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Orodispersible tablets of telmisartan through cyclodextrin-surfactant complexation: A quality by design approach

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ABSTRACT: Telmisartan is a poorly water-soluble drug with dissolution limited bioavailability. In this work, solubility and dissolution rate were aimed to improve through the development of cyclodextrin (CD) complexes containing surfactant; followed by developing them into orodispersible tablets (ODTs). Quality by design approach was adopted in the optimization of CD-surfactant complex as well as in the optimization of ODTs. Type of cyclodextrins, the concentration of the cyclodextrins, and concentration of poloxamer 188 were taken as the factors in the preparation of inclusion complexes by solvent evaporation method. Solubility was taken as the response variable. The optimized formulation of the complex was taken for ODTs preparation. Concentration of povidone, concentration of super-disintegrant and type of super-disintegrant were taken as the independent factors, and disintegration time (DT) and time for 90% dissolution (T90%) were taken as the responses. The tablets were prepared by direct compression technique. The results of both the responses were analyzed by response surface quadratic model for the influence of the factors on them. All three factors were found to have significant influence on both the responses (at $p < 0.05$). Graphical optimization was performed by desirability functions approach in order to have low DT and low T90%. The optimized telmisartan CD-surfactant complex was found to have a solubility of 2.86 mg/mL. The optimized ODTs were found to have 20.4 sec. DT and 7.3 min. T90%. These results indicated that enhancement of solubility of telmisartan as well as dissolution of the ODTs was successfully improved through quality by design approach.

KEYWORDS: Quality by design; solubility enhancement; dissolution enhancement; inclusion complexes; optimization; telmisartan; orodispersible tablets.

1. INTRODUCTION

Telmisartan is a widely used drug alone or in combination in the treatment of hypertension [1]. It is an extremely poorly soluble drug with good permeability as class II drug under biopharmaceutic classification system (BCS) [2]. Thus, it exhibits dissolution limited oral bioavailability which is around 40% only [3]. Cyclodextrins (CD) are extensively used materials for preparation of inclusion complexes for poorly water-soluble drugs in order to improve their solubility and dissolution rate [4]. Among the three different cyclodextrins, high soluble derivatives of β-CD like methyl-β-CD and hydroxylpropyl-β-CD (HP-β-CD) are commonly used for solubility enhancement of poorly soluble drugs.

A good extent of research was carried out and reported on solubility and dissolution enhancement of telmisartan. Some of the previous works reported regarding solubility and dissolution enhancement are by Bhumika P et al. [5], Eshwaraiah MC et al. [6], Borba PA et al. [7], Arora P et al. [8] etc. Bhumika P et al. reported that solid dispersions by solvent evaporation with poloxamer 407 was efficient in enhancing solubility when compared to PEG 6000 and the solubility was found to be increased from 0.0014 mg/mL of pure drug to 0.848 mg/mL of the solid dispersion form. Eshwaraiah MC et al. reported that the solid dispersion prepared with poloxamer 407 at 1:2 ratio to that of the drug was more effective than PEG 4000 and povidone in enhancing the dissolution rate of the telmisartan. Borba PA et al. reported that inclusion

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complexes prepared with HP-β-CD successfully enhance the biopharmaceutical properties of telmisartan. Arora P et al. reported that presence of tween 80 improved the complexation ability of HP-β-CD and dissolution rate of telmisartan. These works summarize that the solubility/dissolution of telmisartan can be effectively improved by using poloxamers and cyclodextrins and mostly by solvent evaporation techniques. Cyclodextrin-surfactant complexes are proved to have improved advantages than individual carriers in many pharmaceutical and food products [8-10]. But no study is reported yet on the combined use of both poloxamers and cyclodextrins for the enhancement of solubility and dissolution of telmisartan. This critical review of the literature suggested that there is a huge scope of utilizing the cyclodextrin-surfactant combination for enhancing solubility and dissolution of poorly soluble drugs. Hence, in the present research work, it was aimed to enhance the solubility and dissolution of telmisartan using cyclodextrin-surfactant combination.

Further, the developed complexed form of the drug was also aimed to be developed into orodispersible tablets (ODTs) so as to improve the dissolution rate further which contribute towards the bioavailability of telmisartan. The ODTs have reported advantages over conventional tablets in terms of rapid disintegration in the mouth even before swallowing followed by rapid dissolution. Previous literature on the development of telmisartan ODTs indicated the use of either direct compression or wet granulation techniques taking the pure drug [11-13]. But, in this method the complexed form of the drug was subjected to kneading with superdisintegrant followed by mixing with other excipients and direct compression to obtain the ODTs. This could provide better enhancement of dissolution rate with a smaller number of carriers. No method was reported on this novel approach.

The present work was designed using quality by design approach. Central composite design was selected to design both the experiments of CD-surfactant complex optimization for increasing solubility as well as ODTs optimization for increasing dissolution rate.

2. RESULTS AND DISCUSSION

2.1 Characterization studies of ICTs

The ICTs were prepared according to the combinations of the factors suggested by the CCD design which were shown in the Table 1. The DSC thermograms were shown in Figure 1(a) and 1(b). The pure DSC thermogram of the pure telmisartan showed a sharp endotherm corresponding to its melting point i.e., 261^{o}C [14] of the crystalline form. In the thermogram of the ICT, an endotherm at around 100^{o}C corresponding to the possible loss of water from the sample. A second endotherm observed at around 310^{o}C could be due to the melting point temperature of the HP-β-CD or due to the loss of water that was bound to HP-β-CD [15]. But, the thermogram of the ICT did not show any sharp endothermic peak corresponding to the melting of telmisartan. This indicated that the crystalline form of the drug might be converted into amorphous form during precipitation upon solvent evaporation [15].

The X-RD spectra were shown in Figure 1(c) and 1(d). The spectrum of the pure telmisartan exhibited so many sharp and intense peaks which indicated crystalline form of the telmisartan. But, the spectrum of the ICT exhibited very few broad and less intense peaks. This result evidently indicated the crystalline telmisartan might get converted into amorphous form in the inclusion complex [15].

The results of solubility studies performed on ICTs were shown in Table 1. All the ICTs exhibited greater solubilities than pure telmisartan (0.006 mg/mL). Besides high hydrophilic nature of the CDs and surfactant taken, this high solubility could be majorly attributed to the conversion of telmisartan from crystalline to amorphous form that was indicated by DSC and X-RD studies. The influence of the formulation factors was shown in Fig 2. Upon increase in the concentration of CD, the solubility was found to be increased. This could be attributed to the availability of a greater number of host molecules for entrapping more guest drug molecules [7]. Further, the solubility was found to be increased upon increase in the concentration of poloxamer 188. This might be due to the association of more amount of telmisartan at higher concentrations of the surfactant thus resulting in increased solubility [16]. The CD type was also found to influence the solubility of telmisartan. The ICTs prepared with HP-β-CD were found to have more solubilities than those of the ICTs prepared with methyl-β-CD. This might be because of the more hydrophilic nature of HP-β-CD than that of methyl-β-CD [17].

2.2 Design validation and optimization of the ICTs

The ANOVA was performed for the suggested linear model and the results shown in Table 2. These ANOVA results indicated that the selected model was significant. All the three formulation factors were found to have significant effect on the solubility at $p< 0.05$. Further, the adjusted and predicted R^2 values

were found to be 0.8196 and 0.7453. The difference between these values was less than 0.2. These results altogether indicated that the selected model can be navigated for the optimization.

Table 1: Formulation compositions of ICTs according to the central composite design and the results of their characterization studies

Run order	Code	Level of Factors			Response: Solubility* (mg/mL)
		A: Conc. of CD#, %w/w	B: Conc. of Surfactant, % w/v	C: Type of CD	
1	ICT1	50.00	0.20	HP-β-CD	2.1 ± 0.3
2	ICT2	66.70	0.10	HP-β-CD	2.7 ± 0.4
3	ICT3	50.00	0.34	Me-β-CD	1.4 ± 0.1
4	ICT4	26.38	0.20	HP-β-CD	1.3 ± 0.2
5	ICT5	50.00	0.06	HP-β-CD	1.5 ± 0.1
6	ICT6	26.38	0.20	Me-β-CD	0.9 ± 0.1
7	ICT7	50.00	0.34	HP-β-CD	1.9 ± 0.3
8	ICT8	33.30	0.30	Me-β-CD	1.5 ± 0.2
9	ICT9	66.70	0.30	Me-β-CD	2.5 ± 0.6
10	ICT10	33.30	0.30	HP-β-CD	1.8 ± 0.2
11	ICT11	73.62	0.20	HP-β-CD	3.1 ± 0.4
12	ICT12	66.70	0.10	Me-β-CD	2.1 ± 0.3
13	ICT13	50.00	0.06	Me-β-CD	0.9 ± 0.2
14	ICT14	33.30	0.10	Me-β-CD	1.2 ± 0.1
15	ICT15	33.30	0.10	HP-β-CD	1.5 ± 0.3
16	ICT16	50.00	0.20	Me-β-CD	1.6 ± 0.2
17	ICT17	66.70	0.30	HP-β-CD	3.0 ± 0.5
18	ICT18	73.62	0.20	Me-β-CD	2.3 ± 0.4

Cyclodextrin
* All the values were expressed as Average ± Standard Deviation for n = 3

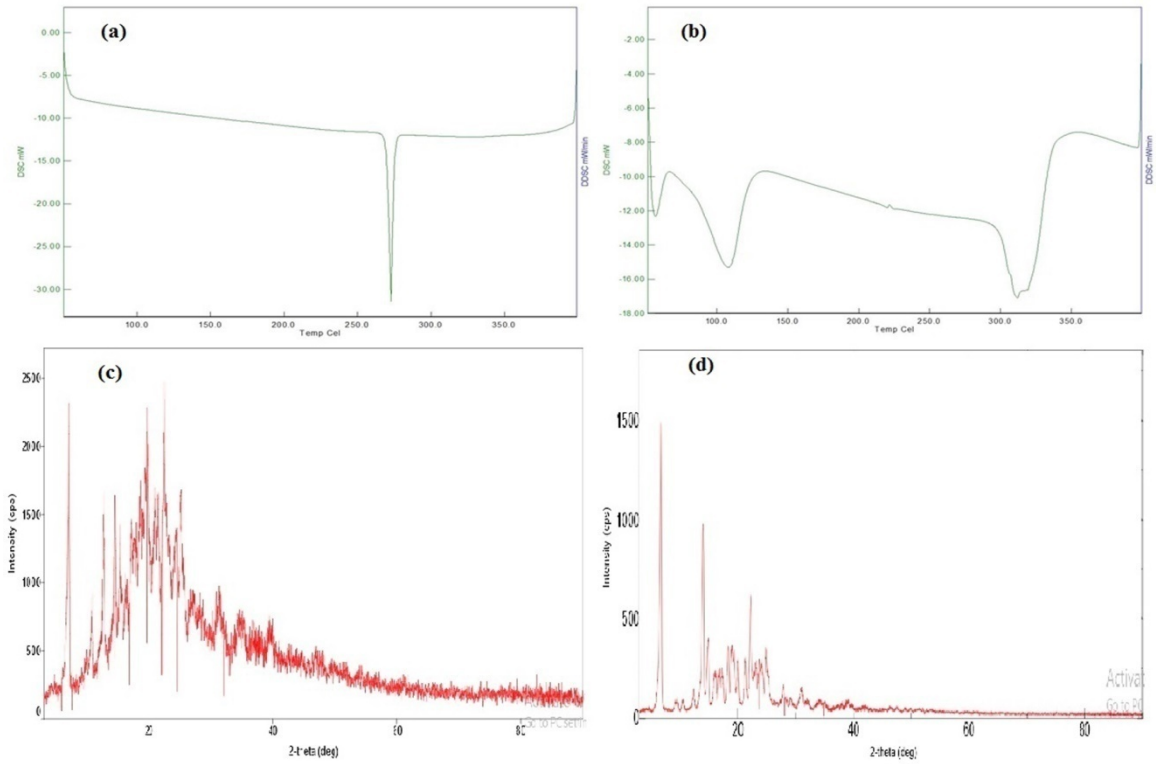

Figure 1: DSC and X-RD spectra of pure telmisartan and its inclusion complex. a) DSC spectrum of pure telmisartan; b) DSC spectrum of telmisartan inclusion complex; c) X-RD spectrum of pure telmisartan; d) X-RD spectrum of telmisartan inclusion complex.

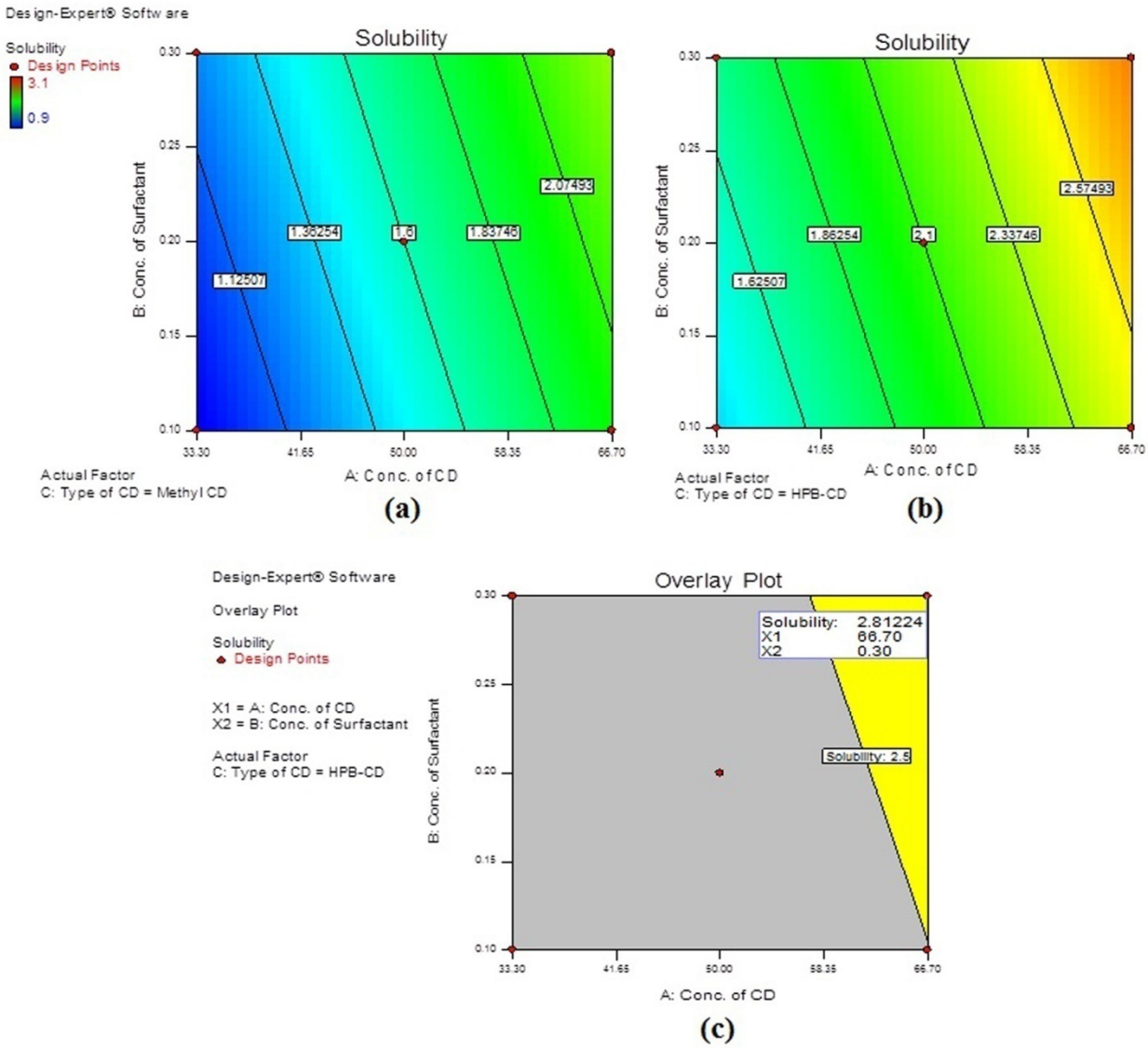

Figure 2: Contour plots indicating the effect of factors A and B on solubility in case of (a) Level 1 of factor C (Methyl-β-CD); (b) Level 2 of factor C (HP-β-CD); and (c) Overlay plot indicating the design space (the yellow region) after optimization

Table 2: Results of ANOVA test for response surface linear model for the Solubility

Source	SS[a]	Df[b]	MSS[c]	F value	p-Value	Inference[d]
Model	6.41	3	2.14	26.74	< 0.0001	**Significant**
A-HPBCD Conc.	4.87	1	4.87	60.95	< 0.0001	**Significant**
B-Tween 80 Conc.	0.41	1	0.41	5.18	0.0391	**Significant**
C-Method	1.12	1	1.12	14.08	0.0021	**Significant**
Residual	1.12	14	0.080			
Cor Total	7.53	17				

Note: [a]-Sum of Squares; [b]-Degrees of Freedom; [c]-Mean Sum of Squares;
[d]-p-Value less than 0.05 indicates model terms are significant

Graphical optimization was performed with the desirability of "maximizing the solubility above 2.5 mg/mL". The yellow region in the overlay plot (shown in Figure 2(c)) obtained after optimization indicates the design space in side which any combination of the factors will result in the solubility above 2.5 mg/mL. One best combination of the factors inside the design space chosen by the software was HP-β-CD as the type

of CD, 66.7% w/w as the CD concentration and 0.3% w/v as the poloxamer concentration. New CD-surfactant complex of telmisartan was prepared at this optimized combination. The solubility of this new optimized complex was found to be 2.86 mg/mL which was correlated with that of the predicted value by the software. Hence, this optimized complex was taken for further development of telmisartan ODTs.

2.3 Characterization of the telmisartan ODTs

The ODTs were prepared according to the factor combinations shown in the Table 3. The average weights of ODTs of all the formulations were in the range of 198.9 – 201.4 mg and the weight variation were within the acceptable limit of 7.5%. The friability values were found to be in the range of 0.18 – 0.31% which were below the maximum limit of 1%. The tensile strength values of all the formulations were in the range of 0.78 – 0.90 N/mm^2 which indicated the ODTs were strong enough to withstand pressures during packing/transportation. The packing fraction values of all the formulations of ODTs were obtained in the range of 0.83 – 0.92 and so the porosity fraction values in the range of 0.17 – 0.08. These values indicated that the tablets were found to have sufficient porosity for penetration of water. The wetting time values were obtained in the range of 12 – 53 sec. The wetting time was found to be decreased upon increase in the concentration of the superdisintegrant. This could be due to the rapid absorption of water at higher amounts of the superdisintegrants that could lead to rapid wetting [18]. The drug content for all the formulations were found to be in the acceptable range of 98.9 – 101.3%.

Table 3: Combination of factors and levels for different ODT formulations according to central composite design and the corresponding results of the responses

S. No.	Run order	Formulation Code	Levels of the factors			Values of Responses*	
			A: Conc. of PVP (%w/w)	B: Conc. of SDis (%w/w)	C: Type of SDis.	R1: DT (sec.)	R2: T90% (min.)
1	18	F1	4.00	0.76	SSG	129 ± 13	19.2 ± 0.7
2	17	F2	2.00	2.00	SSG	91 ± 8	15.6 ± 1.1
3	8	F3	6.00	2.00	SSG	112 ± 9	16.5 ± 0.8
4	19	F4	1.17	5.00	SSG	75 ± 6	14.9 ± 0.6
5	15	F5	4.00	5.00	SSG	82 ± 10	12.3 ± 0.4
6	7	F6	6.83	5.00	SSG	103 ± 5	16.1 ± 0.7
7	13	F7	2.00	8.00	SSG	64 ± 6	10.8 ± 0.5
8	5	F8	6.00	8.00	SSG	79 ± 8	12.1 ± 1.0
9	2	F9	4.00	9.24	SSG	61 ± 4	10.2 ± 0.9
10	6	F10	4.00	0.76	CP	186 ± 7	17.4 ± 0.7
11	14	F11	2.00	2.00	CP	161 ± 12	14.2 ± 0.6
12	20	F12	6.00	2.00	CP	174 ± 9	16.5 ± 0.8
13	21	F13	1.17	5.00	CP	137 ± 13	13.8 ± 1.2
14	22	F14	4.00	5.00	CP	132 ± 10	11.6 ± 0.4
15	27	F15	6.83	5.00	CP	143 ± 8	14.9 ± 0.8
16	9	F16	2.00	8.00	CP	95 ± 5	9.3 ± 0.7
17	26	F17	6.00	8.00	CP	121 ± 6	11.9 ± 0.5
18	1	F18	4.00	9.24	CP	109 ± 11	10.6 ± 0.9
19	16	F19	4.00	0.76	SC	106 ± 8	12.8 ± 1.2
20	24	F20	2.00	2.00	SC	72 ± 9	10.2 ± 1.3
21	3	F21	6.00	2.00	SC	78 ± 4	11.9 ± 0.6
22	11	F22	1.17	5.00	SC	35 ± 6	8.6 ± 0.4
23	12	F23	4.00	5.00	SC	42 ± 2	8.2 ± 0.7
24	23	F24	6.83	5.00	SC	50 ± 5	10.3 ± 0.8
25	4	F25	2.00	8.00	SC	19 ± 3	6.9 ± 0.5
26	25	F26	6.00	8.00	SC	36 ± 4	7.8 ± 0.3
27	10	F27	4.00	9.24	SC	21 ± 2	7.4 ± 0.4

* All the values were expressed as Average ± Standard Deviation for n = 3

The results of the Response 1, DT were shown in Table 3. The influence of all the factors on DT was illustrated in Figure 3(a), 3(b) and 3(c). Upon increase in the concentration of PVP-K30, the DT was found to be increased. This could be attributed to the increasing binding nature of PVP-K30 at higher concentrations [19]. The DT was found to be decreased upon increase in the concentration of superdisintegrant. This might be because of decreased wetting time rapid swelling of the tablet at higher superdisintegrant concentrations [18,20]. The type of CD also influenced the DT as the values were found to be much lesser in case of SC

followed by SSG and relatively higher for CP. This could be attributed to the greatest swelling index of SC which was around 1400 [21] against around to 300 for SSG [22] and much lesser for CP [23].

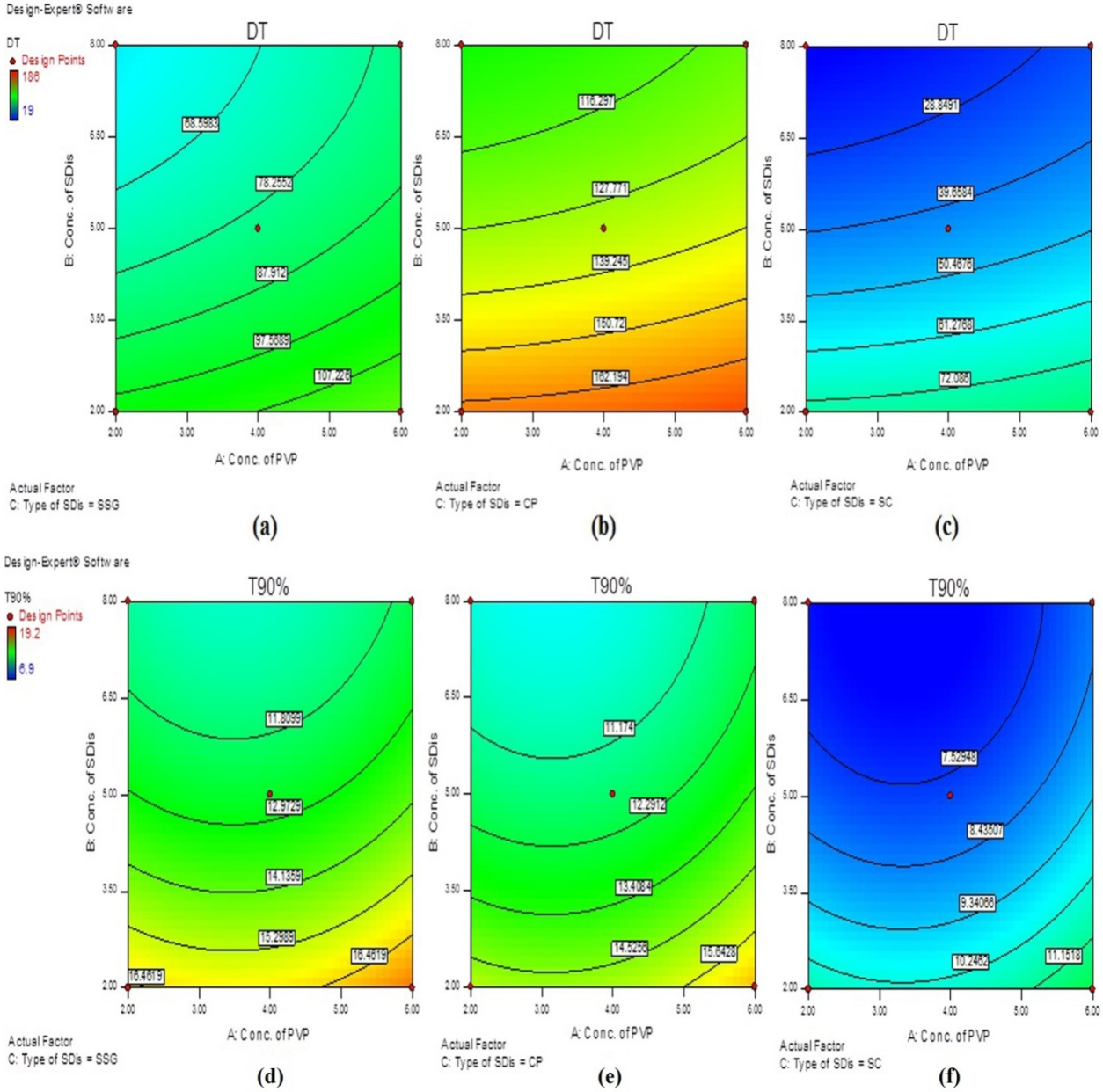

Figure 3: Contour plots showing effect of the factors on the responses. a) Effect of factors A & B on DT in case of SSG as the factor C; b) Effect of factors A & B on DT in case of CP as the factor C; c) Effect of factors A & B on DT in case of SC as the factor C; d) Effect of factors A & B on T90% in case of SSG as the factor C; e) Effect of factors A & B on T90% in case of CP as the factor C; f) Effect of factors A & B on T90% in case of SC as the factor C.

The dissolution data of all the formulations was found to follow first-order kinetics. From this data, the T90% values for all the formulations were calculated and represented in Table 3. The influence of all the factors on T90% was illustrated in Figure 3(d), 3(e) and 3(f). Upon increase in the concentration of PVP-K30, initially the dissolution rate was increased and the T90% was decreased. This could be due to increased hydrophilicity of the tablet at higher concentration of PVP-K30. But, further increase in the PVP-K30 concentration up to 6.83% w/w, the dissolution rate was decreased and hence the T90% was increased. This could be because of the predominant binding nature of the PVP-K30 at such higher concentrations [19]. Upon increase in the concentration of superdisintegrant, the T90% was found to be decreased. This might be because of the rapid disintegration followed by rapid dissolution at higher disintegrant concentrations [18,20]. The ODTs prepared with starch citrate were found to lower T90% than the corresponding ODTs

prepared with SSG and CP. This could be attributed to the high swelling and short disintegration times with SC which could cause rapid dissolution and hence low T90% values [21].

2.4 Design validation and optimization of the ODTs

The ANOVA was performed for the suggested quadratic model for both the responses and the results shown in Table 4. These ANOVA results indicated that the selected model was significant. All the three formulation factors were found to have significant effect on the solubility at $p< 0.05$. Further, the adjusted and predicted R^2 values were found to be respectively 0.9771 and 0.9566 for DT and 0.9280 and 0.8636 for T90%. The difference between these values was less than 0.2 in case of both the responses. These results altogether indicated that the selected model can be navigated for the optimization.

Graphical optimization was performed with the desirability criteria as "minimizing the DT below 30sec" and "minimizing the T90% below 8 min." The yellow region in the overlay plot (shown in Figure 4) with one best combination of the factors inside the design space chosen by the software was 2.27% w/w of PVP-K30; 7.95% w/w of SC as the superdisintegrant. The ODTs was prepared at this optimized combination. The DT and T90% were found to be 15.4 sec. and 7.3 min. which were within the 95% confidence intervals of the predicted value by the software. Hence, the ODTs at this combination were concluded as the optimized ODTs of telmisartan.

Table 4: Results of ANOVA test for response surface quadratic model for both the selected responses

Response	Source	SS[a]	Df[b]	MSS[c]	F value	p-Value	Inference[d]
R1: DT[e]	Model	52952.44	11	4813.86	102.07	< 0.0001	**Significant**
	A-Conc. of PVP	1166.17	1	1166.17	24.73	0.0002	**Significant**
	B-Conc. of SDis.	14963.48	1	14963.48	317.29	< 0.0001	**Significant**
	C-Type of SDis.	35756.07	2	17878.04	379.09	< 0.0001	**Significant**
	AB	27.00	1	27.00	0.57	0.4610	
	AC	74.42	2	37.21	0.79	0.4723	
	BC	366.32	2	183.16	3.88	0.0437	**Significant**
	A^2	19.09	1	19.09	0.40	0.5342	
	B^2	456.09	1	456.09	9.67	0.0072	**Significant**
	Residual	707.41	15	47.16			
	Cor Total	53659.85	26				
R2: T90%[f]	Model	273.73	11	24.88	31.46	< 0.0001	**Significant**
	A-Conc. of PVP	9.83	1	9.83	12.42	0.0031	**Significant**
	B-Conc. of SDis.	131.05	1	131.05	165.70	< 0.0001	**Significant**
	C-Type of SDis.	120.76	2	60.38	76.34	< 0.0001	**Significant**
	AB	8.333×10^{-4}	1	8.333×10^{-4}	1.054×10^{-4}	0.9745	
	AC	0.41	2	0.21	0.26	0.7743	
	BC	3.00	2	1.50	1.90	0.1842	
	A^2	7.70	1	7.70	9.74	0.0070	**Significant**
	B^2	6.40	1	6.40	8.09	0.0123	**Significant**
	Residual	11.86	15	0.79			
	Cor Total	285.59	26				

Note: [a]-Sum of Squares; [b]-Degrees of Freedom; [c]-Mean Sum of Squares; [d]-p-Value less than 0.05 indicates model terms are significant; [e]-Disintegration time; [f]-Time for 90% drug dissolved

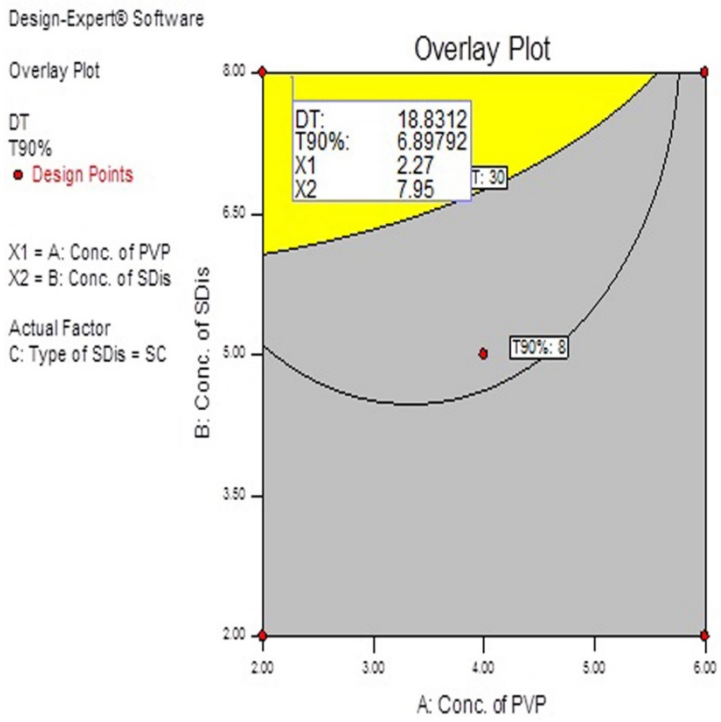

Figure 4: Overlay plot indicating the design space (yellow region) after graphical optimization of telmisartan ODTs

The comparative dissolution profile of pure telmisartan, the optimized complex and the optimized ODTs was shown in Figure 5. The time required to dissolve 90% of telmisartan (T90%) was found to be decreased to 31.2 min. for the optimized ICT from 212.8 min. of pure telmisartan. Further, the T90% was decreased to 7.3 min for the optimized ODTs. These results indicated that both the solubility and dissolution rate of telmisartan were greatly increased upon developing inclusion complexes containing surfactant and further development into ODTs.

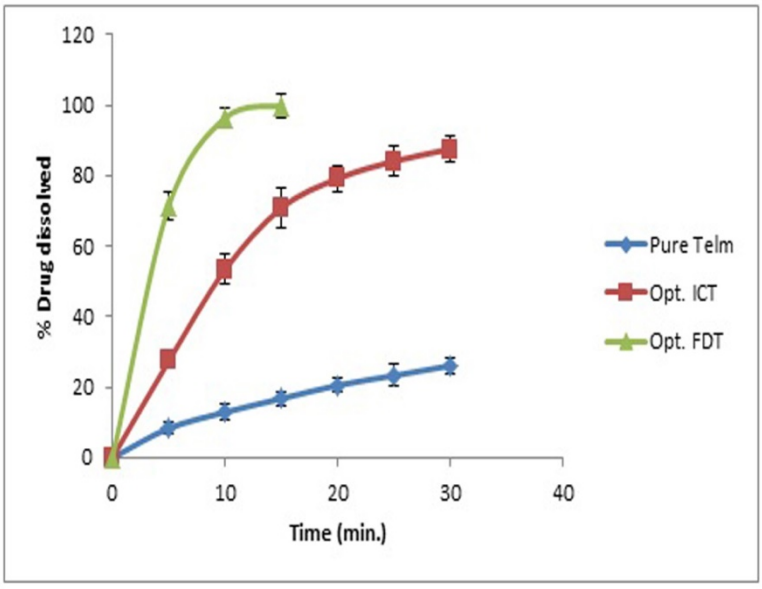

Figure 5: Comparative dissolution profile of pure telmisartan, the optimized telmisartan inclusion complex and the optimized telmisartan ODTs

3. CONCLUSION

The objective of enhancing oral bioavailability of telmisartan through enhancing solubility and dissolution rate performed in this work. The experiment was designed and executed according the much acceptable QbD approach. CCD was selected for the experiments of CD-surfactant complexes as well as for the ODTs. All the selected factors were found to have significant influences on the selected responses at $p< 0.05$. The optimized complexes exhibited a solubility of 2.86 mg/mL against 0.006 mg/mL of pure telmisartan. Further, the optimized ODTs exhibited rapid disintegration of 15.4 sec. and 90% drug was dissolved in less than 8 min. only. These results indicated that the set objectives of the work were achieved successfully with help of statistically justified QbD approach.

4. MATERIALS AND METHODS

4.1 Materials

Telmisartan was obtained as gift samples from Hetero Drugs Pvt. Ltd, Visakhapatnam; Methyl-β-CD, HP-β-CD, Poloxamer-188, sodium starch glycolate (SSG), cross-povidone (CP), starch citrate (SC) and microcrystalline cellulose (MCC) were acquired from Sigma Chemicals Co.; All other chemicals used were of analytical grade.

4.2 Preparation of Inclusion Complexes of Telmisartan (ICTs) by QbD Approach

4.2.1 QbD aspects of ICTs[24]

Quality target product profile (QTPP): The ICTs are developed with the aim of improving solubility and dissolution rate of poorly soluble telmisartan

Critical quality attributes (CQAs): These are also called as responses. Solubility was selected as the critical quality attribute as it is the direct resemblance of the desired quality of the product.

Critical process/formulation parameters (CPPs): These are the factors which influence the CQAs or responses. Upon extensive literature review, three formulation parameters viz. type of CD (categoric factor; at two levels Methyl-β-CD and HP-β-CD), concentration of CD (numeric factor; at five levels in the range of 26.38 – 73.62% w/w of the drug-CD mixture) and concentration of poloxamer 188 (numeric factor; at five levels in the range of 0.06 – 0.34% w/v of the solvent taken) were taken as the CPPs.

Experimental design: With the above nature and levels of the factors, central composite design (CCD) was selected to investigate the influence of the factors on the selected response. The possible combinations of the factors and their levels according to the CCD design were shown in the Table 1. ICTs were prepared at all these combinations.

4.2.2 Preparation of ICTs by solvent evaporation

ICTs were prepared by solvent evaporation method. The solvent should be selected such that the drug, CDs and the surfactant should be soluble in it and also the solvent should be volatile. Hence, based on these factors, mixture of dimethyl sulfoxide (DMSO) and chloroform ($CHCl_3$) at 1:1 ratio was selected. As shown in the Table 1, specific amounts of the drug and the CD were taken and dissolved in the solvent mixture containing desired amount of poloxamer 188. The mixture was subjected to shaking on an orbital shaker at 100 rpm until both the drug and the CD were dissolved. Then the mixture was transferred into a round bottom flask and placed in a Rotavapor for evaporation of the solvent under 60°C temperature and 100 mmHg pressure. The resultant dry powder mixture was collected and stored in air-tight containers until further use.

4.2.3 Characterization studies of the prepared ICTs

Differential scanning calorimetry (DSC): Thermal behavior of the telmisartan in its pure form and in the ICTs was studied using DSC. Samples of about 5 mg were weighed and encapsulated into flat-bottomed aluminum pans with crimped-on lids. These were scanned at a speed of 10°C/min from 50°C to 400°C in the presence of nitrogen which was maintained at a flow rate of 20 ml/min to obtain the spectra.

X-ray diffraction (X-RD) analysis: Physical state of the telmisartan in its pure form and in the ICTs was studied using X-RD studies. The X-RD studies were useful in understanding the physical state of the drug in complexed form so that possible mechanism of dissolution enhancement can be elucidated.

Solubility: Solubility of the pure drug and all the prepared ICTs were determined by using shake flask method [25].

4.2.4 Design validation and optimization

Design validation and optimization were performed using StatEase Design Expert software. The obtained response values for all the factor combinations were analyzed by sequential model sum of squares to determine the statistical model for analyzing the influence of the factors on the solubility. The suitability of the model and the significance of effect of the factor terms on the response were investigated by performing ANOVA test. Later, optimization of the factors towards maximum solubility was performed by desirability functions approach.

4.3 Preparation of Orodispersible Tablets (ODTs)

4.3.1 QbD aspects of ODTs

QTPP: The ODTs were aimed to improve the dissolution rate of telmisartan so as to overcome its dissolution limited bioavailability. Further, to improve the patient compliance by making the tablet dispersed in the oral cavity itself so as to avoid need of water and swallowing difficulties.

CQAs: To characterize the above set QTPP, disintegration time and a dissolution rate indicating parameter (T90%) were selected as the CQAs.

CPPs: From the extensive literature review, three formulation parameters viz. concentration of PVP-K30 (numeric factor; at five levels in the range of 1.17 – 6.83 % w/w of the final tablet weight), concentration of superdisintegrant (numeric factor; at five levels in the range of 0.76 – 9.24 % w/w of the final tablet weight) and type of superdisintegrant (categoric factor; at three levels as SSG, CP and SC) were taken as the CPPs.

Experimental design: With the above nature and levels of the factors, central composite design (CCD) was selected to investigate the influence of the factors on the selected responses. The possible combinations of the factors and their levels according to the CCD design were shown in the Table 3. ODTs were prepared at all these combinations.

4.3.2 Preparation of ODTs

Telmisartan in the form of the optimized CD-surfactant complex was taken at 75 mg equivalent to 20 mg of pure telmisartan for every formulation. 75 mg of this complexed form was mixed with the corresponding amount of the superdisintegrant as per the Table 3. Then mixing was continued like kneading method by addition of little water. This kneaded mixture was dried to evaporate moisture. This mixture was further mixed with the binder PVP-K30 (as per the Table 3), 10 mg of mannitol, 2 mg of magnesium stearate, 2 mg of Aerosil and sufficient amount of MCC to get the final tablet weight of 200 mg. Finally, the mixture was subjected to direct compression using 8mm punch in rotary tablet compression machine to get the tablets.

4.3.3 Characterization of ODTs

Weight variation, friability, disintegration: The prepared ODTs of all the formulations studied for all these tests according to the procedure suggested in Indian pharmacopoeia.

Tensile strength: This test was performed according to the standard procedure reported by Pitt KG et al. [26]

Packing fraction and Porosity: Packing fraction (P_f) indicates the degree of consolidation of tableting powder after compression. It can be calculated using the equation [27]

$$P_f = \frac{w}{\pi r^2 t \rho}$$

where, w – weight of tablet; r and t are radius and thickness of tablet; and ρ is the true density of the tableting powder. Subtracting the packing fraction form 1 gives porosity.

Wetting time: This test was performed according to the general procedure as reported by Gupta B et al. [28].

Dissolution: ODTs of all the formulations were subjected to dissolution test as per the USP-NF specifications. Dissolution was conducted in 900 mL of phosphate buffer pH 7.5 with paddle apparatus rotated at 75 rpm for 30 min. At every 5 min., 5 mL of sample was removed and replaced with fresh medium. The samples were analyzed spectrophotometrically to determine the % drug dissolved. Dissolution rate constant and time for 90% drug dissolved (T90%) were calculated. The same procedure was conducted for the pure telmisartan and the optimized ICT so as to compare their dissolution profiles and thus to understand the significance of the methods adopted in this study.

4.3.4 Design validation and optimization

The suitability of the model and the significance of effect of the factor terms on the responses were investigated by performing ANOVA test. Later, optimization was performed by taking the minimizing DT and minimizing T90% as the desirability criteria by graphical optimization in the software.

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