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Research Article

FORMULATION AND OPTIMISATION OF IMMEDIATE RELEASE TELMISARTAN TABLETS USING FULL FACTORIAL DESIGN

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ABSTRACT

Telmisartan is an angiotensin II (AT_1) receptor antagonist used in the treatment of hypertension. The drug is practically insoluble in water and insoluble in the pH range 3-9. The principal aim of this work was to find out the effect of sodium starch glycolate and β – cyclodextrin on the dissolution profile of immediate release telmisartan tablets and to optimize their values by a 2^2 full factorial design. Other excipients used in the study are microcrystalline cellulose (Avicel PH-101) and magnesium stearate. Both sodium starch glycolate and β – cyclodextrin had contribution towards the immediate release but the effect of sodium starch glycolate is more pronounced from response surface plot as well as from the contour plot. The optimised amount of sodium starch glycolate and β – cyclodextrin were found to be 55.714 mg and 30 mg respectively for 70 % drug release at 30 minutes.

Keywords: Beta – cyclodextrin, Full factorial design, Immediate release tablets, Optimization, Sodium starch glycolate, Telmisartan.

INTRODUCTION

Telmisartan is 4′-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl] methyl] biphenyl-2-carboxylic acid[1]. It is an angiotensin II (AT_1) receptor antagonist [1], which shows peak plasma levels approximately 1 hour after its oral administration and the plasma half-life is about 24 hours[2]. The drug is practically insoluble in water and shows pH dependent solubility. Telmisartan (TSN) is insoluble in the pH range 3-9 and sparingly soluble in strong acids[3]. For this reason absorption oral bioavailability of the drug is dose dependent and is about 42 % following a 40 mg. dose and 85 % following a 160 mg. dose[4]. Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity[5]. So an attempt has been made to develop an immediate release tablet of TSN by direct compression method. For immediate release sodium starch glycolate was taken as super disintegrant[6] & prior to compression the drug was thoroughly mixed with β-cyclodextrin for improving water solubility[7]. Microcrystaline cellulose was employed as a directly compressible ingredient[8, 9]. The objective of the present work was to find out the effect of sodium starch glycolate and β – cyclodextrin on the dissolution profile of immediate release TSN tablets and to optimize their values by a full factorial design.

MATERIALS AND METHODS

Materials

Telmisartan (TSN) was obtained as a gift sample from Torrent Pharmaceuticals, Baddi, H.P., India. β-Cyclodextrin (BCD), sodium starch glycolate extra pure (SSG), microcrystalline cellulose (Avicel PH-101) (MCC) and magnesium stearate (MS) were purchased from Loba chemie. Pvt. Ltd, Mumbai. D-Mannitol (DML) and hydrochloric acid (HCl) were purchased from Merck Pvt. Ltd. Double distilled water (DDW) was prepared in the laboratory from demineralised water. All the reagents used were of analytical grade and were used as received.

Preparation of Tablets

Accurately weighed quantity of TSN was thoroughly mixed with BCD followed by mixing with all other ingredients except lubricant (MS) in a mortar by a pestle. Then the mixture was passed through a sieve (350μm).Then the lubricant was passed through the same sieve & mixed thoroughly & subjected to compression by an 8 mm round flat faced Cadmatch single tablet compression machine. There are four different batches were prepared & 50 tablets were prepared in each batch, according to the formula given in table 1.

Drug content study

Three tablets from each batch were triturated individually & stirred with 0.1N HCl by a magnetic stirrer for one hour to ensure complete mixing. The solution was filtered by a Whatman filter paper and the volume was made up to 100 ml. From the above solution 1ml was again diluted up to 100ml with 0.1 N HCl & the absorbance was measured in a U.V. Visible spectrophotometer at 228nm against 0.1 N HCl as blank.

In-vitro dissolution study

For the dissolution of immediate release tablets United States Pharmacopeia (USP) apparatus-1 (basket type, LABINDIA, DISSO.) was used. Dissolution was carried out in 900 ml. of 0.1N HCl at 37±0.5°C and the basket was rotated at 50 rpm. Samples were withdrawn at an interval of 10 minutes from the starting of dissolution. Each time 5ml. of sample withdrawn was diluted up to 25ml. with 0.1N HCl and analysed for the amount of TSN released, under UV-visible spectrophotometer at 228 nm taking 0.1N HCl as blank.

Identification of the mechanism of drug release

Data of the in-vitro dissolution study were fitted into different mathematical models like Zero order [10], First order [10], Higuchi [11], Hixson Crowell [12] and Korsmeyer Peppas model[11] and their correlation coefficient (R^2) values were used as an indicator of the best fitting for each of the models. Korsmeyer Peppas model was fitted to identify the mechanism of drug release, which was indicated by the release exponent (n) value[13, 14].

Mathematical and statistical analyses

A 2^2 full factorial design was employed considering amount of SSG (X_1) and amount of BCD (X_2) as two independent variables and four different batches were prepared (table 2). Percentage of drug released (% DR) at 30 minute (Y_{30}) was taken as response to study the effect of SSG and BCD on the release profile of TSN in a triplicate manner. Regression coefficients of the independent variables were determined to construct the response surface. Residuals and percentage bias were calculated along with construction of a normal probability plot to check the model accuracy. Analysis of variance (ANOVA) was performed to study the statistical significance of independent variables and their interaction term. Minitab 15 and SAS (for optimisation) were used for statistical and mathematical analyses.

RESULTS & DISCUSSION

Drug content of various formulations was almost nearly equal & the loss was very minimal due to direct compression. Average drug

content of all the four batches with their standard deviation (SD) values are given in table 2.

All the batches have shown an immediate release profile of more than 90% within 70 minutes. Maximum drug was released from F2 within 70 minute (96.88%) & minimum is from F1 (90.76%), because F2 contains maximum amount of β-cyclodextrin & SSG (50 & 60 mg respectively) where as F1contains minimum amount (30 & 40 mg respectively). Among F1 & F3, F3 shows maximum release because it contain maximum amount of SSG, although both contain equal amount of BCD. Similar case was also observed between F2 & F4. Percentage drug released versus time profile of all the four batches was shown in figure 1.

From the R^2 values of different mathematical models it was concluded that F1, F3, & F4 were best fitted to first order dissolution model where as F2 was best fitted to Hixson Crowell dissolution model ($R^2 = 0.961$). R^2 values of all the four batches for different mathematical models were shown in table 4. The n value of Korsmeyer Peppas model ranges from 0.4548 to 0.7401 (table 3), in case of all the batches which indicates that the drug release occurred through diffusion as well as polymer relaxation mechanism [13, 14].

A statistical model including linear and interaction terms was utilized to evaluate the response. Regression equation determining the response was

$Y_{30} = 69.7807 + 4.03343\ X_1 + 1.90419\ X_2 - 0.97141\ X_1\ X_2$, having an R-square value of 0.969, where 69.7807 is the intercept (average response), 4.03343, 1.90419 and 0.971408 were the coefficient of SSG, BCD and interaction term (SSG*BCD). A normal probability plot of the residuals was shown in fig. 2. The points on this plot lie reasonably close to a straight line and higher R-square value lending support to the model chosen for studying the effect of independent variables[15]. It can be seen that in all of the cases there was a reasonable agreement between the predicted and the observed response values, because a low value of the percentage bias[16] was found (table. 4). For this reason, it can be concluded that the predicted responses describe adequately the influence of the selected independent variables on the responses under study and the selected statistical model can be used successfully for prediction and optimization.

Regression coefficient of X_1 was more as compared to X_2 which indicates that SSG have more contribution towards the response. So F3 shows maximum release than F1 because it contain maximum amount of SSG, although both contain equal amount of BCD. For the same reason F2 shows maximum drug release than F4, this was also evident from the response surface plot and its corresponding contour plot. Fig.3a portrays the 3-dimensional response surface plot for Y_{30} while fig.3b portrays the corresponding contour plot. Fig. 3a depicts that response Y_{30} is increasing in a linear trend with both SSG & BCD, but the effect of SSG is more pronounced. Non linearity observed in the contour plot is due to the coefficient of the interaction term (– 0.97141). Results of ANOVA were shown in table 5, which indicates that effect of SSG (p – value < 0.01) is more significant than BCD where as effect due to interaction is minimal (p – value = 0.16).

Two optimised formulations were obtained at two different target values for Y_{30}, such as 70 % and 75 % (table 6). The predicted and observed responses for the optimized tablet formulations showed no significant difference (t-test, p – value = 0.250 and 0.309 for 70 % and 75 % target values respectively).

Table 1: Direct compression formula for one tablet

Ingredients (mg)	F1	F2	F3	F4
Telmisartan	40	40	40	40
β- cyclodextrin	30	50	30	50
Sodium starch glycolate	40	60	60	40
Microcrystaline cellulose	120	120	120	120
D- Mannitol	90	50	70	70
Magnesium stearate	10	10	10	10
Total	330	330	330	330

Table 2: Full factorial design for immediate release TSN tablets and their drug contents

Batch Code	X_1 (Coded Level)	X_2 (Coded Level)	X_1 (Actual Value in mg.)	X_2 (Actual Value in mg.)	Average Drug Content ± SD (n = 3)
F1	-1	-1	40	30	39.7414 ± 0.5565
F2	1	1	60	50	39.8491 ± 0.5424
F3	1	-1	60	30	39.9569 ± 0.6096
F4	-1	1	40	50	39.8491 ± 0.4127

Table 3: R^2 values of all the four batches for different mathematical models and n value of Korsmeyer Peppas model

Batch code	Zero order	First order	Higuchi	Hixson Crowell	Korsmeyer Peppas	Release Exponent (n)
F1	0.8839	0.9946	0.9827	0.9724	0.9356	0.7401
F2	0.8816	0.9866	0.9504	0.9905	0.9531	0.4581
F3	0.8328	0.9673	0.9159	0.9453	0.9169	0.5348
F4	0.8660	0.9643	0.9345	0.9607	0.9154	0.5924

Table 4: Residuals and percentage bias of all the four batches in a triplicate manner

Batch Code (Triplicate)	Observed Response (Triplicate)	Average Observed Response ± SD (n = 3)	Predicted Response	Residuals	% Bias
F1	63.6860		62.8717	0.8143	1.2952
F1	62.2164		62.8717	-0.6553	1.0423
F1	62.7126	62.8717 ± 0.7476	62.8717	-0.1591	0.2531
F2	76.8697		74.7469	2.1228	2.8400
F2	72.9486		74.7469	-1.7983	2.4058
F2	74.4224	74.7469 ± 1.9810	74.7469	-0.3245	0.4341
F3	76.6111		72.8813	3.7298	5.1177
F3	72.7168		72.8813	-0.1645	0.2257
F3	69.3161	72.8813 ± 3.6503	72.8813	-3.5652	4.8918
F4	69.4386		68.6229	0.8157	1.1887
F4	67.4808		68.6229	-1.1421	1.6643
F4	68.9492	68.6229 ± 1.0189	68.6229	0.3263	0.4754

Table 5: Results of ANOVA for independent variables and their interaction term

Sources OF Variation	Degrees OF Freedom	Sum OF Squares	Mean Squares	F - Values	P - Values
SSG	1	195.222	195.222	41.44	< 0.01
BCD	1	43.511	43.511	9.24	0.016
SSG* BCD	1	11.324	11.324	2.40	0.160
Error	8	37.689	4.711		
Total	11	287.746			

Table 6: Optimised values of SSG and BCD with their predicted and observed response values

Target Values for Optimisation	Optimised Value For SSG (Coded Unit)	Optimised Value for BCD (Coded Unit)	Optimised Value for SSG (Actual Value)	Optimised Value for BCD (Actual Value)	Predicted Response in %	Observed Response in % (Average ± SD)
70 %	0.5714	-1	55.714	30	70.1566 %	71.4101 ± 1.3527
75 %	0.8571	1	58.571	50	75.1421 %	76.2449 ± 1.4137

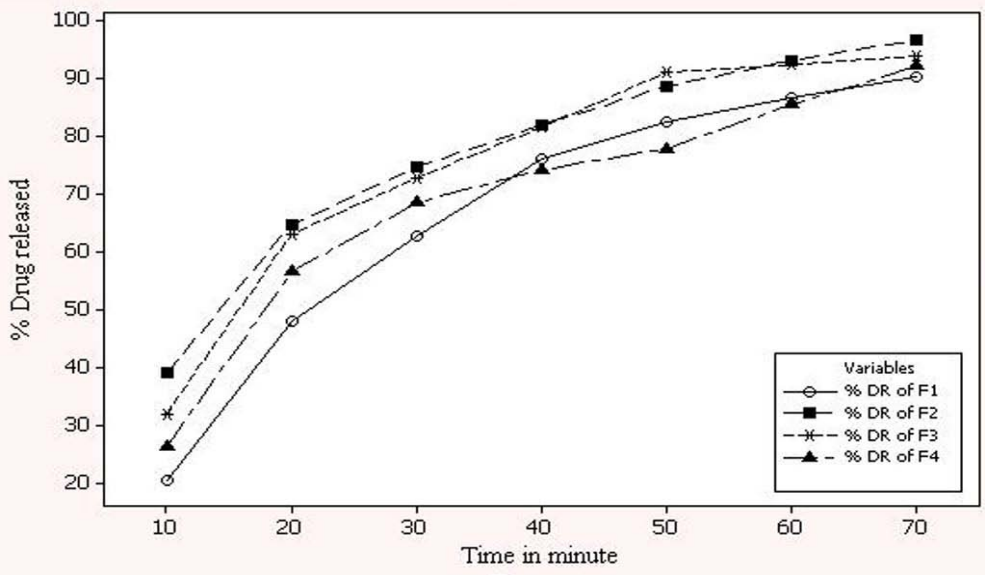

Fig. 1: Percentage drug released versus time profile of all the four batches

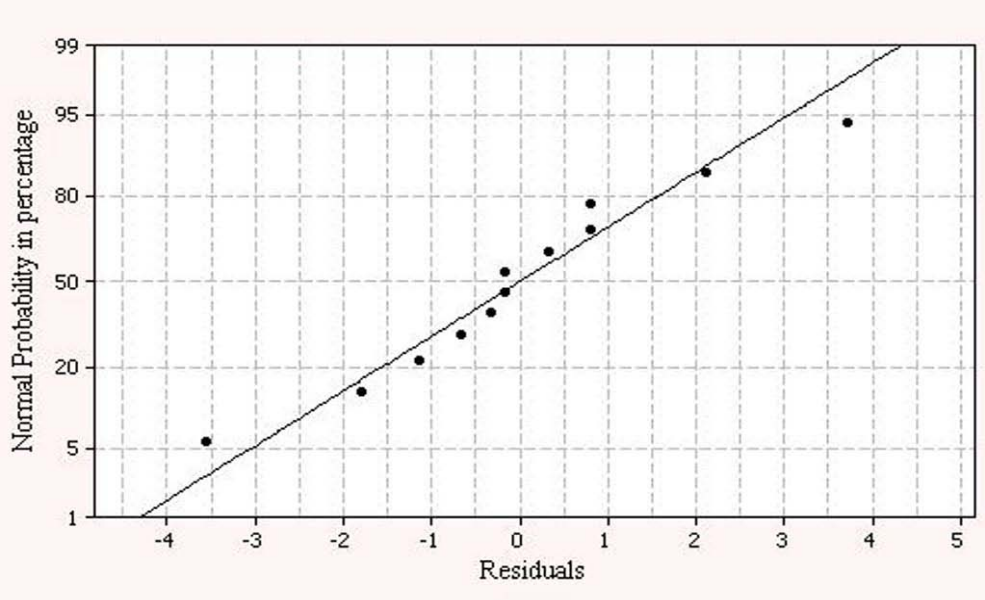

Fig. 2: Normal probability plot of the residuals

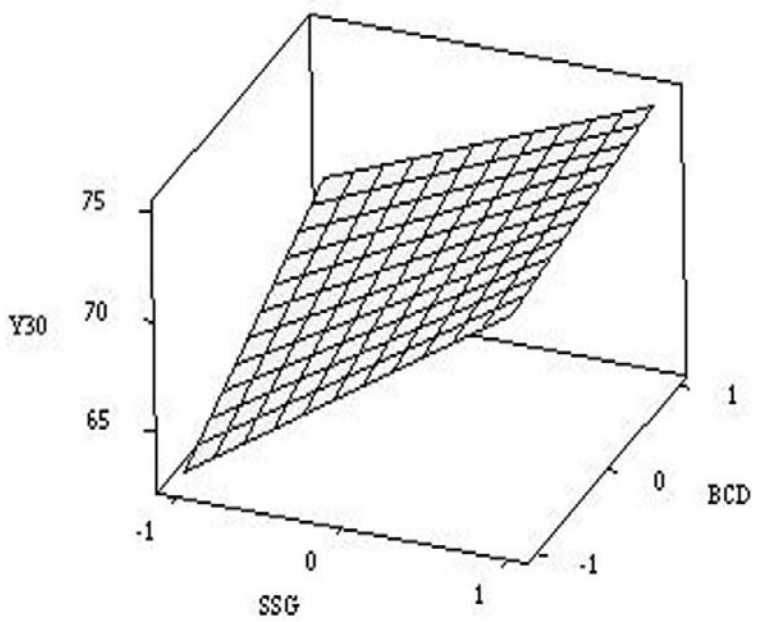

Fig. 3a: Three-dimensional response surface plot

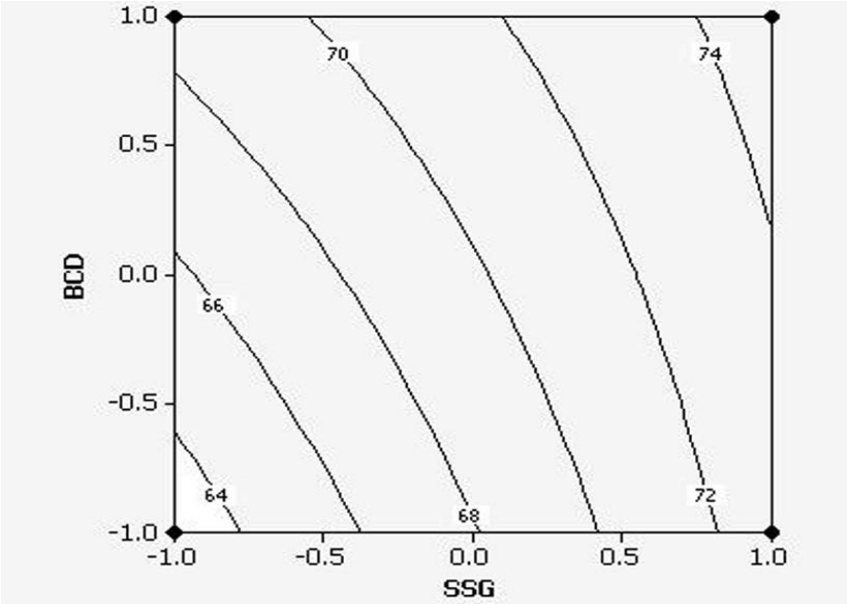

Fig. 3b: Corresponding contour plot

CONCLUSION

Two optimised tablet formulations of telmisartan were achieved by direct compression. They showed satisfactory percentage release (70 and 75) at 30 minutes as per as immediate release pattern is concerned. Batch F1 shown maximum drug release as it contains maximum amount of SSG and BCD. Batch F2 shown maximum drug release than F4 because it contain maximum amount of SSG, although both contain equal amount of BCD. This concludes that effect of SSG is more pronounced on the release profile of telmisartan from its tablet dosage form. Mechanism of drug release was found to be through diffusion as well as polymer relaxation as revealed from the slope of the Korsmeyer Peppas model. Full factorial design was successfully employed with sufficient model accuracy for studying the effect of SSG and BCD on the dissolution profile of telmisartan for their optimisation. Normal probability plot of the residuals proven the accuracy of the linear regression model chosen for studying the effect of independent variables on the release profile of telmisartan. ANOVA study of the linear regression model, response surface plot as well as contour plot shown that effect of SSG is more pronounced than BCD. This may be due to the fact that BCD is physically mixed with telmisartan. Results of t-test confirmed that predicted and observed responses for the optimized tablet formulations showed no significant difference.

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