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DEVELOPMENT OF TELMISARTAN PREMIX CONTAINING AMORPHOUS TELMISARTAN BY SOLVENT CONTROLLED CO PRECIPITATION METHOD

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ABSTRACT

This study was carried out to formulate Telmisartan Premix containing amorphous state of Telmisartan. Controlled co-precipitation technique is based on solvent-antisolvent precipitation mechanism which is developed in the late 1990s & is covered in detail by Shah et al 2012. This method requires the solubility of compound in polar solvent like N,N-dimethyl acetamide, N,N-dimethyl formamide and N-methyl pyrollidone. Different drug to polymer ratio of 1:1 to 1:3 and Solvent quantity were optimized by factorial design. HPMC AS LF was selected as a polymer based on primary polymer screening. Assay and Residual solvent was selected as dependent variable. Based on factorial outcomes and dissolution studies 1:3 drug to polymer ration was optimized with 75 ml of Solvent. From the results it can be concluded that Telmisartan Premix gives higher dissolution in pH 7.5 i.e 80% drug released within 15 min due to amorphous nature of Telmisartan. Further, 1:10 solvent to antisolvent ration was optimized. Chilled pH 4.5 acetate buffer was selected as antisolvent due to low solubility of Polymer and Telmisartan. To get residual solvent within limit, washing solvent amount optimized to remove residual solvent is 10 ml/gm. One factor at a time (OFAT) strategy is applied to optimized stirrer speed and drying time. Based on XRD and Moisture content results 200 RPM of mechanical stirrer and 12 hrs of drying time

optimized. During 6 months accelerated stability studied Telmisartan amorphous state was found.

KEYWORDS: Telmisartan Premix, Solid dispersion, Experimental design.

INTRODUCTION

Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension.[1] Although one of the reasons for slow onset may due to its poorly water soluble characterization.[2]

One way to increase the oral bioavailability of Telmisartan is to increase the concentration of dissolved drug in GI fluids. This can be achieved by increasing the dissolution rate, increasing the drug solubility or combination of both. The most remarkable approach to achieve faster dissolution and high apparent solubility is converting crystalline drug to amorphous drug.[3] Two types of amorphous solid are relevant to the pharmaceutical science, pure amorphous material and solid solution/dispersion.[4] The solid dispersion is defined as dispersion of one or more active ingredients in an inert carrier at the solid state prepared by hot melt extrusion, spray drying or controlled co-precipitation method.[5] Hot melt extrusion (HME) of Telmisartan was not a feasible approach with use of excipients listed in FDA's Inactive Ingredients Database suitable for HME due to limited temperature processing range of polymer.[6] Further, due to very low solubility of Telmisartan in volatile organic solvent, spray drying is also not a viable approach to make its solid dispersion.

Controlled co-precipitation technique is based on solvent-antisolvent precipitation mechanism which is developed in the late 1990s & is covered in detail by Shah et al 2012.[7] The solvent controlled co precipitates also known as Micro bulk precipitates (MBP) with porous structure. Precipitation occurs when the concentration of compound in solution exceeds its saturation solubility. This method requires the solubility of compound in polar solvent like N,N-dimethyl acetamide, N,N-dimethyl formamide and N-methyl pyrollidone. The log P of the compound should be greater than 3 to remain stable in the solid dispersion. Looking to above all criteria, Telmisartan is best fits for controlled co-precipitation method.

In present study Telmisartan premix containing amourphous Telmisartan for faster release and better in vitro dissolution was studied. Telmisartan Premix were optimized for Drug to polymer ratio, Solvent to antisolvent ratio, Washing solvent amount, Stirring time, drying

time. Telmisartan Premix characterization carried out for Description, Drug content, Residual solvent, Bulk density, Moisture content at various stage.

MATERIALS AND METHODS

Materials

Telmisartan was provided from Pure Chem Pvt. Ltd., Ankleshwar, India. hydroxypropylmethylcellulose AS LF (HPMC) by colorcon Pvt Ltd. Eudragit L 100 55 by Evonik Pvt Ltd, N,N - Dimethylacetamide supplied by BASF Pvt Ltd. All other materials used were of pharmaceutical or analytical grade.

Preparation of Telmisartan Premix By Solvent Controlled Co precipitation method

Controlled co-precipitation technique is employed for the manufacturing of the Telmisartan Premix. The various steps, which are involved in the manufacturing, are solubilization of Telmisartan and HPMCAS in DMA, Controlled precipitation under high speed stirring, collection of precipitation and its washing and drying followed by shifting. Critical steps involved in the manufacturing process have been optimized.

A) Solubilization of Telmisartan and hypromellose acetate succinate in DMA

DMA is taken in suitable glass vessel and the temperature of it increased between 80 ± 10°C. To this, hypromellose acetate succinate is added under continuous stirring until it completely dissolves. Telmisartan is added gradually to it under continuous stirring until it is completely dissolved.

B) Controlled co-precipitation under high speed stirring

DMA solution containing Telmisartanand hypromellose acetate succinate is transferred to pH 4.5 Acetate Buffer of temp 5 ± 3°C in a vessel equipped with high speed stirrer. The stirring speed is kept between 2000 rpm and the solution is stirred for 10 minutes.

C) Collection and washing of precipitates

The bulk containing precipitates is transferred to centrifugation filtration assembly and centrifuged for 2-5 minutes. After that the precipitates were collected from filter bag, and dispersed in cold pH 4.5 Acetate Buffer followed by stirring. Again, this bulk is transferred and centrifuged for 2-5 minutes followed by collection of precipitates. Further, two washes with cold purified water is given to the precipitates. Semidried Precipitates were collected.

D) Drying and shifting of precipitates

The semidried precipitates collected were kept in the tray dryer for maximum 12hrs in Tray dryer at 40 °C. The Telmisartan Premix (dried precipitates) after drying is shifted through 40 # sieve and stored in Double LDPE bag. The Telmisartan Premix can be used for further analysis.

Preliminary Screening

As Telmisartan is in crystalline form and during co precipitation its precipitate out in amorphous form it is important to choose a proper polymer as a carrier. So initially Screening was carried out with 1:2 ratios. Various polymers like HPMC AS LF, Eudragit L 100-55, Kollidone VA 64 were used to prepare the dispersion. The Composition is shown in table 1.

Table. 1: Composition of Batches for Polymer screening.

Ingredients	PS1	PS2	PS3
Telmisartan (gm)	3.3	3.3	3.3
HPMC AS LF (gm)	6.6	-	-
Eudragit L 100-55 (gm)	-	6.6	-
Kollidone VA 64 (gm)	-	-	6.6
DMA (Solvent) (ml)	25	25	25

Optimization of Drug to polymer ratio and Solvent Using 3^2 Full Factorial Design

Further, to achieve maximum drug loading with amorphous state of Telmisartan in Polymeric carrier, batches were prepared with Telmisartan and hypromellose acetate succinate in the ratio of 1:1, 1:2 and 1:3. A two-factor, three-level full factorial design was constructed and conducted in a fully randomized order. HPMC AS LF and DMA (DMA is more easy to handle in process as well have miscibility in aqueous phase, so removal from the product is efficient.) has been taken as polymer and organic solvent and Design of Experiment was applied.

Two independent variables, the Drug to polymer Ratio (X1) and Solvent Amount (DMA) (X2) were set at three different levels. The dependent variables measured were Assay (%), Residual Solvent. High and low levels of each variable were coded as 1 and -1, respectively and the mean value as zero. The range of each factor was chosen from the preliminary studies.

Polynomial equation for 3^2 full factorial design: $Y = ß_0 + ß_1X_1 + ß_2X_2 + ß_{11}X_{11} + ß_{22}X_{22} + ß_{12}X_1X_2$ was used. In this equation Y is the dependent variable, $ß_0$ is the arithmetic mean response of the nine runs, $ß_1$ to $ß_{12}$ are the coefficients for factors.

The terms of full model having non-significant p value ($p > 0.05$) have negligible contribution and they were neglected.

The detailed layout of factorial batches for is shown in table 2.

Table. 2: Detailed Layout of Different Factorial Batches.

Ingredients	**Formulation Code**								
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Drug : HPMC AS LF	1:2	1:3	1:2	1:3	1:3	1:1	1:1	1:1	1:2
Telmisartan (gm)	9.9	9.9	9.9	9.9	9.9	9.9	9.9	9.9	9.9
HPMC AS LF (gm)	19.8	29.7	19.8	29.7	29.7	9.9	9.9	9.9	19.8
DMA (ml)	70	80	80	75	70	70	80	75	75

Independent Variable	**Coded Value**			**Actual Value**		
Drug: Polymer Ratio	-1	0	+1	1:1	1:2	1:3
Solvent (DMA) (ml)	-1	0	+1	70	75	80

Optimization of Ratio of solvent (DMA solution): antisolvent (pH 4.5 Acetate Buffer)

Solvent to antisolvent ratio is important for conversion of crystalline form to amorphous form. Optimized batch has been repeated with different Solvent (DMA) to Antisolvent (pH 4.5 Acetate Buffer) ratio. Different ration used for further optimization is 1: 5, 1:10 and 1:20. The Composition is shown in table 3.

Table. 3: Composition of Batches for Solvent to antisolvent ratio.

Ingredients	**A1**	**A2**	**A3**
Telmisartan (gm)	9.9	9.9	9.9
HPMC AS LF (gm)	29.7	29.7	29.7
DMA (Solvent) (ml)	75	75	75
Anti solvent (ml)	375	750	1500

Optimization of Washing Solvent Volume

Washing solvent volume has major impact on residual solvent. Insufficient volume of washing solvent may lead to failure in residual solvent. To optimize the washing solvent volume three batches were planned with optimized formula. Washing solvent volume taken for studies were 10 ml/gm, 20 ml/gm and 30 ml/gm. The Composition is shown in table 4.

Table. 4: Composition of Batches for washing solvent Volume.

Ingredients	W1 (10ml/gm)	W2 (20 ml/gm)	W3 (30 ml/gm)
Temisartan (gm)	9.9	9.9	9.9
HPMC AS LF (gm)	29.7	29.7	29.7
DMA (ml)	75	75	75
Anti solvent (ml)	750	750	750
First wash of Chilled (2 – 8°C) pH 4.5 Acetate Buffer (ml)	200	400	600
Second wash of chilled purified water (ml)	200	400	600

Optimization of Stirrer speed and Drying time

Stirrer Speed and Drying time is optimized by OFAT (One factor at One time). A possible combination of Stirrer RPM and Drying time is as under.

Table. 5: Composition of Batches for Stirrer speed and Drying time.

Formulation code	Speed (RPM)	Drying time (hr)
C1	2000	6
C2	2000	12
C3	2000	24
C4	4000	6
C5	4000	12
C6	4000	24
C7	6000	6
C8	6000	12
C9	6000	24

Evaluation of Telmisartan Premix

The prepared Telmisartan Premix was evaluated for Appearance, Bulk Density, Assay, X-ray diffraction pattern, *in vitro* dissolution studies. For in vitro dissolution studies, Telmisartan Premix was placed in a 900 ml of phosphate buffer pH 7.5 (As recommended by OGD) at 75 RPM using USP type-2 apparatus.[8] The temperature of the dissolution media was maintained at 37±0.5°C. During the study, 5 ml of aliquots were withdrawn at 3, 5, 10, 15, 30 min and were replaced by fresh buffer. The amount of Telmisartan Dissolved in the media was determined by UV method. Stability study was conducted at accelerated condition of 75 ± 5% relative humidity and 40 ± 2ºC temperature in the stability chamber for 6 months. After 1, 3 and 6 months Premix were evaluated for the XRD Pattern, drug content and physical appearance as well as change *in vitro* drug release pattern.

RESULT AND DISCUSSION

Preliminary Screening

Premix has been prepared using 1:2 ratios of Telmisartan and different polymers. From the result it was found that HPMC AS LF gives better assay results than Eudragit L100-55. XRPD graphs reflect that HPMC AS LF gives semi crystalline pattern. As HPMC LF and Eudragit are not soluble in water and Kollidone is soluble in water so while washing it may got washed away which results in repeatedly lower assay. So that after Assay results further analysis not performed on same. HPMC AS is selected for further development of Telmisartan premix.

Table. 6: Results of Polymer Screening.

Batch Code	Polymer	%Assay	XRPD	Solubility (mg/ml)
PS1	HPMC AS LF	95.54 %	Semi crystalline	0.35
PS2	Eudragit L 100-55	85.20 %	Crystalline	0.01
PS3	Koliidone VA64	49.94 %	ND	ND

ND indicates not determined.

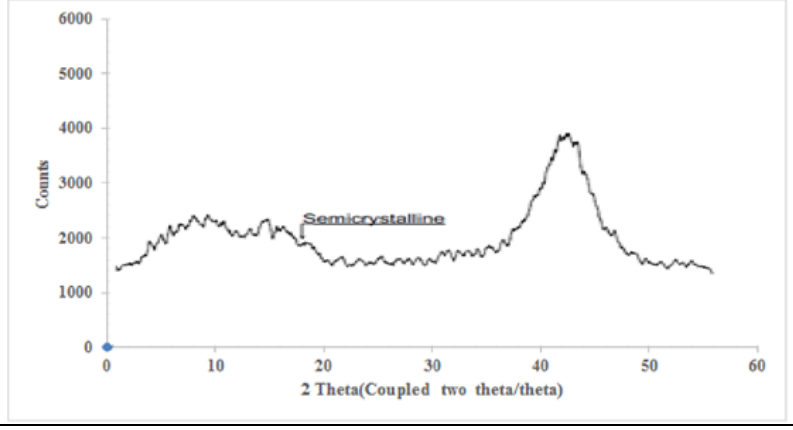


Fig. 1: XRD pattern of PT1.

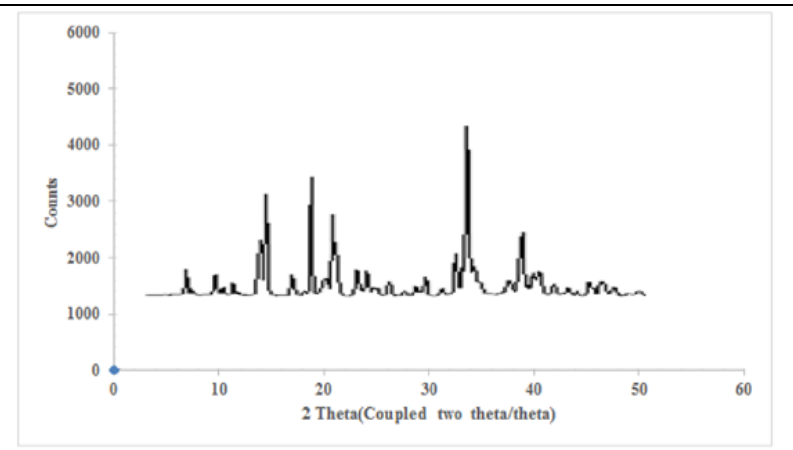


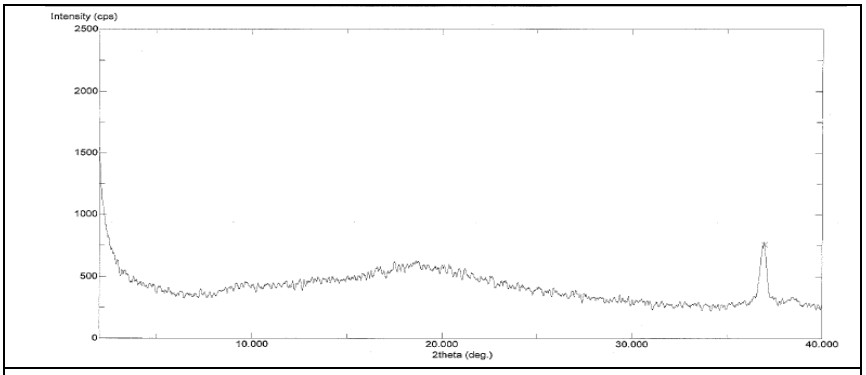
Fig. 2: XRD pattern of PT2.

Evaluation of factorial batches F1 to F9

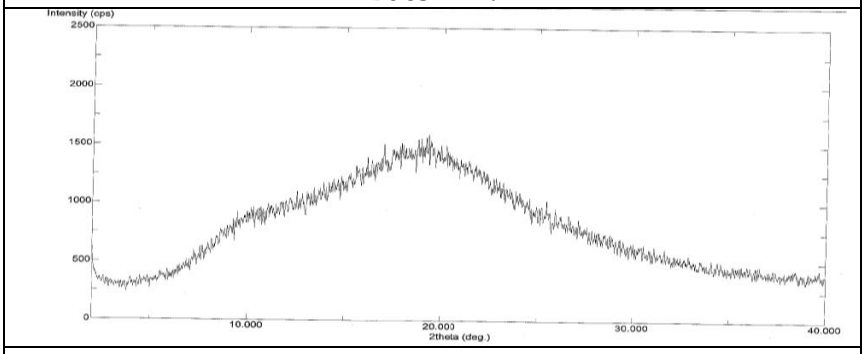
The factorial batches prepared for optimization of Drug to polymer ratio and Solvent volume were evaluated and summary of results are as per Table 7.

Table. 7: Evaluation Parameters of Factorial Batches of Telmisartan Premix.

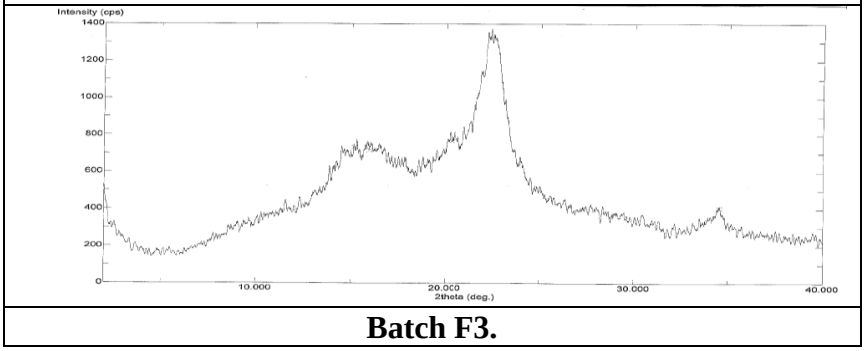
Batch No.	Bulk density (gm/ml)	XRD	Assay (%)	Residual Solvents (ppm)	Moisture content (%w/w)
F1	0.41	Semi crystalline	84.13	280	3.21
F2	0.47	Amorphous	90.12	1500	3.48
F3	0.42	Semi crystalline	87.51	1200	3.65
F4	0.48	Amorphous	97.15	320	2.41
F5	0.45	Amorphous	90.31	220	3.15
F6	0.38	Semi crystalline	80.25	250	2.10
F7	0.33	Semi crystalline	80.23	1000	3.25
F8	0.37	Semi crystalline	84.21	480	2.84
F9	0.42	Semi crystalline	89.12	360	2.45



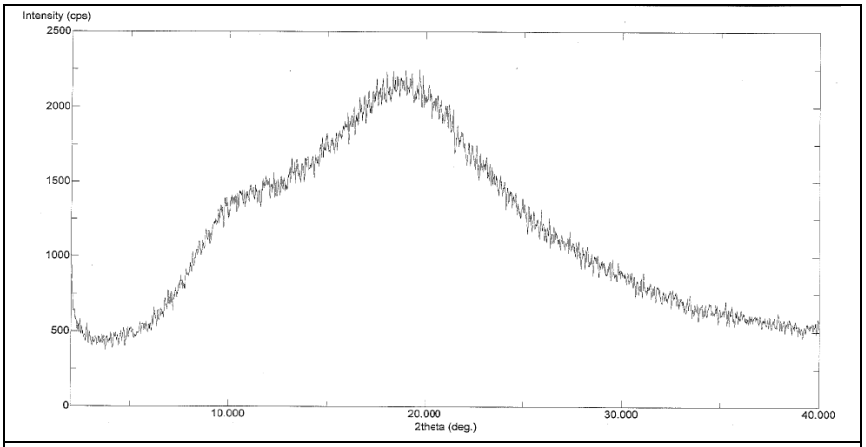
Batch F1.



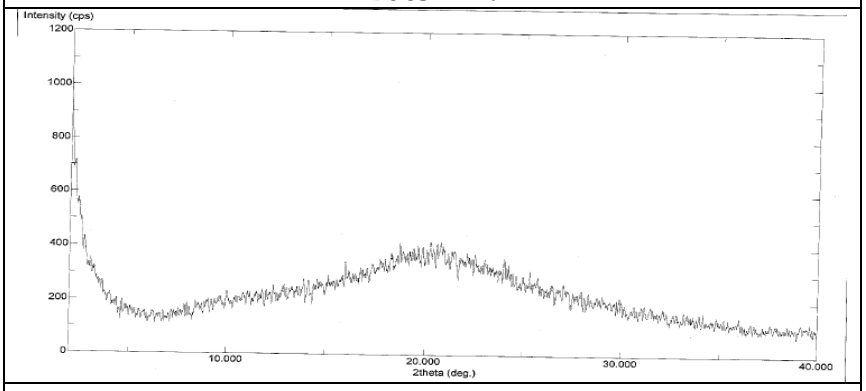
Batch F2.



Batch F3.

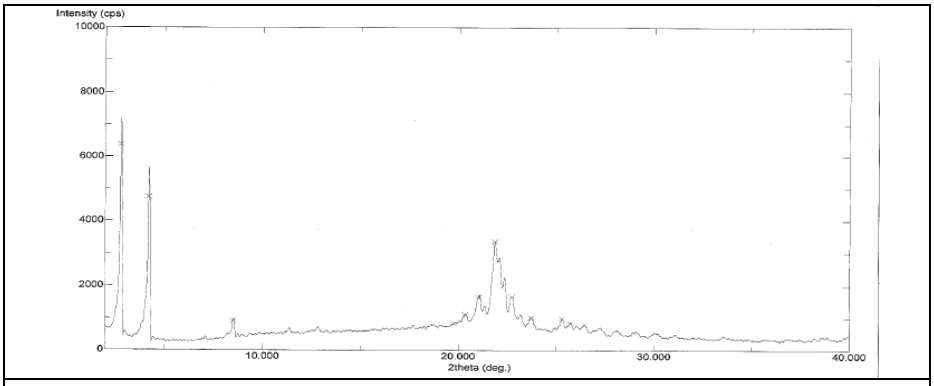


Batch F4.

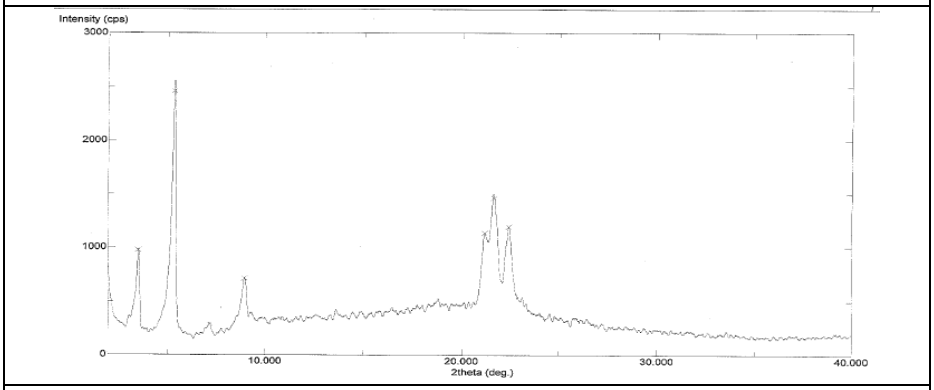


Batch F5

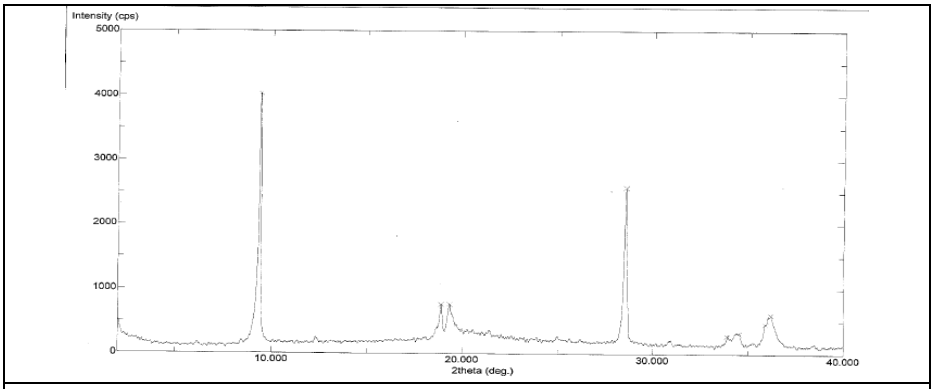
Fig. 3: XRD pattern of Batch F1 to F5.



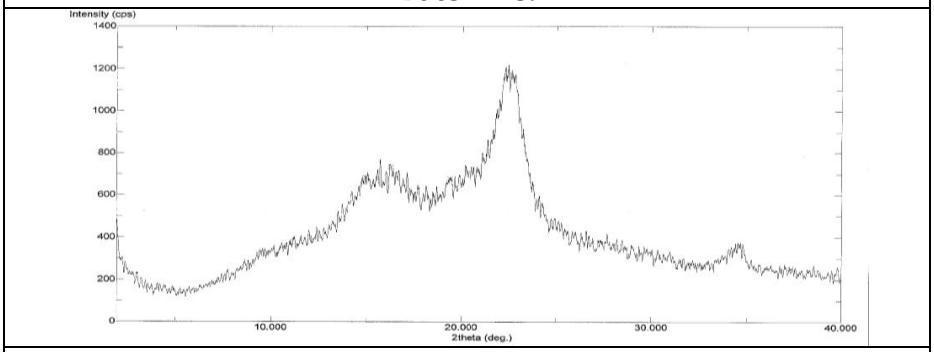
Batch F6



Batch F7



Batch F8.



Batch F9.

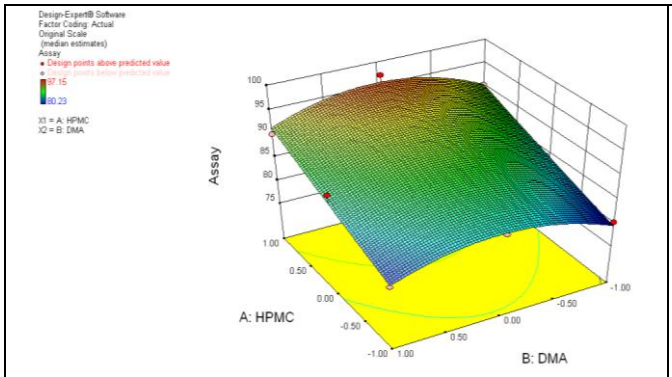
Fig. 4: XRD pattern of Batch F6 to F9.

Statistical Analysis of Factorial Design Batches

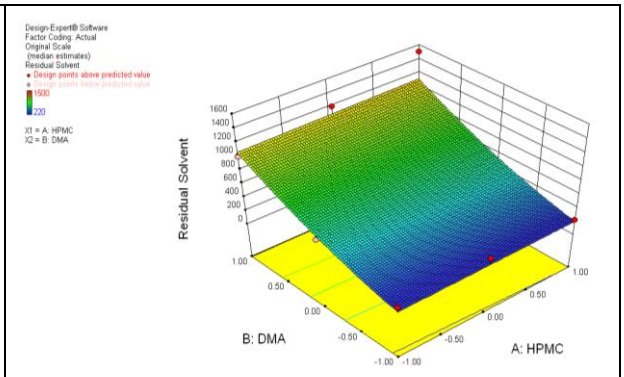
The summary of regression analysis and ANOVA for all the independent variable and response is shown in table 8. The 3D surface plot are shown in respective figure 5.

Table. 8: Summary Output of Regression Analysis and ANOVA.

Response	P-Value	Final Equation (actual factor)
Assay (%)	0.0219	Assay (%) =9.490+ (0.2934 * Drug:Polymer ratio) + (0.0285 * Amount of DMA)- (0.2513* Amount of DMA* Amount of DMA)
Residual Solvent (ppm)	0.0064	Residual solvent (ppm) = 23.46 + (0.351 * Drug:Polymer ratio) + (9.602* Amount of DMA)



3D surface plot of Assay (%)



3D surface plot of Residual Solvent (ppm)

Fig. 5: 3D Surface Plot of Responses.

Interpretation of Regression analysis

1. Assay (%)

As the P-value of model is significant indicates that relationship statistically significant. From the P- value of Coefficients, it seems that Drug to polymer ratio has positive impact of Assay. As the Drug to polymer ratio increase, maximum drug content can be achieved. As DMA amount is insignificant term but quadratic coefficient of the same has negative impact on assay which indicates excess amount of DMA may lowers the drug content.

2. Residual solvents (ppm)

From the above equation it was found that, variable X_1 i.e. Drug: Polymer ratio having non significant P-value indicates selected Drug: Polymer ratio effect on response was not significant. Variable X_2 i.e. Amount of DMA shows positive effect on the residual solvent with significant P-value. As the amount of DMA increases, residual solvent will increase.

In vitro Drug Release of factorial batches

Based on results from factorial batches Batch No. F2, F4, F5 having Drug to polymer ration of 1:3 contains Amorphous form of Telmisartan. Further Dissolution of These batches in pH 7.5 Phosphate buffer dissolution media was performed. The data for *in vitro* release are shown in table 9.

Table. 9: *In Vitro* Drug Release Study.

Batch Code	% Drug Release				
Time	3 min	5 min	10 min	15 min	30 min
F2	72.1	87.6	91.5	93.86	95.28
F4	79.25	89.25	92.85	96.65	97.24
F5	74.15	86.78	90.18	97.15	97.36

Results indicates average of triplicate.

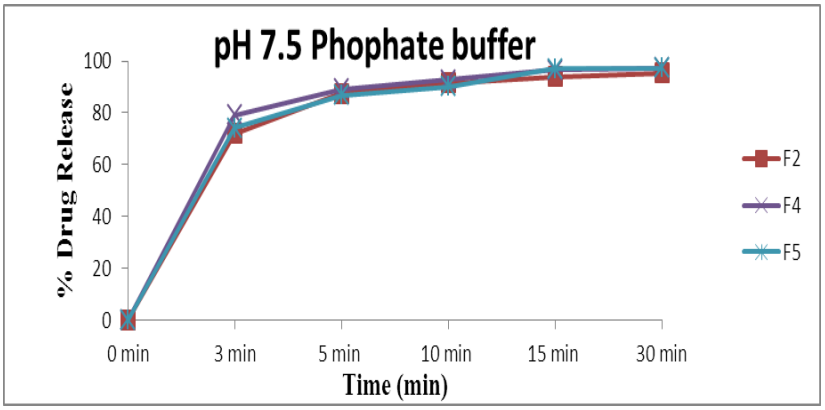


Fig. 6: Comparison of Dissolution profile.

Selection of Optimum batch from Overlay plot

It has been observed that at drug to polymer ratio of 1:1 and 1:2, Telmisartan is found to be semi-crystalline, implicating that these two ratios cannot be adequate to carry Telmisartan in amorphous state. From the overlay plot it has been shown that Batch no. F4 can be used for further process optimization. So Drug: polymer ration of (1:3) and Amount of DMA (75 ml) will help to prepare optimized formula further.

Optimization of Ratio of solvent (DMA solution): antisolvent (pH 4.5 Acetate Buffer)

Different ratios of Solvent (DMA) to Antisolvent (pH 4.5 Acetate Buffer) were studied. Solvent (DMA) to Antisolvent (pH 4.5 Acetate Buffer) ratio of 1:5 showed semicrystalline state of Telmisartan Premix. This was attributed due to higher amount of DMA present in the final composition of solvent/antisolvent system, which resulted into crystallization of Telmisartan. So, solvent to antisolvent of ratio 1:10 was finalized for the Telmisartan Premix preparation. Results summarized in below Table 10.

Table. 10: Summary of Solvent to Antisolvent Ratio.

Batch Code	Appearance	Bulk density (gm/ml)	XR-D	Assay (%)	Residual Solvents (ppm)	Moisture content (%w/w)
A1	White to off white powder	0.42	Semi crystalline	95.10	200	2.41
A2	White to off white powder	0.48	Amorphous	98.70	ND	2.13
A3	White to off white powder	0.47	Amorphous	80.12	ND	2.51

ND indicates not detected.

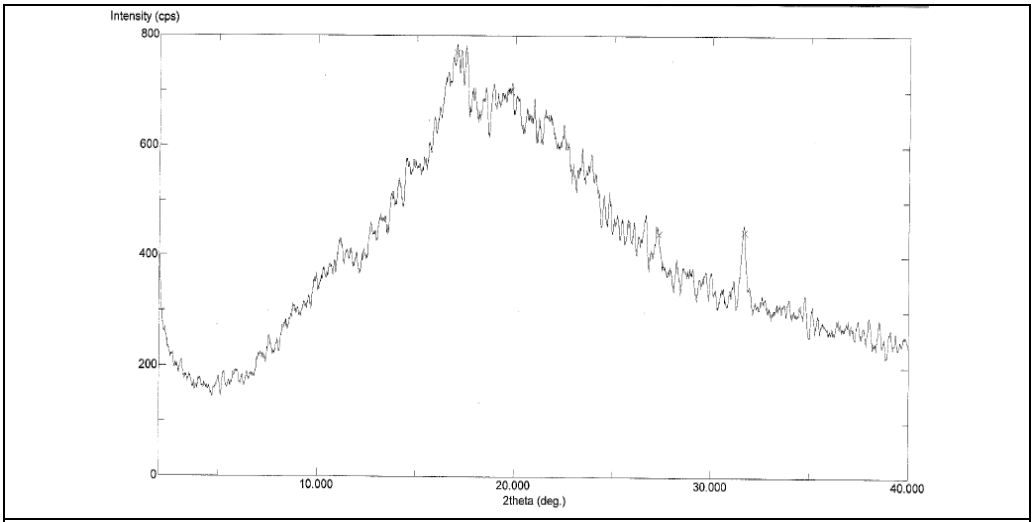


Fig. 7: XRD pattern of A1.

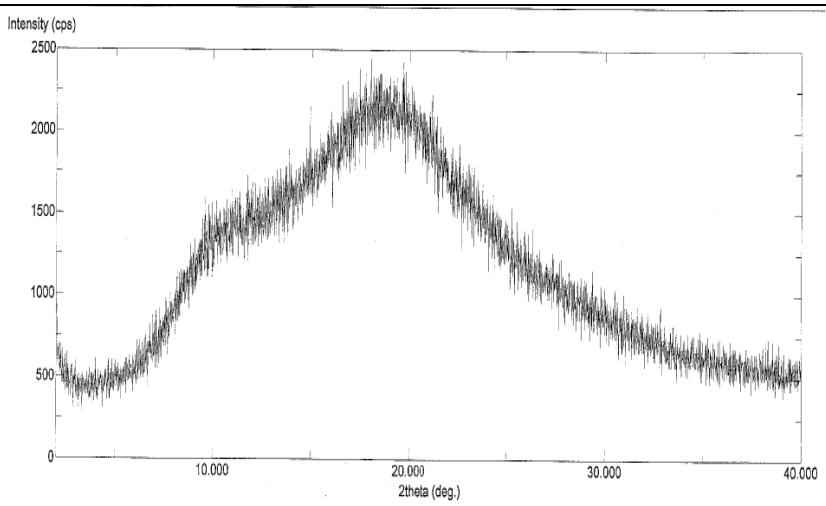


Fig. 8: XRD pattern of A2.

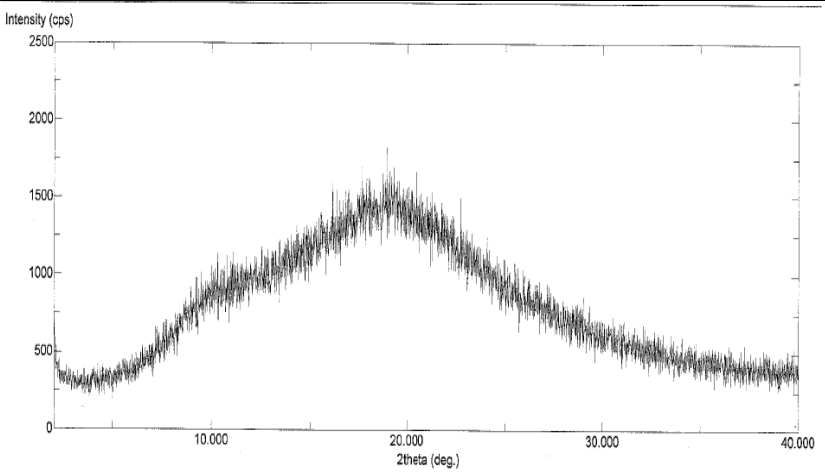


Fig. 9: XRD pattern of A3.

Optimization of Washing Solvent Volume

Volume of washing liquid (first 1 wash with chilled (2 – 8°C pH 4.5 Acetate Buffer), to convert unreacted solution in micro precipitates and then wash with chilled purified water (2 – 8 °C) is finalized at 10 ml per gm. Although residual solvents get during W1 was 400 ppm which is well within limit. The major reason of consistently lower residual solvent is, DMA is miscible with water and it is easy to remove it. Residual solvent results observed during three different washing solvent volume were summarized in below table 11.

Table. 11: summary of Optimization of Washing Solvent Volume.

Formulation	Residual Solvents (ppm)	Moisture content (%w/w)
W1 (10ml/gm)	400	2.12
W2 (20 ml/gm)	ND	2.84
W3 (30 ml/gm)	ND	3.54

ND indicates not Detected.

Optimization of Stirrer speed and drying time

Based on results obtained from Experimental batches, optimized stirrer RPM is 2000 RPM and 12 hrs of drying time. It was observed that stirrer RPM have impact on Crystalline nature of Telmisartan. At Higher RPM crystallinity has been increased the probable reason is due to localized energy input to the precipitation at the point of contact. Analytical finds of experimental batches to evaluate the impact of Stirrer speed and drying time on Assay, Residual solvent and Moisture content were shown in below table 12.

Table. 12: Results of C1 to C9 batches.

Formulation code	Appearance	Bulk density (gm/ml)	XR-D	Assay (%)	Moisture content (%w/w)
C1	White to off white powder	0.43	Amorphous	98.82	4.94
C2	White to off white powder	0.47	Amorphous	96.78	2.84
C3	White to off white powder	0.45	Amorphous	98.51	1.01
C4	White to off white powder	0.46	Amorphous	96.32	5.12
C5	White to off white powder	0.48	Amorphous	98.12	2.12
C6	White to off white powder	0.47	Amorphous	97.23	1.1
C7	White to off white powder	0.46	Semicrystalline	91.12	4.22
C8	White to off white powder	0.47	Semicrystalline	92.45	2.82
C9	White to off white powder	0.46	Semicrystalline	89.14	1.01

Stability Study of Optimized Batch

After SIx month of accelerated stability study (40ºC ± 2ºC and 75% RH ± 5%) of optimized batch, XRD pattern, Assay and In vitro dissolution test were performed. The results are shown in table 13. Results were shown no more drastically change in In-vitro drug release profile.

Table. 13: Evaluation of Stability Study.

Parameter	Initial	1 Month	3 Month	6 months
Assay (%)	98.87	98.60	97.94	98.01
XRD	Amorphous	Amorphous	Amorphous	Amorphous
Residual Solvent (ppm)	245	Not performed	220	230

Table. 14: In-vitro drug release profile.

Time (min)	Initial	1 Month	2 Month	3 Month	6 months
0	0	0	0	0	0
3	80.24	82.79	82.00	82.70	81.89
5	87.77	86.32	86.50	87.00	86.68
10	96.36	95.01	94.46	95.06	94.44
15	97.00	95.56	97.33	96.65	96.66
30	99.48	97.12	99.20	97.71	98.45

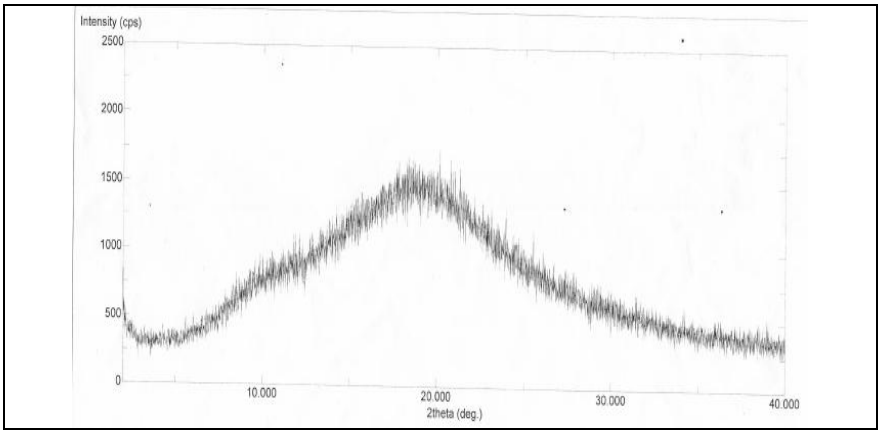


Fig. 10: XRD pattern of Initial time point.

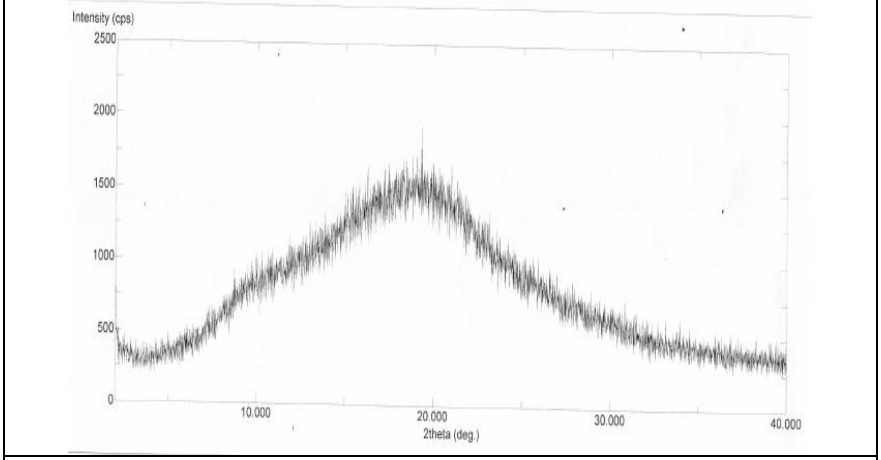


Fig. 11: XRD pattern after 1 month.

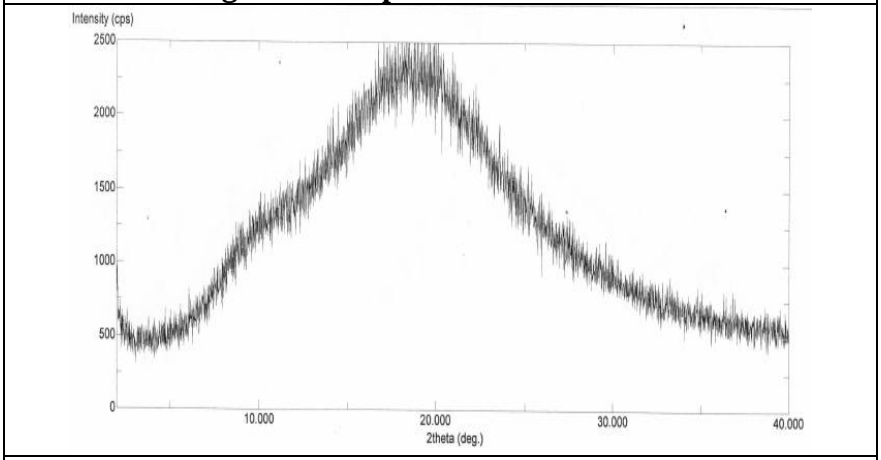


Fig. 12: XRD pattern after 3 months.

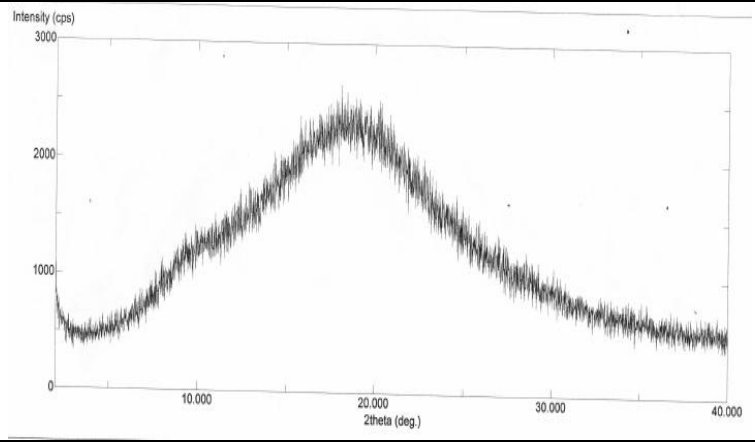


Fig. 13: XRD pattern after 6 months.

CONCLUSION

A Design of Experiment approach was used to demonstrate the effect of Drug to polymer ratio. The amorphous state and its stability of Telmisartan premix is affected by drug to polymer ratio, solvent to antisolvent ratio, pH and Temperature of antisolvent. The development of Telmisartan Premix in amorphous form is alternate approach to imprve in vitro dissolution which may improve bioavailability. Based on the need, further premix can be converted in suitable solid oral dosage form.

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