1983). Hydroxypropylmethylcellulose (HPMC), which is commonly used in hydrophilic matrix drug delivery systems, is mixed with alkylhydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups. The hydration rate of HPMC increases with an increase in the hydroxypropyl content (Colombo, Bettini, & Peppas, 1999; Khurahashi, Kami, & Sunada, 1996). HPMC has been found to be a very versatile material for the formulation of soluble matrix tablets. It is widely accepted pharmaceutical excipients and is included in all major compendia. Because HPMC is available in a wide range of molecular weight, effective control of gel viscosity is easily achieved (Bettini et al., 2001). Different factors that can influence drug release from hydrophilic matrices have been discussed and presented elsewhere (Gao et al., 1996; Jamzad, Tutunji, & Fassihi, 2005; Williams, Reynolds, Cabelka, Sykora, & Mahaguna et al., 2002). Among these, the type, amount, and properties of the polymer used play a fundamental role (Ford, Rubinstein, McCaul, Hogan, & Edgar, 1987; Mitchell et al., 1993).

Statistical experimental design methodologies are powerful, efficient and systematic tools in the design of pharmaceutical dosage forms, allowing a rational study of the influence of formulation parameters on the selected responses with a shortening of the experiment time and an improvement in the research and development work (Gabrielsson, Lindberg, & Lundstedt, 2002; Lunstedt et al., 1998; Pani, Nath, & Bhunia, 2010; Renoux, Demazieres, Cardot, & Aiache, 1996).

A meglitinide derivative, antidiabetic drug Nateglinide is a weak acid ($pK_a = 3.1$), practically insoluble in water and acidic environment, and highly permeable (class II drugs in accordance to Biopharmaceutics Classification System, BCS) drug (Pani et al., 2010). The oral bioavailability of nateglinide is nearly 75% and its elimination half-life is 1.44 h (McLeod, 2004). The elimination half-life of nateglinide can be improved by formulating its controlled release tablets by using HPMC as a matrix polymer.

The present investigation aims at the design, development and optimization of controlled release tablet of a model drug,

* Corresponding author. Tel.: +91 8018544152.
E-mail address: niharpani@gmail.com (N.R. Pani).

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nateglinide by using different grades of HPMC alone or in combination. The drug release profile of the tablets was to compare with theoretical release profile by determining similarity (f_2) and difference factors (f_1). The dissolution data were fit into the model dependent factors (zero order, first order, Higuchi model and Korsmeyer-Peppas) to investigate the rate kinetics and mechanism of drug release.

An attempt of systematic formulation approach was taken for optimization of controlled release tablets by 3^2 full factorial design to investigate the joint influence of two formulation variables, i.e., concentration of HPMC K15M and HPMC K100M on the percentage of drug release at 1 h (DR_1) and, 6 h (DR_6). The drug release profile of the formulation having similarity with theoretical drug release profile has considered as optimum formula.

2. Materials and methods

2.1. Materials

Nateglinide (NTG) was the kind gift from Glenmark Pharmaceuticals Ltd., Nashik, Cross carmelose sodium (CCS), Lactose, Microcrystaline cellulose (MCC), Talc, Colloidal silicon dioxide (Aerosil) were purchased from Loba Chemie Ltd, Mumbai, Hydroxypropyl-methyl-cellulose (HPMC) K4M, K15M and K100M, Polyvinyl pyrollidone (PVP) were purchased from SD fines Ltd., Mumbai. All other chemicals were of analytical grade and purchased from Merck India Ltd. and Rankem Ltd., Mumbai.

2.2. Calculation of controlled dose

The rate of drug release from dosage form is independent of the amount of drug remaining in the dosage form and constant over time according to zero order release kinetics. The release from the controlled release dosage form should follow zero-order kinetics, as shown in Eq. (1).

$$K_r^0 = \text{Rate in} = \text{Rate out} = K_e \times C_d \times V_d \quad (1)$$

where, 'Rate in' is the rate of availability of drug in the body, 'Rate out' is the rate of elimination of drug from the body, K_r^0 is the zero-order rate constant for drug release (amount/time), K_e is the first-order rate constant of overall drug elimination (h^{-1}), C_d is the desired drug level in the blood (amount/volume), and V_d is the volume in which the drug is distributed. The elimination half-life ($t_{1/2}$) of nateglinide is 1.44 h, K_e is 0.48125 h^{-1} ($K_e = 0.69/t_{1/2}$), C_d is 2.40 mg/L, and V_d is 10.51 L so, K_r^0 is 12.14 mg/h (Eq. (1)) (McLeod, 2004). The rate constant for drug release should also be equal to the elimination rate constant so as to maintain the steady-state condition in blood. Nateglinide is not completely absorbed from the gastrointestinal tract; the oral bioavailability is 75%. Hence, the drug release rate should be 25% more than that of the elimination rate, which would be 15.174 mg/h (12.139 mg/h × 125/100). For a system in which the maintenance dose releases drug by a zero-order process for a specified period of time, the total dose calculation as Eq. (2).

$$W = [D_i - (K_r^0 \times T_p)] + K_r^0 \times T_d \quad (2)$$

where, W is total dose, D_i is the initial dose, K_r^0 is the zero-order rate constant, T_p is the time of peak plasma drug level and T_d is the total time (hours) desired for sustaining the release of drug from the single dose.

If the D_i is 60 mg, T_p is 1.4 h, T_d is 12 h and K_r^0 is 15.17 mg/h, then the total dose would be 225.09 mg (as per Eq. (2)).

Table 1
Results of analysis of isothermal stress testing samples after 3 weeks of storage at stressed conditions ($n = 3$).

Samples	Ratios (drug–excipient)	% Drug remaining[a] ($n = 3$)	
		Control samples[b]	Stressed samples[c]
NTG	–	100.6 ± 0.5	99.4 ± 1.5
NTG + MCC	1:2	100.1 ± 1.7	99.7 ± 1.1
NTG + HPMC	1:1	101.2 ± 1.2	100.5 ± 1.3
NTG + CCS	1:1	100.6 ± 1.3	99.1 ± 2.3
NTG + PVP	2:1	100.5 ± 1.1	99.6 ± 1.3
NTG + talc	3:1	100.2 ± 1.4	99.6 ± 2.2
NTG + Aerosil	3:1	100.3 ± 1.6	99.1 ± 1.6

[a] Values expressed as average ± standard deviation.
[b] Drug excipient blends without added water and stored in refrigerator.
[c] Drug excipient blends with 10% (w/w) added water and stored at 50 °C for 3 weeks.
Abbreviations: NTG, nateglinide; MCC, micro crystaline celluose; HPMC, hydroxy propyl methyl cellulose; CCS, cross carmelose sodium; pvp, polyvinylpyrolidone.

2.3. Calculation of theoretical release profile

In 12 h controlled release formulation of nateglinide, drug should release 60 mg in the first hour like conventional tablet, i.e., 26.63% w/w of total dose (225.09) and 15.03 mg (6.67% w/w of total dose) per hour for remaining 11 h.

2.4. 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 (Kandarapu, Grover, Chawla, & Garg, 2001; Pani, Nath, & Acharya, 2011). 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.

2.5. Isothermal stress testing

For isothermal stress testing (Kandarapu et al., 2001; Pani et al., 2011), drug and different excipients (Table 1) were weighed 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.

2.6. Formulation of tablets

The controlled release tablets of nateglinide were prepared through wet granulation technique by incorporating HPMC K15M and K100M followed by 'full 3^2 factorial design' (Table 2). Nateglinide, microcrystalinecellulose (MCC), HPMC and polyvinylpyrolidone (PVP) were dispensed accurately. Each ingredient was shifted through # 80 sieve, transferred in to a polyethylene bag and mixed

Table 2
3^2 Full factorial design layout for controlled release NTG tablets.

Batch code[a]	Variable levels in coded form[b]		DR_1 (%, w/w) ($n = 3$)[c]	DR_6 (%, w/w) ($n = 3$)[c]
	X_1 (%)	X_2 (%)		
CR-1	−1	−1	58.35 ± 1.31	93.12 ± 1.91
CR-2	−1	0	44.15 ± 0.41	78.80 ± 0.91
CR-3	−1	1	30.34 ± 1.51	64.70 ± 0.78
CR-4	0	−1	41.05 ± 0.45	76.25 ± 2.15
CR-5	0	0	29.39 ± 1.40	62.08 ± 1.17
CR-6	0	1	18.44 ± 0.52	47.98 ± 2.65
CR-7	1	−1	25.10 ± 0.43	60.09 ± 1.25
CR-8	1	0	15.86 ± 1.33	45.32 ± 1.16
CR-9	1	1	6.80 ± 1.28	30.74 ± 0.86
Check point	−0.5	+0.5	28.15 ± 1.67	60.98 ± 2.42

Codes values	Actual value	
	X_1	X_2
−1	5	5
0	10	10
+1	15	15
−0.5	7.5	7.5
+0.5	12.5	12.5

[a] All batches contained 5% (w/w) of polyvinylpyrolidone; 2% (w/w) of cross carmelose sodium; 2% (w/w) of talc; 2% (w/w) Aerosil and microcrystallinecellulose upto 100% (w/w).
[b] X_1, amount of HPMC K15M (%, w/w); X_2, amount of HPMC K100M (%, w/w).
[c] Data are shown as mean ± SD.
Abbreviations: DR1, drug release at 1 h; and DR6, drug release at 6 h.

for 20 min. The 'dry mix' was evaluated for flow properties and loss on drying (LOD) and subjected for wet granulation by kneading with sufficient quantity of ethanol to obtain a lump mass. The wet mass was dried at 45 °C in tray dryer till the LOD of dried granules was equivalent to LOD of the 'dry mix' (20–30 min). The dried granules were shifted through #20 sieve, weighed and subjected for the evaluation of flow properties. The remaining ingredients of Table 2, i.e., crosscarmelosesodium (CCS), talc and aerosil were added to dried granules and mixed for 5 min to get lubricated granules. The lubricated granules were evaluated and converted into tablets at 5–6 kg/cm^2 hardness by using 8 mm standard concave punch set in 16 station rotary tablet punching machine. The tablets were double wrapped in polyethylene bag till further study.

2.7. Evaluation of granules and tablets

The prepared granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, and Hausner ratio. The prepared tablets were evaluated for weight variation, friability, hardness and thickness (Lachman, Liberman, & Kanig, 1987).

In vitro drug release study was carried out in United States Pharmacopeia (USP) dissolution apparatus II (TDT-08L; Electrolab, Mumbai, India) by rotating paddle at 50 rpm in 1000 ml of 0.1 N HCl + 0.5% sodium lauryl sulphate for first 2 h and in 1000 ml of simulated intestinal fluid (phosphate buffer, pH 6.8) for another 10 h as dissolution medium maintaining temperature at 37 ± 0.5 °C. An aliquot of 5 ml was withdrawn at different time intervals (1, 2, 3, 4, 6, 8, 10 and 12 h) and equal volume of fresh dissolution medium was replaced to maintain the sink condition. The samples were filtered through nylon membrane filter (0.45 μm pore size), suitably diluted and analyzed in UV–visible spectrophotometer at 216 nm to determine the amount of drug release (Pani et al., 2010). The fresh dissolution medium replacement was considered in the calculation of amount of drug release. The cumulative percent drug release was plotted against time to determine the release profile.

2.8. Determination of difference and similarity factors

The in vitro drug release profile of the formulations (test) was compared with the theoretical release profile (reference) of controlled release tablets of nateglinide by 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. (3).

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100 \quad (3)$$

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 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. (4).

$$f_2 = 50 \ \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{j=1}^{n} |R_j - T_j|^2 \right]^{-0.5} \times 100 \right\} \quad (4)$$

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

2.9. 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 drug release process from controlled released tablets of NTG, 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).

2.9.1. 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 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.

$$Q_t = K_0 t \tag{5}$$

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.

2.9.2. 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 and Robinson, 2000). In the case of drug release from reservoir devices as well as multi particulate systems the first order kinetics is followed.

$$\log C = \log C_0 - \left(\frac{K_1 t}{2.303}\right) \tag{6}$$

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.

2.9.3. 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 (Higuchi, 1963; Wai-Yip and Robinson, 2000). This relation can be used to describe drug dissolution from several types of modified-release dosage forms by the following Eq. (7)

$$Q_t = K_H (t)^{1/2} \tag{7}$$

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

2.10. 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.

$$\frac{M_t}{M_\infty} = K_p t^n \tag{8}$$

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 et al., 1983; Narasimhan, 2001; Takahara, Takayama, & Nagai, 1997).

2.11. Full factorial design

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 (Acharya, Patra, & Pani, 2014; Bhunia, Dutta, & Chaudhuri, 2011; Bolton, 1990; Franz, Browne, & Lewis, 1988; Pani et al., 2010). The percentage (5%, 10% and 15%) of HPMC K15M (X_1), and HPMC K100M (X_2), were selected as independent variables. The percentage of drug release at 1 h (DR_1) and, 6 h (DR_6) were selected as dependent variables.

2.12. Stability study

The factorial batches were subjected to accelerated stability ($40 \pm 2\,^\circ C/75 \pm 5\%$ relative humidity) testing. After a specified period of time (1, 2, and 3 months), samples were withdrawn and subjected to assay and in vitro dissolution studies. The stability study was conducted as per the International Conference on Harmonization (ICH) guidelines (Pani et al., 2011).

3. Result and discussion

3.1. Determination of theoretical release profile

Ideally, a controlled release tablet should release the required quantity of drug with predetermined kinetics in order to maintain an effective drug plasma concentration. To achieve this, the tablet should be formulated so that it releases the drug in predetermined and reproducible manner. By considering the drug's biopharmaceutic and pharmacokinetic profile, one can determine the required release from the tablet. The amount of NTG releases at different time interval from the 12 h controlled release tablets were calculated theoretically by considering the reported pharmacokinetic data of NTG. The theoretical amount of nateglinide release from its controlled release tablets was 26.63% w/w in 1 h, 33.3% w/w in 2 h, 39.97% w/w in 3 h, 46.64% w/w in 4 h, 59.98% w/w in 6 h, 73.32% w/w in 8 h, 86.66% w/w in 10 h and 100.00% w/w in 12 h, which was considered as reference drug release profile for the comparison with drug release profile of test formation. The results showed that about 26.63% w/w of the drug should be released during first hour, which is in accordance with the conventional dose amount of a NTG tablet.

3.2. 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 143 °C in DSC thermogram of NTG. However, the endothermic peak of NTG was well preserved at $143 \pm 2\,^\circ C$ in the DSC thermogram of NTG-excipients mixtures (Fig. 1). This result inferred that there was no interaction between drug and excipients (Kandarapu et al., 2001).

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).

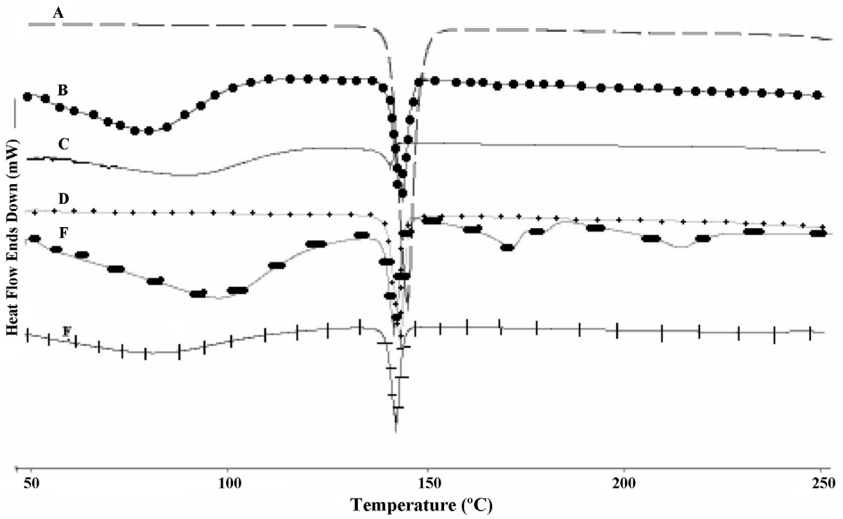

Fig. 1. Comparision of DSC thermogram of NTG with drug–excipients mixture. (A) nateglinide (NTG); (B) hydroxy propyl methyl cellulose + NTG; (C) povidone + NTG; (D) talc + NTG; (E) cross carmelose sodium + NTG; (F) microcystaline cellulose + NTG.

3.3. Evaluation of physical parameters of granules and tablets

The flow properties of granules can be judged from the angle of repose, compressibility index and Hausner ratio. The angle of repose (θ) <30 °C indicates free flowing material and >40° with poor flow properties. The compressibility index <10% indicates excellent flow properties and >38% with poor flow properties. The Hausner ratio 1.00–1.11 indicates free flowing and >1.60 with poor flow properties (Lachman et al., 1987). Values for angle of repose (θ), compressibility index (%), and Hausner ratio for all prepared granules were found to be in the range of 20.4–25.4 °C, 6.11–7.32%, and 1.04–1.07, respectively, which showed that the granules were free flowing and can be used for tablet compression. Percentage of weight variation was observed within the limit of ±5% (w/w) for all the prepared tablets, which is well accepted for uncoated tablets as per United State Pharmacopeia, National Formulary (USP, 2004). Friability test of the prepared tablet of all batches was passed (weight loss <1%, w/w), which assumed that tablets have sufficient mechanical integrity and strength.

3.4. Analysis of model independent and dependent factors of dissolution study

The amount of drug release from the tablets of all factorial batches was determined at predetermined time points (Fig. 2) and the dissolution model independent factors, f_1 and f_2 were calculated by considering theoretical release profile as a reference. The results of dissolution model independent factors (Table 3) revealed that the drug release profile of CR-3 (f_1 = 11.92 and f_2 = 55.38), CR-5 (f_1 = 6.17 and f_2 = 68.90) and CR-7 (f_1 = 2.1 and f_2 = 86.05) are best fitted to the theoretical 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 (Takahara et al., 1997). Hence, the drug release profile of CR-7 was showed superior fit to the theoretical drug release profile among other tablets.

The correlation coefficient of zero order (R_0), First order (R_1) and Higuchi (R_H) kinetics of all formulations was determined. The in vitro drug release of CR-7 was best explained by zero order equation with highest linearity (R_0 = 0.998), followed by Higuchi's equation, (R_H = 0.992) and first order (R_1 = 0.973). 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).

3.5. Mechanism of drug release

The drug release mechanism from controlled release devices is very complex, and not yet completely understood. Although some processes may be classified as either purely diffusional or purely erosion controlled, many others can only be interpreted as being governed by both. To evaluate the mechanism of drug release of controlled release tablets of nateglinide, the in vitro dissolution profile was fitted into the Korsmeyer-Peppas (KP) equation. The correlation coefficient (R_p), slope (n_p) and intercept (K_p) of KP equation various factorial batch formulations are depicted in Table 3. The value of R_p of all formulations showed the good linearity between log cumulative amount of drug release and log time.

The K_p value of CR-1 (n_p = 0.249), CR-2 (n_p = 0.363) and CR-3 (n_p = 0.488) was 1.757, 1.618 and 1.468 respectively which indicates that K_p decreases and n_p increases as the concentration of HPMC K15M increases (from 5% to 15% w/w of tablets) at fixed concentration (5% w/w) of HPMC K100M. The values of K_p and n_p of the formulation CR-4, CR-5 and CR-6 (Table 3) revealed that K_p decreases and n_p increases as the concentration of HPMC K15M increases (from 5% to 15% w/w of tablets) at fixed concentration

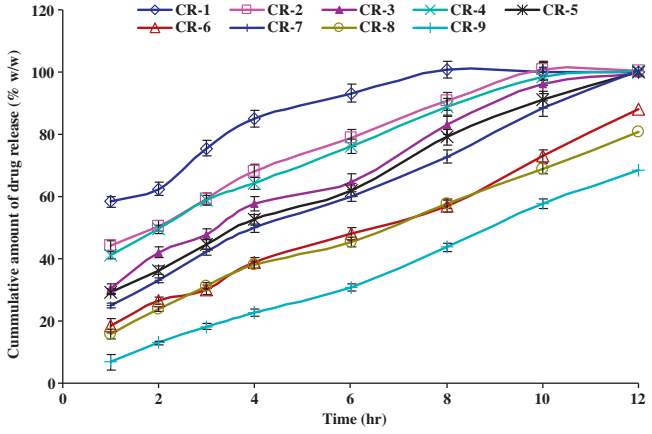

Fig. 2. In vitro drug release study of factorial batch tablets.

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

	Model independent factors		Parameters of model dependent factors				
	f_1	f_2	Zero order	First order	Higuchi	K-Peppas	
			R_0	R_1	R_h	R_p	n_p
TR*			1.000	0.985	0.988	0.988	0.544
CR-1	44.72	27.06	0.908	0.889	0.955	0.973	0.249
CR-2	26.99	38.54	0.979	0.958	0.993	0.991	0.363
CR-3	11.92	55.38	0.989	0.962	0.992	0.994	0.488
CR-4	23.82	41.23	0.984	0.962	0.996	0.995	0.381
CR-5	6.17	68.90	0.997	0.977	0.992	0.991	0.511
CR-6	18.69	47.22	0.996	0.979	0.980	0.989	0.614
CR-7	2.10	86.05	0.998	0.973	0.992	0.994	0.561
CR-8	22.40	43.18	0.997	0.960	0.992	0.998	0.644
CR-9	44.01	29.21	0.997	0.961	0.979	0.997	0.916

* Theoretical release.

(10% w/w) of HPMC K100M. The inverse relationship of K_p and direct relationship of n_p was found with concentration of HPMC in CR-7, CR-8 and CR-9 which contain 5%, 10% and 15% of HPMC K15M respectively at fixed concentration of HPMC K100M (15% w/w). The result of K_p values revealed that the rate of drug release decreases as the concentration of HPMC increases in the formulations.

The n_p value indicated that the mechanism of drug release from the tablets of CR-3 ($n_p = 0.488$) follows fickian diffusion ($n_p < 0.5$) and the tablets of CR-5 ($n_p = 0.511$) and CR-7 ($n_p = 0.561$) followed anomalous diffusion ($0.5 < n_p < 1$) during the entire period of drug release (12 h). Fickian diffusion is characterized by a linear dependence of release of drug with the square root of time that is concentration dependent. The fundamental principle of diffusion is based on Fick's laws, which describe the macroscopic transport of molecules by a concentration gradient. Anomalous diffusion of drug release mechanism signifies a coupling of the diffusion and erosion mechanism which indicate that the drug release is controlled by more than one process. Hence the drug release from the tablets of CR-5 and CR-7 is controlled by both diffusion and erosion process in 12 h of study of drug release.

3.6. Optimization of formulations by factorial design

The amount of HPMC K15M (X_1) and HPMC K100M (X_2) in tablets were chosen as independent variables in a 3^2 full factorial design. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (9)$$

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 nonlinearity. As shown in Table 2, The DR_1 and DR_6 value for the 9 batches (F1–F9) showed a wide variation (i.e., 6.80–58.35 and 30.74–93.12% (w/w), respectively). The data indicates that the dependent variables such as DR_1 and DR_6 are dependent on the selected independent variables such as concentration of HPMC K15M and 100M in the tablets. The fitted equations (full and reduced) relating the responses DR_1 and DR_6 to the transformed factor are shown in Table 2. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). Table 4a shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors (Mendenhall & Sincich, 1989). The high values of correlation coefficient for DR_1 and DR_6 indicate a good fit (Table 4a). The equations may be used to obtain estimates of the response as a small error of variance was noticed in the replicates.

The significance test for regression coefficients was performed by applying the Student t test. A coefficient is significant if the calculated t value is greater than the critical value of t. The significance level of coefficient b_{11} was found to be $p = 0.227$ and 0.619 in full model for DR_1 and DR_6, respectively; hence it was omitted from the full model for both the cases to generate the reduced models. The results of statistical analysis are shown in Table 4b. The coefficients b_1, b_2, b_{22}, and b_{12} were found to be significant at $p < 0.05$, hence they were retained in both the reduced model. The reduced model was tested in portions to determine whether the coefficient b_{11} contributes significant information for the prediction of DR_1 and DR_6 or not (Franz et al., 1988). The results of multiple linear regression analysis (reduced model) of DR_{1h} and DR_{6h} reveal that the coefficient 'A' and 'B' bears a negative sign. It signifies that the concentration of HPMC K15M and K100M is inversely proportional to $DR_{1\,h}$ and $DR_{6\,h}$. The graphical representation (3-dimensional plot) of the regression equation of $DR_{1\,h}$ (Fig. 3) and $DR_{6\,h}$ (Fig. 4) was obtained by using the software Design Expert 7. The 3-D plot showed that a downward trend of the wire mesh was depicted at higher level (+1) and the upward trend was at lower level of (−1) of both the grade of HPMC concentration. It predicted that the $DR_{1\,h}$ and $DR_{6\,h}$ was inversely proportional to the concentration of both HPMC K15M and HPMC K 100M.

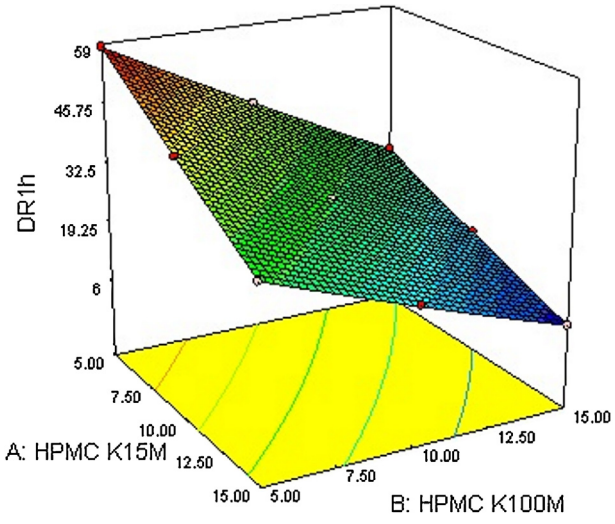

Fig. 3. 3-Dimensional response curve of drug release at 1 h (DR_1).

Table 4a
Calculations for testing the model in portions.

	DF	SS	MS	F	R^2	p	Adj R^2
For % of dissolution at 1 h							
Regression							
FM	5	2.02×10^3	0.41×10^3	10.04×10^3	0.999	<0.0001	0.999
RM	4	2.02×10^3	0.51×10^3	9.48×10^3	0.999	<0.0001	0.999
Error							
FM	3	0.12	0.04				
RM	4	0.21	0.05				
For % of dissolution at 6 h							
Regression							
FM	5	2.92×10^3	0.58×10^3	13.65×10^3	1	<0.0001	0.999
RM	4	2.92×10^3	0.73×10^3	02.07×10^3	1	<0.0001	0.999
Error							
FM	3	0.12	0.04				
RM	4	0.14	0.04				

Abbreviations: DF, degrees of freedom; SS, sum of squares; MS, mean of squares; F, Fischer's ratio; R^2, regression coefficient; p, test of significance; FM, full model; and RM, reduced model.

Table 4b
Summary of regression analysis results.

Response	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
For % of dissolution at 1 h						
FM	29.48	−11.48	−14.18	0.21	0.48	2.43
RM	29.63	−11.48	−14.18		0.48	2.43
For % of dissolution at 6 h						
FM	62.05	−14.34	−16.75	0.08	0.03	0.23
RM	62.10	−14.34	−16.75		0.03	0.23

Abbreviations: FM, full model; and RM, reduced model.

The result of theoretical release profile of nateglinide (Table 3) was considered as desired response for statistical optimization of formulation. The desired responses $DR_{1\,h}$ and $DR_{6\,h}$ were predicted from point prediction method by using Design expert software 7 and the formulation (CR-7) prepared at '−1' (5% w/w) and '+1' (15% w/w) levels of factor 'X_1' (concentration of HPMC K15M) and 'X_2' (concentration of HPMC K100M) respectively was considered optimum formulation.

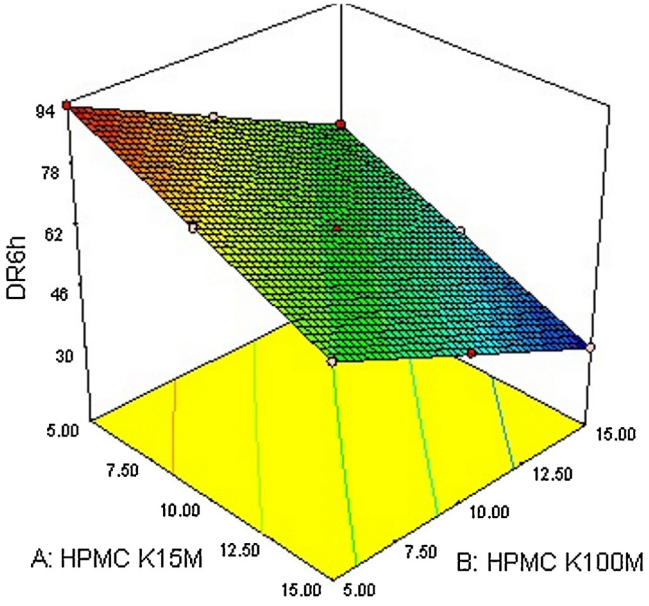

Fig. 4. 3-Dimensional response curve of drug release at 6 h (DR_6).

3.7. Validation of experimental model

A checkpoint batch was prepared at $X_1 = -0.5$ level and $X_2 = +0.5$ (Table 3). From the reduced model, it is expected that the calculated value of $DR_{1\,h}$ and $DR_{6\,h}$ in checkpoint should be 28.15 and 60.98 respectively. The experimental value of $DR_{1\,h}$ and $DR_{6\,h}$ in check point batch (Table 3) was close with calculated value. Thus, from the results of statistical optimization technique it can be conclude that all models are mathematically significant.

3.8. Stability study

The optimized formulation (CR-7) was evaluated after 3 months of storage at accelerated stability condition ($40 \pm 2\,^{\circ}C$ and $75 \pm 5\%$ RH). Stability studies of factorial batches indicate no significant change in appearance of the tablets, assay ($p < 0.05$), disintegration time ($p < 0.05$), and percentage drug release ($p < 0.05$).

4. Conclusion

The current study focused on the formulation of controlled release tablets of nateglinide by using HPMC as a matrix forming water soluble polymer. The combination of both the HPMC K15M and K100M at different concentrations in the tablets of various formulations (CR-1 to CR-9) was attempted through a response surface approach involving 3^2 randomize full factorial design to optimize the concentration of HPMC K15M and HPMC K100M. Though, the drug release profile of the tablets of CR-3, CR-5 and CR-7 was similar to the theoretical drug release profile, the maximum value of similarity factor (f_2) and minimum value of difference factor (f_1) was observed in the tablets of CR-7. Moreover, the rate constants of various model dependent factors (K_0, K_1, K_H and K_p) of theoretical drug release profile were more closer to the model dependent factors of the tablets of CR-7 than that of other formulations. The results of

statistical analysis of drug release profile of factorial batches tablets revealed that the concentration of the HPMC is inversely related to the responses like $DR_{1\,h}$ and $DR_{6\,h}$. The desired responses $DR_{1\,h}$ and $DR_{6\,h}$, were predicted from point prediction method and the formulation (CR-7) prepared with 5% w/w of HPMC K15M and 15% w/w of HPMC K100M was considered as optimum formulation. The optimized formulation (CR-7) was also found to be stable as stability studies conducted after 3 months of storage at accelerated stability conditions. However, a systematic statistical approach is to be adopted to reach an optimum criterion of the formulation at the shortest time period and minimum efforts.

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