Research Article *ISSN: 2277-8713*
Dhrupesh Panchal, IJPRBS, 2012; Volume 1(4): 75-101 *IJPRBS*

ISSN: 2277-8713
IJPRBS
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INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF CANDESARTAN CILEXETIL

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Accepted Date:
09/07/2012
Publish Date:
27/08/2012

Keywords
Sustained release matrix tablet
Candesartan cilexetil
Ethyl cellulose

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Abstract

To formulate and evaluate the sustained release matrix tablet of Candesartan cilexetil using different ratio of hydrophilic and hydrophobic polymers in order to increase the drug bioavailability, therapeutic efficiency, reduce dosing frequency and improvement of patient compliance. Different formulations were prepared by wet granulation method using various release rate controlling hydrophilic polymer like HPMC K 15M, HPMC K 100M and hydrophobic polymers like ethyl cellulose. Drug-excipients compatibility was carried out by FTIR. Different formulations were evaluated for hardness, thickness, friability, swelling index, drug content and in vitro drug release. Mathematical analysis of the release kinetics was carried out to determine the mechanism of drug release. In vitro release data was fitted to various models to ascertain the kinetic of drug release. Response surface graph was prepared to examine the effect of independent variable on dependent variable.

A 3^2 full factorial design was applied to check the effect of varying the concentration of HPMC K 100M (X1) and ethyl cellulose (X2) on the dependent variable i.e. cumulative percentage drug released in 1 hr (Q1), 20 hrs (Q20) and diffusion coefficient (n). It was observed that optimized batch FB5 containing HPMC K 100M (35%) and ethyl cellulose (15%) gives 31.2 % and 82.2 % drug release after 1 hr and 20 hrs, respectively which is nearer to theoretical profile. The studies indicate that the formulation was effective in providing drug release up to 24 hrs with immediate release dose calculated as per theoretical profile.

INTRODUCTION

Candesartan cilexetil is an antihypertensive agent used in the treatment of hypertension and heart failure. However, its extensive first pass metabolism results in poor bioavailability, showing 15 to 40 % bioavailability. It has a plasma half life of 9 hrs and peak plasma concentration reaches within 3 to 4 hrs.[1, 2] It may be given once or twice daily with total daily dose ranging from 8 mg to 32 mg for the treatment of hypertension and heart failure. It produces toxicity like renal and hepatic impairment if given in higher doses resulting inconvenience to the patient and the possibility of reduced compliance with prescribed therapy.[3, 4]

Long term treating of any disease requiring high frequency administration of drug is a cumbersome practice for any patient. To avoid such problems sustain release dosage form are much better alternative compared to conventional dosage form because administration of one single sustain release dose maintain the desired drug plasma level. With the advancement in design of sustain release dosage form drug with higher efficacy are being prepared which release drug at a constant predetermined rate. The release of drug from particle depend on the polymer used to form particle and the quantity of drug contained in it. Extensive *in vitro* and *in vivo* studies of such dosage form are done to make it more safe and effective toward treatment of diseases.[5]

Sustained release (also called extended release) tablets are a common dosage form. A sustained release (SR) tablet is typically

designed to release drug over 12-24 hrs and might contain three times the dose of drug that is contained in an immediate release tablet. In this way a patient need take a tablet only once a day rather than three times a day if immediate release tablets were used. This not only has the advantage of convenience for the patient but ideally provides more constant levels of drug in the body. Fluctuating drug levels can result in the patient being exposed to levels of drug which are too high at times, leading to harmful side-effects and sub-therapeutic levels at other times. Sustained release tablets can smooth these fluctuations leading to better control of the patient's illness or symptoms.[6]

Hence, in the present study, an attempt has been made to develop sustained release matrix tablets of candesartan cilexetil using HPMC K 100M in combination with ethyl cellulose and sustained release pattern of candesartan cilexetil was evaluated by *in vitro* drug release for 24 hrs. The drug release data were plotted using various kinetic equations (zero order, first order, Higuchi's model, Korsmeyer-peppas model and Hixson-Crowell cube root model) to evaluate the drug release mechanism and kinetics.

MATERIALS & METHODS

MATERIALS

Candesartan cilexetil was obtained as gift sample from Smilax laboratory, Hyderabad. HPMC K 100M was obtained from Dow chemicals ltd. Ethyl cellulose was obtained from Hercules corporations. Isopropyl alcohol was obtained from Rankem fine chemicals. PVP K-30, Magnesium stearate and Talc were obtained from S.D. fine chemicals, Mumbai.

METHODS

Drug-excipient compatibility study

FTIR absorption spectra of pure drug and physical mixture were recorded in the range of 400-4000 cm^{-1} by KBr disc method using FTIR spectrophotometer.

Preparation of theoretical release profile of candesartan cilexetil [7]

Calculation of steady state concentration

$C_{ss} = D_m / V_d$

C_{ss} = 4 mg / 0.13 litre

= 30.76 mg / litre

Calculation of immediate release dose (IR)

$IR = C_{ss} \times V_d / F$

$= 30.76 \times 0.13 \times 100 / 40$

$= 10$ mg

Calculation of maintenance dose (MD)

$MD = IR (1+0.693 \times t / t_{1/2})$

$= 10 (1+0.693 \times 24 / 9)$

$= 10 (2.848)$

$= 28.48$ mg ≈ 32mg

(Note: Conventional dose of candesartan cilexetil is 32 mg)

Where, C_{ss} is steady state concentration, D_m is minimum conventional dose of drug, V_d is volume of distribution of drug, IR is immediate release dose, F is fraction bioavailable, MD is maintenance dose, t is time up to which sustain release is required, $t_{1/2}$ is half life of drug. Theoretical release profile of candesartan cilexetil was depicted in Table 6.

Optimization of variables using full factorial design

A 3^2 randomized full factorial design was employed in the present study. In this design 2 factors were evaluated, each at 3 levels and experimental trials were performed for all 9 possible combinations. Amount of HPMC K 100M (X_1) and amount of ethyl cellulose (X_2) were chosen as independent variables in 3^2 full factorial design, while Q_1 and Q_{20} (% drug release after 1hrs and 20 hrs, respectively), diffusion coefficient (n) was taken as dependent variables as depicted in Table 1. Levels selected for independent variables were depicted in Table 2. The composition of factorial design batches (FB1-FB9) were depicted in Table 3. The prepared formulations were evaluated for assay, friability, hardness, swelling and *in vitro* release study. Statistical treatment was carried out to the factorial design batches using design expert DX8 statease software.

Preparation of candesartan cilexetil sustained release matrix tablet by wet granulation method [8]

Accurately weighed quantity of candesartan cilexetil, HPMC K 100M, ethyl cellulose and lactose were screened through screen # 60. The screened powders were transferred to mortar and mixed for 10 minutes and then granulated with 10% w/v solution of PVP K-30 in isopropyl alcohol. The wet mass was passed through sieve #16 and granuler materials were dried in an oven at 45°C for 2 hrs. The dried

granules were passed through sieve # 20.The granules were collected and mixed with talc and magnesium stearate. The lubricated blend was compressed using 9 mm flat-faced punches on rotary tablet machine.

Evaluation parameter of sustained release matrix tablets

Evaluation parameter of granules

Angle of repose [9]

The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1}(h/r)$$

Where, h is height of the powder cone, r is radius of the powder cone, θ is angle of repose.

Bulk density and tapped density [9]

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density and the tapped density were calculated using the following formula.

$$\text{Bulk density} = W/V_0$$

$$\text{Tapped density} = W/V_f$$

Where, W is weight of the powder, V_0 is initial volume, V_f is final volume.

Compressibility index (Carr's index) [9]

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is.

$$CI = (T_d - B_d) \times 100/T_d$$

Where, T_d is tapped density and B_d is bulk density.

Hausner's ratio [9]

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Hausner's ratio = T_d / B_d

Where, T_d is tapped density and B_d is bulk density.

Evaluation parameter of tablets

Thickness [9]

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier calliper. Average thickness and standard deviation values were calculated.

Hardness [9]

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability test [9]

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

% friability was calculated as follows.

% Friability = $(W_1 – W_2) \times 100/W_1$

Where, W_1 is initial weight of the 10 tablets, W_2 is final weight of the 10 tablets after testing. Friability values below 0.8% are generally acceptable.

Weight variation test [9]

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows.

%Weight variation = $(W_A – W_I) \times 100/ W_A$

As the total tablet weight was 350 mg, according to IP 1996, out of twenty tablets ±5 % variation can be allowed for not more than two tablets.

Drug content (Assay) [9]

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 90% to 110% of the standard amount. Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 32 mg of candesartan cilexetil was transferred to a 100 ml volumetric flask containing 100 ml of phosphate buffer of pH 6.8. It was shaken by mechanical means for 1 hr. Then it was filtered through a whatman filter paper. From this resulted solution 1ml was taken, diluted to 100 ml with phosphate buffer of pH 6.8 and absorbance was measured against blank at 224 nm.

In vitro drug release characteristics [9]

Drug release was assessed by dissolution test under the following conditions: n = 3, USP type II dissolution apparatus (paddle method) at 50 rpm in 900 ml of 0.1N HCl for first 2 hrs and phosphate buffer pH 6.8 from 3 to 24 hrs, maintained at 37°C ± 0.5°C. The pH change was carried out by adding 4.6 gm of sodium hydroxide, 3.06 gm of monobasic potassium phosphate and 4.005 gm of dibasic sodium phosphate.[10] An aliquot (5ml) was withdrawn at specific time intervals and replaced with the same volume of pre-warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through whatman filter paper and drug content in each sample was analyzed by UV-visible double beam spectrophotometer at 224 nm.

Mechanism of drug release [11]

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in korsmeyer-peppas model.

$$Mt / M\infty = K \times t^n$$

Where, $Mt/M\infty$ is fraction of drug released at time t, K is release rate constant, n is release exponent. The n value is used to characterize different release mechanisms.

Swelling studies [9]

The dissolution jars were marked with the time points of 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hrs. One tablet was placed in each dissolution jar containing 900 ml of 0.1 N HCl at 37 °C ± 0.5°C and the apparatus was run at 50 rpm using paddle. After 2 hrs, 0.1 N HCl was replaced with 900 ml of phosphate buffer pH 6.8. The tablets were taken out after completion of the respected stipulated time span as mentioned above and weighed after the excess of water at the surface had been removed with filter paper. The wetted samples were then dried in an oven at 40°C up to constant weight. The increase of the weight on the tablet reflects the weight of the liquid uptake. It was estimated according to following equation.

$$Q = 100(W_w - W_i) / W_i$$

Where, Q is percentage swelling, W_w is masses of the hydrated samples before drying, W_i is initial starting dry weight.

Kinetic modeling of dissolution data [11]

To analyze the *in vitro* release data, various kinetic models namely zero order model (cumulative % drug release vs. time), first order model (log cumulative % drug remaining vs. time), Higuchi model (cumulative % drug release vs. square root of time), Hixson-Crowell cube root model (cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time) were used to describe the release kinetics.

Statistical analysis

Polynomial models, including interaction terms for all response variables using multiple linear regression analysis using Microsoft Excel 2007. A polynomial model together with interaction terms was generated for the response variable (Q_1, Q_{20} and n) by means of multiple linear regression analysis. 3D response plots were constructed using sigma plot software. One optimum checkpoint was selected and performed over the entire experimental domain. Values were predicted for the amount of HPMC K 100M and ethyl cellulose using a mathematical model developed for the optimized formulation. Composition of drug and excipients in checkpoint formulation was shown in Table 4.

Comparison of dissolution profiles for selection optimum batch [9, 12]

The similarity factor (f_2) given by SUPAC guidelines for a modified release dosage form was used as a basis to compare dissolution profiles. The dissolution profiles are considered to be similar when f_2 is between 50 and 100. The dissolution profiles of products were compared using an f_2 which is calculated from following formula.

$$f_2 = 50 \times \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5} \times 100\right\}$$

Where, n is the dissolution time and R_t and T_t are the reference (here is the theoretical dissolution profile of candesartan cilexetil) and test dissolution value at time t.

Stability study of optimized batch [12]

To determine the change in physical properties and *in vitro* release profile on storage, optimized batch tablets were stored at 40ºC ± 0.5 ºC and 75% ± 5% relative humidity in stability chamber. Samples were evaluated after one month for drug content, *in vitro* drug release study, weight variation, hardness and friability.

RESULTS AND DISCUSSION

Drug-excipients compatibility study

The FTIR spectra of pure candesartan cilexetil and physical mixture are shown in Figure 1 and Figure 2 respectively.

Candesartan cilexetil exhibits peak due to hydroxyl (2800-2850 cm^{-1}), ketone (1700-1750 cm^{-1}), carbonyl (1200-1250 cm^{-1}), O-substitution (700-750 cm^{-1}) and aromatic C-H (2850-2950 cm^{-1}) group as depicted in Table 5. Figure 1 show FTIR spectra of pure drug and Figure 2 show FTIR spectra of physical mixture. From Figure 2 it was observed that there were no changes in their main peaks in the FTIR spectra of physical mixture of drug and polymers. Hence, it was concluded that no physical or chemical interactions of candesartan cilexetil with ethyl cellulose and HPMC K 100M.

Theoretical release profile (TP) of candesartan cilexetil

Theoretical release profile of candesartan cilexetil is shown in Table 6.

Evaluation parameter of sustained release matrix tablets

Evaluation parameter of granules

The results for granules of factorial batches FB1 to FB9 are shown in Table 7.

From result it was found that the granule prepared for factorial batches have Angle of repose (23.55 ± 0.51 to 28.45 ± 0.61), Hausner's ratio (1.10 ± 0.03 to 1.21 ± 0.03) and Carr's index (9.52 ± 0.04 to 17.4 ± 0.02) as depicted in Table 7, which shows good flow property and compressibility of granules.

Evaluation parameter of tablets

Weight variation test

In weight variation test, the pharmacopoeia limit for percent deviation for tablets of more than 325 mg is ± 5%. The average percent deviation of all tablets was found to be within the limit. Hence, all formulations complies the weight variation test as per IP.

From result it was found that the tablets prepared batches FB1 to FB9 have hardness (7.5 ± 0.09 to 9.1 ± 0.06), friability (0.22 ± 0.09 to 0.67 ± 0.05) and drug content (95.3 ± 0.10 to 100.2 ± 0.13) as depicted in Table 8, which were within the range of pharmacopoeial specification.

Swelling study

Swelling study of factorial design batches FB1-FB9 were depicted in Figure 3.

It can be evident from Figure 3 that the percentage swelling index at 12 hr from the batches prepared by using 3^2 full factorial design were found to be FB1(102.71%), FB2 (138.52 %), FB3 (104.28 %), FB4 (111.42 %), FB5 (140.29 %), FB6 (102.57 %), FB7 (114.28 %), FB8 (134.28 %), FB9 (128.00 %), respectively.

***In vitro* dissolution study**

In vitro dissolution study of factorial design batches FB1-FB9 were depicted in Figure 4.

It can be evident from Figure 4 that the cumulative percentage drug release from the batches prepared by using 3^2 full factorial design were found to be FB1(99.4 % in 20 hr), FB2 (99.8 % in 20 hr), FB3 (99.5 % in 22 hr), FB4 (96.9 % in 22 hr), FB5 (98.2 % in 24 hr), FB6 (94.4 % in 24 hr), FB7 (100.4 % in 24 hr), FB8 (97.5 % in 24 hr), FB9 (96.5 % in 24 hr), respectively.

Kinetic modeling of dissolution data

The kinetics of the dissolution data were well fitted to zero order, first order, Higuchi model, Hixson-Crowell and korsmeyer-peppas model as evident from regression

coefficients. Here all formulation follows Higuchi release kinetics as depicted in Table 9.

To find out release mechanism the *in vitro* release data were fitted in korsmeyer-peppas equation where *n* is a factor, which indicates the mechanism of the release. The release exponent *n* was determined and given in Table 10. For all batches it was found that n value was greater than 0.45 and less than 1.0 which indicates anomalous transport mechanism.

A statistical model incorporating interactive and polynominal terms was used to evaluate the responses.

$$Y = B_0 + B_1X_1 + B_2X_2 + B_{12}X_1X_2 + B_{11}X_1^2 + B_{22}X_2^2$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high values. The interaction terms (X_1X_2) show 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. The dissolution profile for 9 batches showed a variation i.e. initial 1 hr release ranging from 30.06 % to 33.33 % and drug released after 20 hrs ranging from 78.9 % to 99.8% and diffusion coefficient ranging from 0.452 to 0.525 as depicted in Table 11. The fitted equations (full and reduced) relating the responses, Q_1, Q_{20} and diffusion coefficient (n) to the transformed factor are depicted in the Table 12. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e. negative or positive). Table 13 shows the results of analysis of variance (ANOVA) which was performed to identify insignificant factors. Data were analyzed using design of expert version 8.

R^2 value for Q_1, Q_{20} and diffusion coefficient (n) are 0.9838, 0.9818 and 0.7864 respectively indicating good correlation between dependent and independent variables. The reduced models were developed for response variables by omitting the insignificant terms with $P>0.05$. The terms with $P<0.05$ were considered statistically significance and retained in the reduced model.

Where, DF is degree of freedom, SS is sum of square, MS is mean of square and F is Fischer's ratio.

Full and reduced model for Q_1

The polynomial equation was generated by multiple linear regressions. The equation derived is as under:

$$Y = 31.18 + 0.458\ X_1 - 1.005X_2 + 0.325\ X_1X_2 - 0.515X_1^2 - 0.245X_2^2$$

The significance levels of the coefficients b_{12} and b_{22} were found to be P= 0.126 and 0.211 respectively as depicted in Table 12, so they were omitted from the full model to generate a reduced model. The coefficients b_0, b_1, b_2, b_{11} were found to be significant at P<0.05 hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{12} and b_{22} contribute significance information to the prediction of Q_1. Table 13 shows the results of the analysis of variance (ANOVA) which was performed to identify insignificant factors.

Where, X data is the concentration of ethyl cellulose, Y data is the concentration of HPMC K 100M and Z data is drug release after 1 hr (Q_1). The results of regression analysis reveal that on increasing the values for X_1 and X_1X_2 increase in Q_1 is observed, because coefficient b_1 and b_{12} bears a positive as depicted in Figure 5.

Full and reduced model for Q_{20}

The polynomial equation was generated by multiple linear regressions. The equation derived is as under:

$$Y = 83.24 - 8.345\ X_1 - 2.946X_2 - 0.40\ X_1X_2 - 0.322X_1^2 + 6.795X_2^2$$

The significance levels of the coefficients b_{11} and b_{12} were found to be P= 0.753 and 0.782 respectively as depicted in Table 12, so they were omitted from the full model to generate a reduced model. The coefficients b_0, b_1, b_2, b_{22} were found to be significant at P<0.05 hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{11} and b_{12} contribute significance information to the prediction of Q_{20}. Table 13 shows the results of the analysis of variance (ANOVA) which was performed to identify insignificant factors.

Where, X data is the concentration of ethyl cellulose, Y data is the concentration of HPMC K 100M and Z data is drug release

after 20 hrs (Q_{20}). The results of regression analysis reveal that on increasing the values for X_2^2, increase in Q_{20} is observed, because coefficient b_{22} bears a positive as depicted in Figure 6.

Full and reduced model for diffusion coefficient (n)

The polynomial equation was generated by multiple linear regressions. The equation derived is as under:

$$Y = 0.489 - 0.02 X_1 + 0.002X_2 - 0.016 X_1X_2 + 0.017X_1^2 + 0.009X_2^2$$

The significance levels of the coefficients b_1, b_2, b_{11}, b_{22} and b_{12} were found to be P= 0.081, 0.832, 0.197, 0.577 and 0.347 respectively as depicted in Table 12, so they were omitted from the full model to generate a reduced model. Table 13 shows the results of the analysis of variance (ANOVA) which was performed to identify insignificant factors.

Where, X data is the concentration of ethyl cellulose, Y data is the concentration of HPMC K 100M and Z data is diffusion coefficient (n). The results of regression analysis reveal that on increasing the values for X_2, X_1^2 and X_2^2 increase in n is observed, because coefficient b_2, b_{11} and b_{22} bears a positive as depicted in Figure 7.

Evaluation of check point batches

***In vitro* dissolution study**

In vitro dissolution study of check point batch FB10 was depicted in Figure 8.

To assess the reliability of above described factorial batches, a check point batch was prepared. The experimental value of check point batch was compared with the theoretical value for % drug release after 1 hr (Q_1) and after 20 hrs (Q_{20}) and it shows that the drug release after 1 hr is 31.3 % and 20 hrs is 83.4 % which was found to be nearer to the theoretical value as depicted in Figure 8.

Comparison of dissolution profiles for selection of optimum batch

Similarity factor were calculated for all formulations (showing sustained effect for 24 hrs) considering theoretical profile as the reference standard. The values for the same are depicted in Table 14.

It can be seen that formulations FB1, FB2, and FB4 have lowest values of f_2 i.e. 30.19, 45.73 and 48.79 respectively suggesting that these formulation show greatest

deviation from theoretical profile as compared to other formulated products. Other formulations show f_2 values between 50-75 indicating differences of dissolution profiles with that theoretical profile. The values of similarity factor (f_2) for the batch FB5 showed maximum value 70.69. Hence, formulation batch FB5 was considered as optimum batch.

Results of stability study

In order to determine the change *in vitro* release profile on storage, stability study of formulation FB5 was carried out at 40 ± 0.5 °C in a humidity jar having 75 ± 5 % RH. Samples evaluated after one month showed no change in the *in vitro* drug release pattern as depicted in Figure 9.

The value of similarity factor was 73.95 indicating good similarity of dissolution profiles before and after stability studies as depicted in Table 15.

CONCLUSION

In present investigation, factorial batches FB1-FB9 were prepared using 30%, 35%, 40% concentration of HPMC K 100M and 10%, 15%, 20% concentration of ethyl cellulose. Among the FB1-FB9 batches, FB5 batch containing 35% HPMC K100M and 15% ethyl cellulose gives 31.2% drug release after 1 hr and 82.2 % drug release after 20 hrs which is nearer to theoretical release profile and it also shows 140.29% swelling after 12 hrs as compared to other batches. Optimized batch FB5 follows Higuchi release kinetic and has n value 0.5102 which indicate anomalous diffusion type mechanism of drug release.

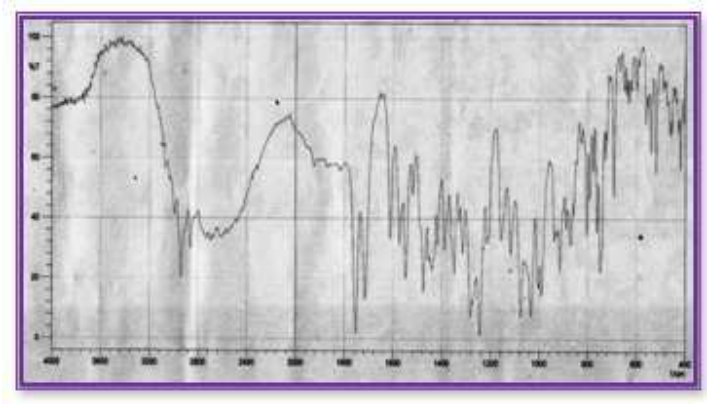

Figure 1 FTIR spectrum of candesartan cilexetil

ISSN: 2277-8713
IJPRBS

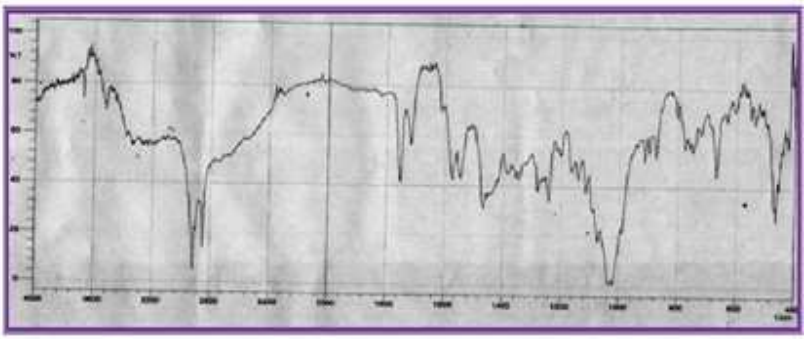

Figure 2 FTIR spectrum of physical mixture

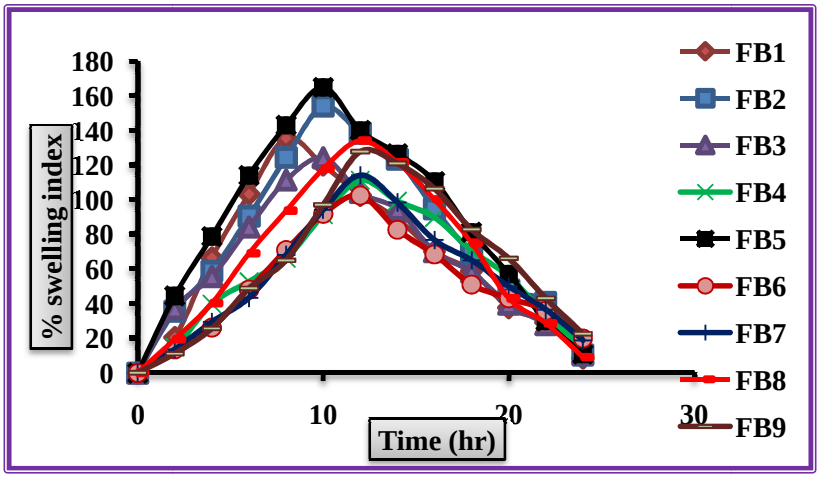

Figure 3 Comparative swelling profile of factorial batches FB1-FB9

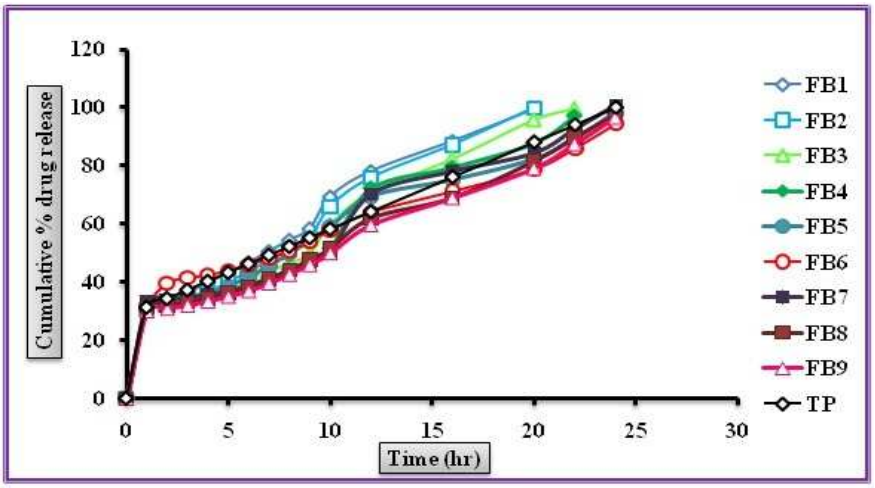

Figure 4 Dissolution profiles of factorial batches FB1-FB9 and TP

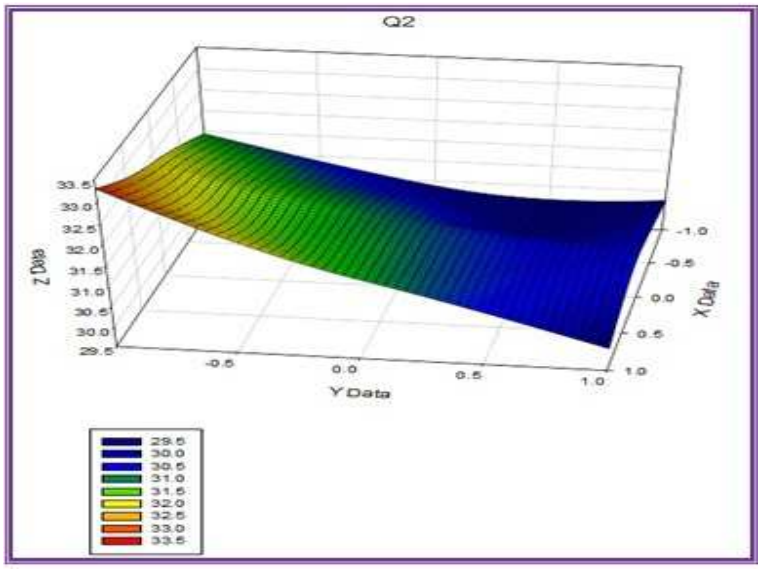

Figure 5 Response surface plot showing the influence of concentration of HPMC K 100M and Ethyl cellulose on response Q_1 i.e. % drug release after 1 hr

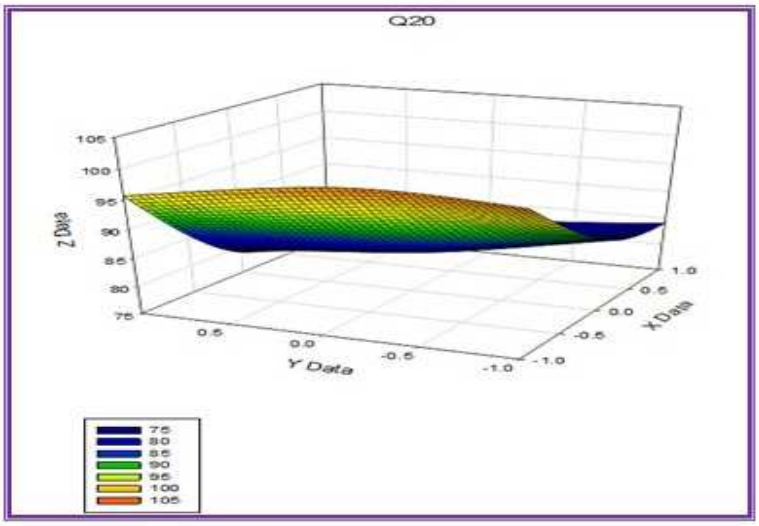

Figure 6 Response surface plot showing the influence of concentration of HPMC K 100M and Ethyl cellulose on response Q_{20} i.e. % drug release after 20 hr

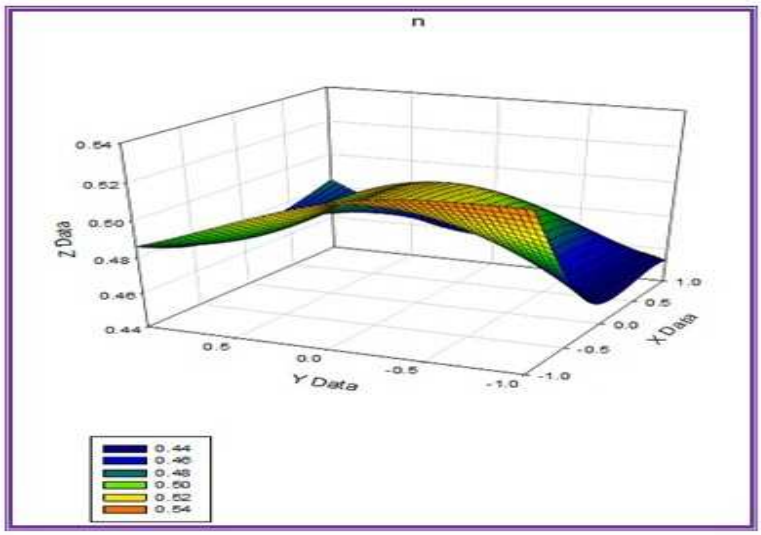

Figure 7 Response surface plot showing the influence of concentration of HPMC K 100M and Ethyl cellulose on response n i.e. diffusion coefficient

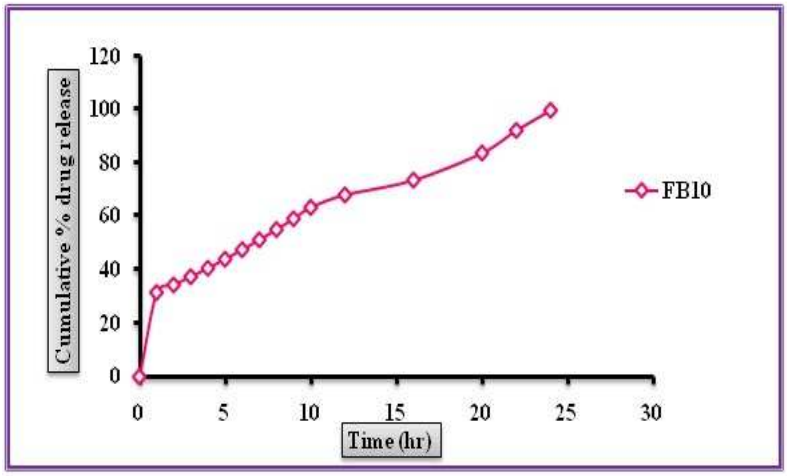

Figure 8 Dissolution profile of check point batches FB10

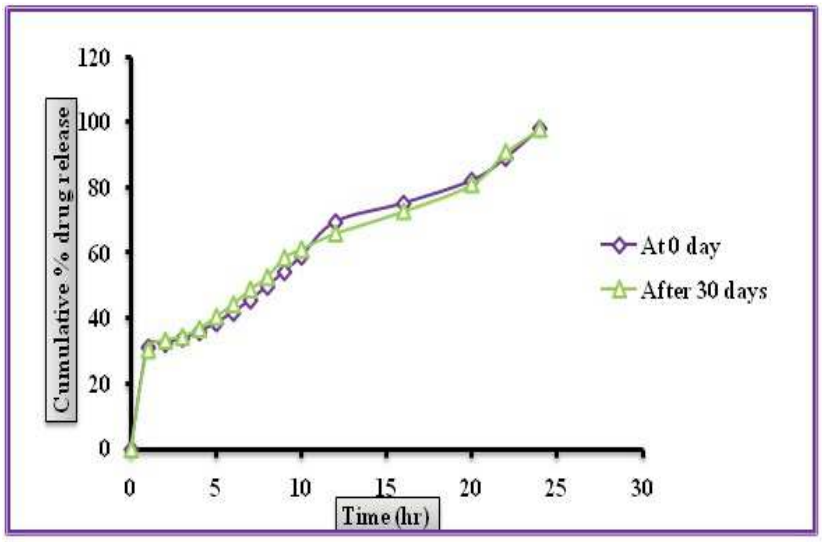

Figure 9 Cumulative % drug release of batch FB5 at 0 day and after one month

Table 1

Independent variables and dependent variables

3^2 full factorial design				
Independent variable		**Dependent variable**		
X_1	**X_2**	**Q_1**	**Q_{20}**	**n**
Amount of HPMC K 100M	Amount of ethyl cellulose	% drug release after 1 hr.	% drug release after 20 hrs.	Diffusion coefficient

Table 2

Selection of levels for independent variables

Level	Low	Medium	High
Variable	-1	0	+1
X_1	105 mg (30%)	122.5 mg (35%)	140 mg (40%)
X_2	35 mg (10%)	52.5 mg (15%)	70 mg (20%)

Table 3

Composition of factorial design formulations for sustained release matrix tablets

Excipients (mg)	Batch code								
	FB1	**FB2**	**FB3**	**FB4**	**FB5**	**FB6**	**FB7**	**FB8**	**FB9**
Candesartan cilexetil	32	32	32	32	32	32	32	32	32
HPMC K 100M	105	105	105	122.5	122.5	122.5	140	140	140
Ethyl cellulose	35	52.5	70	35	52.5	70	35	52.5	70
Lactose	149.5	132	114.5	132	114.5	97	114.5	97	79.5
PVP K-30	18	18	18	18	18	18	18	18	18
Talc	7	7	7	7	7	7	7	7	7
Mg. stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
TOTAL	350	350	350	350	350	350	350	350	350

Table 4

Composition of drug and excipients in check point batches

Excipients(mg)	**Batch code (FB10)**
Candesartan cilexetil	32
HPMC K 100M	113.75
Ethyl cellulose	61.25
Lactose	114.5
PVP K-30	18
Talc	7
Mg. stearate	3.5
TOTAL	350

Table 5

FTIR interpretation data of candesartan cilexetil and physical mixture

Functional group	Frequency (cm^{-1})	
	Candesartan cilexetil	**Physical mixture**
-O-H Stretching	2800-2850	2800-2850
-C=O Stretching	1700-1750	1700-1750
-C-O Stretching	1200-1250	1200-1250
O-Substitution	700-750	700-750
Aromatic C-H Stretching	2850-2950	2850-2950

Table 6

Theoretical release profile (TP) of candesartan cilexetil

Time (hr)	Theoretical release profile (%)	Time (hr)	Theoretical release profile (%)
1	31.25	13	67.11
2	34.23	14	70.10
3	37.22	15	73.09
4	40.21	16	76.08
5	43.20	17	79.07
6	46.19	18	82.06
7	49.18	19	85.05
8	52.17	20	88.04
9	55.16	21	91.03
10	58.15	22	94.01
11	61.14	23	97.00
12	64.12	24	100

Table 7

Evaluation parameters for granules of factorial batches FB1-FB9

Parameter	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Carr's Index (%)
FB1	24.22 ± 0.51	1.25 ± 0.07	1.48 ± 0.05	1.18 ± 0.09	15.54 ± 0.06
FB2	25.15 ± 0.43	1.26 ± 0.05	1.49 ± 0.03	1.18 ± 0.06	15.43 ± 0.05
FB3	28.45 ± 0.61	1.23 ± 0.03	1.49 ± 0.06	1.21 ± 0.03	17.4 ± 0.02
FB4	27.57 ± 0.55	1.21 ± 0.04	1.45 ± 0.02	1.19 ± 0.07	16.55 ± 0.06
FB5	24.15 ± 0.32	1.25 ± 0.03	1.51 ± 0.03	1.20 ± 0.03	17.21 ± 0.04
FB6	25.03 ± 0.62	1.22 ± 0.02	1.38 ± 0.07	1.13 ± 0.05	11.59 ± 0.06
FB7	23.55 ± 0.51	1.23 ± 0.06	1.36 ± 0.05	1.10 ± 0.03	9.55 ± 0.03
FB8	26.44 ± 0.31	1.24 ± 0.02	1.38 ± 0.07	1.11 ± 0.02	9.52 ± 0.04
FB9	25.32 ± 0.61	1.24 ± 0.06	1.38 ± 0.03	1.11 ± 0.05	9.91 ± 0.05

Note: All values represent mean ± SD (n=3)

Table 8

Evaluation parameters for tablets of factorial batches FB1-FB9

Parameter	Hardness (Kg/cm^2)	Thickness (mm)	Diameter (mm)	Friability (%)	Drug content (%)
FB1	7.5 ± 0.09	3.66 ± 0.04	9.48 ± 0.02	0.36 ± 0.06	96.7 ± 0.18
FB2	9.1 ± 0.06	3.85 ± 0.02	9.50 ± 0.04	0.22 ± 0.09	97.6 ± 0.12
FB3	8.2 ± 0.02	3.87 ± 0.03	9.47 ± 0.02	0.38 ± 0.02	97.8 ± 0.17
FB4	9.0 ± 0.08	3.98 ± 0.06	9.45 ± 0.03	0.67 ± 0.05	98.5 ± 0.23
FB5	8.7 ± 0.05	3.89 ± 0.08	9.47 ± 0.04	0.57 ± 0.07	99.5 ± 0.10
FB6	8.4 ± 0.04	3.87 ± 0.07	9.45 ± 0.05	0.48 ± 0.09	95.8 ± 0.20
FB7	8.0 ± 0.06	3.88 ± 0.05	9.48 ± 0.02	0.32 ± 0.03	100.2 ± 0.13
FB8	7.7 ± 0.03	3.99 ± 0.05	9.44 ± 0.05	0.48 ± 0.02	98.8 ± 0.15
FB9	8.4 ± 0.04	3.87 ± 0.03	9.40 ± 0.06	0.27 ± 0.04	95.3 ± 0.10

Note: All values represent mean ± SD (n=3)

Table 9

Drug release kinetic data of factorial batches FB1-FB9

	Coefficient of determination (R^2)				
Batch	**Zero order**	**Higuchi**	**First order**	**Hixson Crowell**	**K-peppas**
FB1	0.960	0.978	0.812	0.923	0.960
FB2	0.934	0.983	0.873	0.869	0.933
FB3	0.924	0.971	0.854	0.852	0.924
FB4	0.909	0.964	0.849	0.934	0.909
FB5	0.957	0.984	0.847	0.911	0.957
FB6	0.928	0.946	0.782	0.926	0.928
FB7	0.897	0.961	0.846	0.823	0.897
FB8	0.923	0.974	0.852	0.911	0.923
FB9	0.919	0.972	0.844	0.910	0.918

Table 10

Drug release mechanism of factorial batches FB1-FB9 as per k-peppas model

Batch	n value	Release mechanism
FB1	0.5251	Anomalous diffusion
FB2	0.5186	Anomalous diffusion
FB3	0.4865	Anomalous diffusion
FB4	0.4522	Fickian diffusion
FB5	0.5102	Anomalous diffusion
FB6	0.4727	Anomalous diffusion
FB7	0.4530	Fickian diffusion
FB8	0.4582	Fickian diffusion
FB9	0.4847	Anomalous diffusion

Table 11

Effect of independent variables on dependent variables by 3^2 full factorial of candesartan cilexetil sustained release matrix tablet

Batch code	Independent Variable		Dependent Variable		
	X_1	X_2	Q_1 (%)	Q_{20} (%)	n
FB1	-1	-1	31.44	99.42	0.525
FB2	-1	0	30.38	99.8	0.518
FB3	-1	1	30.26	95.66	0.486
FB4	0	-1	32.3	87.77	0.452
FB5	0	0	31.2	82.25	0.510
FB6	0	1	30.69	78.9	0.472
FB7	1	-1	33.3	84.12	0.453
FB8	1	0	31.47	81.62	0.458
FB9	1	1	30.06	79.07	0.484

Table 12

Summary of results of regression analysis

			Q_1			
Response(Q_1)	**b_0**	**b_1**	**b_2**	**b_{12}**	**b_{11}**	**b_{22}**
FM	31.18	0.458 P=0.014	-1.005 P=0.001	0.325 P=0.126	-0.515 P=0.018	-0.245 P=0.211
RM	31.18	0.458	-1.005	----	-0.515	----
			Q_{20}			
Response(Q_{20})	**b_0**	**b_1**	**b_2**	**b_{12}**	**b_{11}**	**b_{22}**
FM	83.24	-8.345 P=0.001	-2.946 P=0.030	-0.4 P=0.782	-0.322 P=0.753	6.975 P=0.013
RM	83.24	-8.345	-2.946	----	----	6.795
			n			
Response(n)	**b_0**	**b_1**	**b_2**	**b_{12}**	**b_{11}**	**b_{22}**
FM	0.489	-0.02 P=0.081	0.002 P=0.832	-0.016 P=0.347	0.017 P=0.197	0.009 P=0.577
RM	0.489	----	----	----	----	----

Where, FM = Full model and RM = Reduced model

Table 13

ANOVA for Q_1, Q_{20} and diffusion constant (n)

			Q_1		
	DF	**SS**	**MS**	**F**	**Significance F**
Regression	5	8.712	1.742	36.44	0.006
Residual	3	0.143	0.047	----	----
Total	8	8.856	----	----	----
			Q_{20}		
	DF	**SS**	**MS**	**F**	**Significance F**
Regression	5	567.96	113.59	32.40	0.0081
Residual	3	10.515	3.505	----	----
Total	8	578.48	----	----	----
			n		
	DF	**SS**	**MS**	**F**	**Significance F**
Regression	5	0.004	0.0009	2.209	0.2732
Residual	3	0.001	0.0004	----	----
Total	8	0.006	----	----	----

Table 14

Similarity factor (f_2) of batches FB1-FB9

Batch	Similarity factor (f_2)
FB1	30.19
FB2	45.73
FB3	63.56
FB4	48.79
FB5	70.69
FB6	64.93
FB7	57.73
FB8	55.78
FB9	51.51

Table 15

Tablet parameters of batch FB5 after stability study

Parameters	Zero time	After one month
Assay (%)*	99.5 ± 0.10	96.8 ± 0.45
Friability (%)*	0.57 ± 0.07	0.43 ± 0.16
Hardness (kg/cm^2)*	8.7 ± 0.05	9.1 ± 0.09
Similarity Factor (f_2)	70.69	73.95

Note: * values represent mean ± SD (n=3)

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