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Solid Dispersion of Telmisartan 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 is to improve the dissolution profile of telmisartan by solid dispersion and to find out the effect of sodium starch glycolate and β – cyclodextrin on the dissolution profile of telmisartan tablets. The study also includes optimization of the amount of sodium starch glycolate and β – cyclodextrin by a 3^2 full factorial design. Other excipients used in the study are microcrystalline cellulose (Avicel PH-101), D- mannitol, magnesium stearate and talc. Both sodium starch glycolate and β – cyclodextrin had contribution towards the enhanced release profile of telmisartan (about 80 % drug is released in 40 minutes) but the effect of β – cyclodextrin is more pronounced as revealed from response surface plots as well as from their corresponding contour plots. The optimized amount of β – cyclodextrin and sodium starch glycolate was found to be 2.0 gm and 1.6 gm respectively. The predicted and observed responses for the optimized solid dispersions shown no significant difference (paired t-test, p – value = 0.2834 and 0.3403 for percentage drug released at 20 and 40 minutes respectively).

Keywords: Beta – cyclodextrin, Dissolution, Optimization, Regression equations, Sodium starch glycolate, Telmisartan.

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INTRODUCTION

Telmisartan is 4′-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl] methyl] biphenyl-2-carboxylic acid. It is an angiotensin II (AT_1) receptor antagonist,[1] which shows peak plasma levels approximately one 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 40mg. dose and 85 % following a 160mg. 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, 6] So in the present study an attempt has been made to improve the dissolution profile of TSN by solid dispersion using a 3^2 full factorial design. Cyclodextrins are powerful carriers for improving the therapeutic efficacy of drugs with poor aqueous solubility through solid dispersion. However, exploitation of this cyclodextrin property is hindered by the relatively low water solubility and high molecular mass of natural cyclodextrins.[7] So here β – cyclodextrin (BCD) is used along with sodium starch glycolate (SSG) to improve the aqueous solubility of TSN. Microcrystalline cellulose was employed as a directly compressible ingredient along with magnesium stearate, talc and D- mannitol in order to compress the powdered solid dispersion materials into a tablet dosage form.[8, 9]

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), D- mannitol, magnesium stearate (MS) and talc were purchased from Lobachemie. Pvt. Ltd, Mumbai. and Hydrochloric acid (HCl) was 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 solid dispersion

A mixture of BCD and SSG were dissolved in water and TSN was dissolved separately in methanol. The above two solutions were mixed in equal ratio (1:1 v/v) and stirred in a magnetic stirrer with heating at 80^0C for time enough to completely evaporate the solvents. Finally the sticky mixture was dried in a vacuum oven at 80^0C. Then the dried solid dispersion powder was passed through a 250µm sieve and stored in a desiccator over silica gel self-indicating coarse for

further use.[10] Total nine different batches of solid dispersion were prepared according to a 3^2 full factorial design having BCD and SSG as two independent variables. Details of the formulation design for solid dispersion are given in Table 1.

Table 1. 3^2 Full factorial design of TSN for solid dispersion with % yield, % DC and % EE.

Code of Solid dispersion	BCD in mg (Coded Values)	SSG in mg (Coded Values)	TSN in mg	% Yield (Average ± SD)	% DC (Average ± SD)	% EE (Average ± SD)
S1	4.8 (+1)	4.8 (+1)	1.6	93.57 ± 1.59	13.73 ± 0.2	96.06 ± 1.4
S2	4.8 (+1)	3.2 (0)	1.6	90.63 ± 1.85	15.82 ± 0.4	94.90 ± 2.38
S3	4.8 (+1)	1.6 (-1)	1.6	89.25 ± 2.38	18.53 ± 0.4	92.67 ± 2.02
S4	3.2 (0)	4.8 (+1)	1.6	88.75 ± 2.11	15.62 ± 0.39	93.73 ± 2.36
S5	3.2 (0)	3.2 (0)	1.6	88.08 ± 2.98	18.49 ± 0.5	92.45 ± 2.52
S6	3.2 (0)	1.6 (-1)	1.6	86.25 ± 1.95	22.52 ± 0.39	90.07 ± 1.56
S7	1.6 (-1)	4.8 (+1)	1.6	86.08 ± 2.01	17.82 ± 0.45	89.10 ± 2.24
S8	1.6 (-1)	3.2 (0)	1.6	85.42 ± 2.22	21.54 ± 0.74	86.17 ± 2.96
S9	1.6 (-1)	1.6 (-1)	1.6	84.86 ± 2.77	28.32 ± 0.72	84.97 ± 2.17

Preparation of tablets containing solid dispersion of telmisartan

The amount of solid dispersion powder equivalent to 40 mg of TSN was passed through a 250 µm sieve. Then MCC, MS, D- mannitol and talc were passed through the same sieve, mixed thoroughly and subjected to compression by an 8 mm round flat faced Cadmatch single tablet compression machine. Amount of solid dispersion equivalent to 40 mg of TSN (EASD), MCC, D- mannitol, MS and talc used are given in Table 2.

Table 2. Tablet formulation of telmisartan solid dispersion

Code of Tablet	Ingredients in mg/tablet					
	EASD	MCC	MS	Talc	D - mannitol	Total
T1	291.40	120	9	18	11.60	450
T2	252.85	120	9	18	50.15	450
T3	215.81	120	9	18	87.19	450
T4	256.01	120	9	18	46.99	450
T5	216.34	120	9	18	86.66	450
T6	177.64	120	9	18	125.36	450
T7	224.46	120	9	18	78.54	450
T8	185.67	120	9	18	117.33	450
T9	141.24	120	9	18	161.76	450

Percentage yield and drug content study

Prepared solid dispersion powders of TSN were dried to a constant weight in a desiccator over silica gel self indicating coarse for percentage yield determination. Accurately weighed quantity (100 mg) of solid dispersion powders from each batch were triturated individually and stirred with 0.1M HCl by a magnetic stirrer for two 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 10 ml was again diluted up to 100ml with 0.1M HCl and the absorbance was measured under U.V. Visible spectrophotometer at 228 nm against 0.1M HCl as blank [6]. Percentage yield, percentage drug content (% DC) and percentage entrapment efficiency (% EE) are determined in a triplicate manner.

In-vitro dissolution study and mechanism of drug release

For the dissolution of directly compressed tablets containing solid dispersion powders of TSN, United States Pharmacopeia (USP) apparatus-1 (basket type, LABINDIA, DISSO.) was used. Dissolution was carried out in 900 ml. of 0.1M HCl at 37±0.5^{o}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 5 ml. of sample withdrawn was diluted up to 25 ml with 0.1M HCl and analysed for the amount of TSN released under UV-visible spectrophotometer at 228 nm taking 0.1M HCl as reference standard or blank. Data of the in-vitro dissolution study were fitted into different mathematical models like Zero order,[11] First order,[11] Higuchi,[12] Hixson Crowell [13] and Korsmeyer Peppas model [14] 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 determined from the release exponent (n) values.[15, 16]

Mathematical and statistical analyses

A 3^2 full factorial design was employed considering amount of BCD (X_1) and amount of SSG (X_2) as two independent variables and 9 different batches were prepared (table 1). Percentage of drug released (% DR) at 10 minute (Q_{10}) and 20 minute (Q_{20}) were taken as two response variables to study the effect of BCD and SSG 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, their square terms and their interaction terms. Minitab 15 and SAS (for optimization) were used for statistical and mathematical analyses.[17]

RESULTS AND DISCUSSION

Percentage yield and drug content study

Percentage yield was found to be highest from S1 (93.57 ± 1.59) and lowest from S9 (84.86 ±

2.77). % EE was decreasing from S1(96.06 ± 1.4) to S9 (84.97 ± 2.17), because the amount of BCD decreases from S1 to S9. The drug was entrapped within the hydrophilic matrices of BCD; hence amount of BCD used in the solid dispersion was played an important role in controlling the % EE. Results of % yield, % DC and % EE were reported in Table 1 as average ± SD (n = 3).

In-vitro dissolution study and mechanism of drug release

Dissolution profile of all the formulations are improved successfully through solid dispersion. All the nine formulations have shown more than 80 % drug release profile in 40 minutes. Initial % DR was highest from T1 (30.4 ± 2.02) and lowest from T9 (8.66 ± 0.86), because T1 contains highest amount of both BCD and SSG (2.4 gm each), whereas T9 contains least amount of both BCD and SSG (0.8 gm each). Drug release pattern was more rapid from T1 and follows a descending pattern from T1 to T9, because the amount of BCD decreases from T1 to T9, which is mainly responsible for enhancing the dissolution profile of telmisartan by solubilizing the drug in its hydrophilic matrices. In case of T1, T2 and T3, % DR was decreased from T1 to T3 although these three formulations have equal amount of BCD (2.4 gm), because the amount of SSG was decreased from T1 to T3. Dissolution profile of all the nine formulations (Figure 1) have shown that SSG plays a less important role in enhancing the dissolution of telmisartan, but it is helpful in promoting disintegration of the tablet hence dissolution.

From the R^2 values of different mathematical models it was concluded that all the formulations were best fitted to Korsmeyer Peppas model whereas T9 was best fitted to Hixson Crowell dissolution model ($R^2 = 0.9221$). The n value of Korsmeyer Peppas model ranges from 0.5032 to 0.9341 (Table 3), in case of all the batches which indicates that the drug release occurred through diffusion as well as polymer relaxation mechanism.[15, 16] R^2 values of all the nine batches for different mathematical models along with slope of Korsmeyer Peppas model were shown in Table 3.

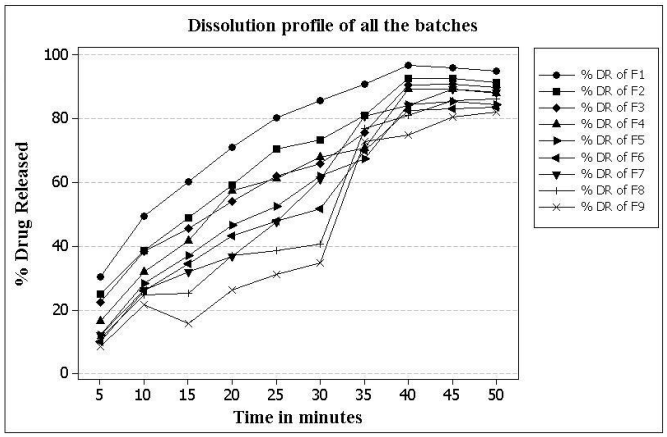

Figure 1: Dissolution profile of all the batches.

Table 3. R^2 values of different mathematical models and release exponent value of Korsmeyer Peppas model

Tablet code	R^2 values of different mathematical models					Release exponent (n)
	Zero Order	First Order	Higuchi	Hixson Crowell	Korsmeyer Peppas	Korsmeyer Peppas
T1	0.8813	0.9274	0.9557	0.8219	0.9701	0.5032
T2	0.9439	0.9325	0.9814	0.8961	0.9901	0.5899
T3	0.9631	0.9156	0.9781	0.9214	0.9877	0.6101
T4	0.9432	0.9235	0.9764	0.8771	0.9792	0.7329
T5	0.9646	0.9372	0.9807	0.8967	0.9797	0.8317
T6	0.9633	0.9327	0.9661	0.9042	0.9738	0.8926
T7	0.9608	0.9316	0.9527	0.9341	0.9778	0.8897
T8	0.9227	0.8837	0.8880	0.9282	0.9368	0.9022
T9	0.9028	0.8726	0.8507	0.9221	0.8894	0.9341

Mathematical and statistical analyses

Regression equations including linear and interaction terms were utilized to evaluate the effect of factors on the response variables. The regression equations describing percentage of drug released (% DR) at 20 minute (Q_{20}) and 40 minute (Q_{40}) were as follows.

$$Q_{20} = 42.82 + 11.00\,X_1 + 5.44\,X_2 + 1.32\,{X_1}^2 + 1.86\,{X_2}^2 + 0.45\,X_1X_2$$

$$Q_{40} = 85.34 + 7.08\,X_1 + 4.08\,X_2 + 1.30\,{X_1}^2 + 0.31\,{X_2}^2 - 0.78\,X_1X_2$$

According to the results of ANOVA only linear terms were having statistically significant effect (p – value < 0.0001) on Q_{20}, whereas square terms (p- value = 0.814) and interaction terms (p – value = 0.858) have no statistical significant effect on Q_{20}. On the other hand linear terms (p – value < 0.0001), square terms (p- value = 0.044) and interaction terms (p- value = 0.037) were having statistically significant effect on Q_{40}. Regression equations of Q_{20} and Q_{40} revealed that effect of BCD was more prominent than that of SSG, because coefficient of BCD (11.00 and 7.08 in Q_{20} and Q_{40} respectively) was larger than that of SSG (5.44 and 4.08 in Q_{20} and Q_{40} respectively) in both the equations. The contour lines in both the contour plots are running from the BCD axis and become slightly curvilinear as they progress towards the SSG axis. This pattern of contour lines had shown that the response variables were increased with increasing values of SSG and BCD, but the effect of BCD was more pronounced, which was also evident from the positive sign of the coefficients of SSG, BCD and their respective response surface plots (Figure 2).This prominent effect of BCD was due to the fact that it solubilized TSN through solid dispersion and increases the drug dissolution profile. Though the effect of SSG was less prominent as compared to BCD, but SSG plays a role of adjuvant in improving the dissolution profile of TSN. Process optimization was done by setting the target values of Q_{20} and Q_{40} at 55%

and 90% respectively. Optimized values of BCD and SSG were 2.0 gm and 1.6 gm respectively. The predicted and observed responses for the optimized solid dispersions shown no significant difference (paired t-test, p – value = 0.2834 and 0.3403 for Q_{20} and Q_{40} respectively).

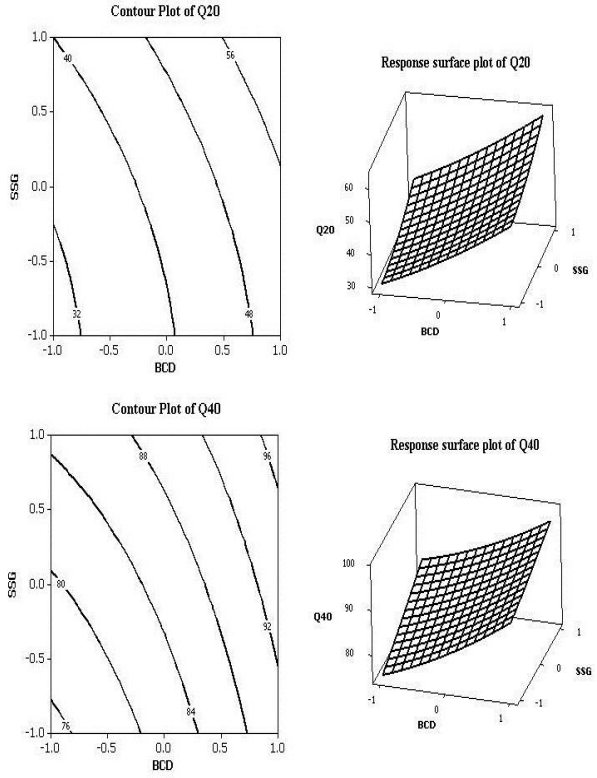

Figure 2: Contour plots of Q_{20}, Q_{40} and their corresponding response surface plots.

CONCLUSION

Dissolution profile of telmisartan was successfully improved through solid dispersion. The solid dispersion powders compressed into tablets had portrayed satisfactory drug release pattern (more than 80%) at 40 minutes as per as immediate release pattern is concerned. Batch T1 shown maximum drug release as it contains maximum amount of SSG and BCD. Effect of BCD is more pronounced than SSG on the release profile of telmisartan. Mechanism of drug release was found to be through diffusion as well as polymer relaxation as revealed from slope of the Korsmeyer Peppas model. A 3^2 full factorial design was successfully employed with sufficient model accuracy for studying the effect of BCD and SSG on the dissolution profile of telmisartan for their optimization. Regression equations of the model, response surface plot as well as contour plot had shown that effect of BCD is more pronounced than SSG. This result was attributed to the dissolution enhancement property of BCD through solid dispersion. Results of paired t-test confirmed that predicted and observed responses for the optimized tablet formulations showed no statistical significant difference.

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