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FORMULATION OF BINARY AND TERNARY MIXTURES OF POORLY WATER-SOLUBLE DRUG TELMISARTAN AND THEIR *IN-VITRO* EVALUATION FOR ENHANCED SOLUBILITY AND DISSOLUTION BY SOLID DISPERSION TECHNIQUE

Prashanta Basnet^{*1}, Uttam Budhathoki² and Ashwinee Shrestha²

Aadee Remedies Pvt. Ltd.¹, Plant Manager, Lalitpur, Nepal.

Department of Pharmacy², School of Science, Kathmandu University, Dhulikhel, Nepal.

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Correspondence to Author:

Prashanta Basnet

Research Scholar,
Aadee Remedies Pvt. Ltd., Plant
Manager, Lalitpur, India.

E-mail: robby.basnet@gmail.com

ABSTRACT: The present study was carried out to enhance the dissolution rate of poorly water-soluble drug Telmisartan, by solid dispersion technique using different carriers and super disintegrants by solvent evaporation method. Solid dispersions were prepared with mannitol and PEG 6000 in different ratios of 1:1, 1:3 and 1:5. *In-vitro* dissolution profile of solid dispersion (SD) with drug and mannitol in the ratio of 1:3 (SDM2) was found to be highest among all 12 formulations. This SD was further adsorbed with Neusilin US2 to form a ternary mixture. Crospovidone was used due to its promising role in dissolution enhancement of telmisartan based on previous studies. For optimization of concentration of Neusilin US2 and crospovidone in solid dispersion, Central Composite Design was applied for two factors at two level which gave 13 formulations. Tablets were prepared and evaluated for physiochemical properties. Response surface plot and contour plot were drawn, and an optimum formulation was selected. This formulation contained 40 mg of Neusilin and 14 mg Crospovidone (CCDF4). The *in-vitro* dissolution studies of optimized formulation CCDF4 and marketed product was carried out in USP Type II apparatus at different time intervals of 10, 20, 30 and 45 minute at 75 rpm in phosphate buffer, pH 7.5. Solid state characterization was evaluated by FTIR. It showed that the drug was stable in different polymers used in the study. Hence, Solid dispersion technique can be successfully used for the improvement of the dissolution profile of Telmisartan.

INTRODUCTION: Hypertension is one of the most common chronic conditions and is characterized by persistent elevated arterial pressure. In hypertension, there is an increasing blood pressure, where the systolic pressure is more than or equal to 130 mmHg and the diastolic pressure is more than 80 mmHg¹.

According to the Biopharmaceutics Classification System (BCS), aqueous solubility and permeability are the most important variables affecting drug bioavailability. Telmisartan is classified as Class II i.e., drugs that have low solubility and high permeability characteristics after oral administration, it shows low dissolution profile and poor absorption and reduced oral bioavailability².

The enhancements of oral bioavailability of such poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. Drugs that undergo dissolution rate limited gastrointestinal absorption generally show

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improved dissolution and bioavailability as a result of reduction in particle size. However, micronizing of drugs often leads to aggregation and agglomeration of particles, which results in poor wettability. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have reduced the incidence of these problems and enhanced dissolution³.

There are different methods for the preparation of solid dispersion such as Solvent Evaporation, Kneading, Wet milling, Spray drying, Solvent Wetting, Kinetisol Dispersing, Fusion, Agitation Granulation, Fluid Nozzle Spray Drying, Twin Screw Extruder, Microwave Irradiation, Dropping Method, Spray Freeze Drying Method, Freeze Drying, Supercritical Antisolvent Process Ultra-Rapid Freezing, Pulse Combustion Dryer System, Liquid Filled Dispersion, Solvent Fusion Method and Cyclodextrin Complexation⁴.

Nomura *et al.*, 1996 first used solvent evaporation method to prepare a solid dispersion of β -carotene in PVP by using chloroform as a cosolvent. Solutions or mixed crystals could be prepared by dissolving a physical mixture of two solid components in a common solvent followed by evaporation of the solvent. The solvent is usually removed by evaporation under reduced pressure at varying temperatures. The choice of solvent and its removal rate are critical to the quality of the dispersion⁵.

The major advantage of the solvent method is that thermal decomposition of drugs and carriers associated with the fusion method can be avoided⁴.

Carriers used to produce SDs have a pivotal role in controlling the drug release since they can enhance or retard the drug dissolution, whether achieved through diffusion or dissolution-based mechanism, as previously mentioned. A drug carrier should have fair solubility in various solvents, specifically in water and lacking toxicological and pharmacological effects. Chemically, the carrier should have thermal stability and compatibility with the formulated drug⁶.

The objective of this study was to prepare solid dispersions of Telmisartan using two hydrophilic carriers Mannitol and PEG 6000 by solvent evaporation method, further adsorption of the best

solid dispersion formulation with ternary agent Neusilin US2 and studying the effect of Crospovidone as a superdisintegrant on the dissolution profile of Telmisartan immediate release tablets.

MATERIALS AND METHODS:

Materials: Telmisartan and its reference standard (Potency: 99.381 and Loss on drying: 0.226%) were provided as gift samples by Deurali-Janta Pharmaceuticals Pvt. Ltd, Dhapasi, Kathmandu, Nepal. Excipients such as Mannitol, PEG 6000, Avicel PH102, Crospovidone, Sodium Lauryl Sulphate, Colloidal Silicon Dioxide and Magnesium Stearate were received from Chemidrug Industries Pvt. Ltd, Thankot, Kathmandu, Nepal as gift samples. Similarly, Neusilin US2 was received from Fujichemicals, Japan as gift sample. The marketed product was purchased from local retail pharmacy and was used as reference product for data analysis.

Methods:

Analytical Method Development: A 25 mg of Telmisartan reference standard (RS) with potency 99.381% and moisture content of 0.226% was weighed accurately and 20 ml of methanol was added in 50 ml volumetric flask then sonicated for 10 minutes. After that, the volume was made to 50 ml with methanol and labeled as a stock solution. The series of dilution were prepared ranging between 2-25 $\mu\text{g/ml}$. The spectrum of this solution was run from 200 to 400 nm range in UV-visible spectrophotometer.

Analytical Method Validation: UV-visible spectrophotometric method for assay was developed and validated. Assay method Validation was done in terms of Linearity, Specificity, Accuracy and Precision, Limit of detection (LD) and Limit of Quantification (LQ) and Range⁷.

Linearity: Various concentrations of reference standard Telmisartan solution were prepared in methanol. The absorbance of the solution was detected in UV-visible spectrophotometer. Absorbance versus concentration curve was plotted. The value of correlation coefficient (R^2) and linear equation was determined for the linearity of the plot.

Precision: The precision test was performed by analyzing the samples of formulated batches of Telmisartan along with the optimized batch using same reagent in same instrument in same day and different days to check the reproducibility of the method. The test was carried out using the methods of assay. The values obtained were calculated for Relative Standard Deviation (RSD) and the method was said to be precise if the value of RSD was found to be less than 2% using equation 1.

$$\% \text{ Relative Standard Deviation} = (\text{Standard deviation}) / \text{Mean} \times 100 \dots\dots\dots (1)$$

Accuracy: The accuracy was performed in three different concentrations of samples of optimized batch of Telmisartan. The test was performed by preparing the sample solution of 15, 20 and 25 µg/ml of Telmisartan which are 25% above and below the assay concentration. The test was carried out using the method of assay. Accuracy of the analytical method is indicated by recovery of analytical result. The recovery is determined by using equation 2.

$$\% \text{ Recovery} = \text{Analytical result} / \text{True result} \times 100 \dots\dots\dots (2)$$

Specificity: The specificity test was carried out by measuring the spectrum of Telmisartan reference standard, sample containing Telmisartan and the excipient (blank) used in the formulation at the spectrum range 200-400 nm in UV visible spectrophotometer using methanol as the solvent. No peak of excipient except Telmisartan should be obtained at wavelength 296 nm.

Limit of Detection: Various concentrations of Telmisartan RS were prepared in methanol as mentioned in calibration curve. Limit of detection was calculated by using equation no 3.

$$\% \text{ Limit of Detection} = 3.3 \times \text{standard deviation of the response} / \text{slope of the calibration curve} \times 100 \dots\dots\dots (3)$$

Limit of Quantification: Various concentrations of Telmisartan were prepared in methanol as mentioned in calibration curve. Limit of quantification was calculated by using equation no 4.

$$\% \text{ Limit of Quantification} = 10 \times \text{standard deviation of the response} / \text{slope of the calibration curve} \times 100 \dots\dots\dots (4)$$

Range: Various concentrations of Telmisartan RS were prepared in methanol and absorbance was measured in assay method. The range was determined as value of limit of quantification as minimum and the value obtained from the linearity data as maximum.

Phase Solubility Studies: The phase solubility studies were carried out according to the method reported by Higuchi and Connors. Excess amount of Telmisartan was added to the screw capped vials containing 20 ml of aqueous carrier solution at various concentrations and placed on a rotary shaker and agitated at $37 \pm 0.5^\circ \text{C}$ for 48 hours. After equilibrium, the solutions were carefully filtered through Whatman No. 41 filter paper ⁸.

The Gibbs free energy of transfer (ΔG°_{tr}) of Telmisartan from pure water to the aqueous solution of carrier was calculated as follows:

$$\Delta G^\circ_{tr} = (-2.303RT \log S_0/S_s) \dots\dots\dots (5)$$

Where, S_0/S_s is the ratio of molar solubility of Telmisartan in aqueous solutions of carrier to that of the same medium without carrier.

1:1 complex apparent stability constant (K_a) was determined as follows:

$$K_a = \text{Slope} / (\text{Intercept} (1 - \text{Slope})) \dots\dots\dots (6)$$

Where, slope and intercept were obtained from the graph of %w/v of Telmisartan vs. aqueous concentration of carrier (PEG 6000 and Dmannitol) in %w/v

Physical Mixture Preparation: Telmisartan and each of hydrophilic carriers (PEG 6000 and Mannitol) were weighed accurately in different ratios (1:1, 1:3 and 1:5) and mixed thoroughly in mortar and pestle with trituration for about 10 min. These mixtures will then be passed through sieve number #60 and finally stored in air tight containers till further use ⁹.

Solid Dispersion Preparation: Telmisartan and each of hydrophilic carriers were weighed accurately in various ratios (1:1, 1:3 & 1:5) and transferred to china dish containing sufficient quantity of ethanol to dissolve. Ethanol was evaporated on heating mantle at 60°C .

The solid mass was then passed through the sieve number #60 and finally stored in air tight container till further use⁹.

Drug Contents: The drug content of pure Telmisartan, physical mixtures and solid dispersions was carried out by validated analytical method in UV-Visible spectrophotometer.

Dissolution Study of Solid Dispersions: The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its *in-vivo* behaviour. *In-vitro* release profile for each solid dispersion as well as pure drug was performed using USP XXII type2 dissolution apparatus. Sample equivalent to 20 mg of Telmisartan was added to 900ml of 0.1 N Hydrochloric acid containing 1% w/v sodium lauryl sulphate at 37± 0.5 °C and stirred at 50 rpm for 90 minutes.

Ternary Blend Preparation:

Step 1: Neusilin, Crospovidone, Avicel and optimized solid dispersion were sieved through #40 mesh.

Step 2: Magnesium stearate, Aerosil and SLS were sieved through #60 mesh.

Step 3: Different weights of Neusilin and SD were taken for different Neusilin: SD ternary blend formation and mixed thoroughly in a plastic bag for ten minutes.

Step 4: Powder from step 1 was mixed with step 3 in a plastic bag and mixed sufficiently.

Step 5: Powder from step 4 was again mixed with powder of step 2 and mixed well in a plastic bag for lubrication. Finally, 13 different bulk formulations are prepared for compression.

Evaluation of Pre-compression Parameters of the Final Blend: Angle of repose, bulk density, tapped density % Carr's index and Hausner's ratio of the final powder blend were determined.

Central Composite Design: Central Composite designs can fit a full quadratic model. They are often used when the design plan calls for sequential experimentation because these designs can include information from a correctly planned factorial experiment.

Minitab 16 was used for optimization of the formulation through response surface methodology. The best solid dispersion in terms of dissolution profile was selected for further optimization by taking Crospovidone and Neusilin US2 as two factors. CCD gave 13 different formulations with varying concentrations of Crospovidone and Neusilin US2¹⁰.

Evaluation of Tablets: Tablets were evaluated for their physicomachanical properties such as hardness, thickness, diameter, friability and disintegration time.

Drug Content of Tablets: Three tablets of each batch were taken, powdered and sample equivalent to 25 mg Telmisartan was accurately weighed and transferred to a 100 ml of volumetric flask. Then, about 70 ml of methanol was added and allowed to sonicate for 10 minutes. The solution was allowed to cool to room temperature and volume was adjusted suitably. The solution was filtered through Whatman paper number 41 and observed in Uv-Visible Spectrophotometer at 296 nm after suitable dilution.

In-vitro Dissolution Test: The dissolution test was carried out using USP Apparatus II (paddle); 900 ml of phosphate buffer pH 7.5 was used as medium at 37±0.5°C and 75 rpm.

Comparison of Formulated Tablets with Marketed Tablets: Optimized formulation was compared with marketed tablet for dissolution study to know about the dissolution profile of the optimized batch.

Similarity Factor and Dissimilarity Factor:

Similarity Factor: Similarity between the two products is assessed by using similarity factor. The similarity factor (F_s) is a logarithmic transformation of the sum-squared error of differences between the test T_j and reference products R_j over all points.

R_j over all points.

$$F_s = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{j=1}^n (R_j - T_j)^2 \right]^{-0.5} \times 100 \right\} \dots \dots (4)$$

Where, n is the sampling number, R_j and T_j are the % dissolved of reference and the test products at each time points.

F_s value higher than 50 and close to 100 shows the similarity of the dissolution profiles¹¹.

Dissimilarity Factor: The difference factor (F_d) measures the percent error between two curves over all time points:

$$F_d = \left[\frac{\sum_{i=1}^n (R_i - T_i)}{\sum_{i=1}^n R_i} \right] \times 100 \dots \dots \dots (5)$$

The percentage error is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles.

F_d values should be close to 0 to be similar¹¹.

Comparison of Formulated Tablets with Marketed Tablets: Optimized formulation was compared with marketed tablet for dissolution study to know about the dissolution profile of the optimized batch.

Drug Release Kinetics: Mathematical models for the drug release studies plays a significant role as it establishes a mechanism of drug release and provides more general guidelines for the development of other systems. Drug release kinetics also play pivotal role towards pharmacokinetics behavior and therapeutic actions. Zero Order, First Order and Higuchi models were used to determine the possible drug release pattern of immediate release tablets.

Comparison of Formulated Tablets with Marketed Tablets: Optimized formulation was compared with marketed tablet for dissolution study to know about the dissolution profile of the optimized batch.

Fourier Transform IR (FTIR) Spectroscopy: FTIR spectroscopy has been used to quantify the interaction between drug and carrier. FTIR spectra of Telmisartan, Mannitol, PEG 6000 and Neusilin were analyzed. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1} .

RESULTS AND DISCUSSION:

Analytical Method Validation:

Linearity: From reference standard solution, different volumes were withdrawn and suitably diluted with methanol to get concentration of 2, 5,

10, 16, and 20 and 25 $\mu\text{g/ml}$, respectively. The absorbance of each solution was measured by UV visible spectrophotometer at 296 nm using methanol as a blank.

The curve of absorbance versus concentration was plotted as shown in **Fig. 1**. $Y = 0.0513x$ linear equation was obtained and correlation coefficient (R^2) value was found to be 0.9997 which signifies that the method of analysis of Telmisartan by UV-visible spectrophotometer was suitable and can be performed in varying concentration during study.

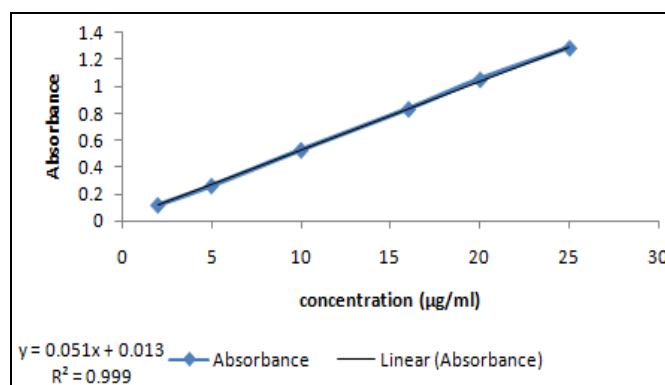


FIG. 1: STANDARD CALIBRATION CURVE OF TELMISARTAN IN METHANOL

Specificity: After scanning the reference standard solution, sample solution and placebo solution in the range of 200-400 nm, in the UV-visible spectrophotometer, a prominent peak was observed by the reference standard solution and sample solution at 296 nm in methanol, while a flat line was observed in the placebo at the same range of wavelength. These showed that analytical method is specific and free of interference from excipients.

Accuracy and Precision: The method of analysis was found to be accurate as the mean recovery values laid within the limit of 98.00 to 102.00% with a lower limit of 99.91% and upper limit of 101.81% while the relative standard deviation (RSD) was found to be 0.44%. Thus, the method of analysis was found to be accurate and precise.

Limit of Detection (LOD): By using the data from linearity curve and using the equation 3, detection limit was calculated to be 0.579 $\mu\text{g/ml}$.

Limit of Quantification (LOQ): By using the data from linearity curve and using the equation 4, quantification limit was calculated to be 1.756 $\mu\text{g/ml}$.

Range: The range of analytical procedure was determined from the data obtained from the Limit of Quantification and Linearity Curve. The range of concentration for the quantification of Telmisartan in this analytical procedure is 1.756µg/ml to 30µg/ml.

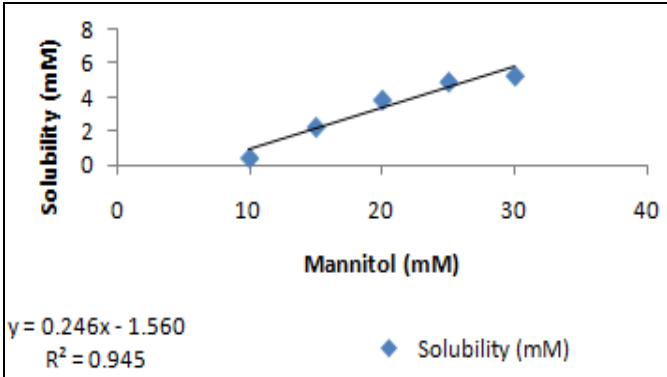


FIG. 2: PHASE SOLUBILITY DIAGRAM OF TELMISARTAN IN DIFFERENT CONCENTRATION OF MANNITOL IN DISTILLED WATER AT 37 ± 0.5 °C

The Gibbs free energy of transfer (ΔG°_{tr}) and apparent stability constants (K_a) are derived from Fig. 2 and 3 respectively for mannitol and PEG 6000 and are shown in Table 1.

TABLE 1: STABILITY CONSTANT, GIBB FREE ENERGY, SLOPE AND STABILITY CONSTANTS AT 37 ± 0.5 °C

Concentration	ΔG°_{tr} (KJ/mol) at 310 K	
(mM)	Mannitol	PEG 6000
10	-1588.19	-5685.45
15	-5722.02	-7364.79
20	-7090.09	-7445.25
25	-7718.32	-7839.39
30	-7869.67	-8297.92
K_a	0.209426	0.220515
Slope	0.2463	0.1751
Intercept	1.5604	0.9626

Table 1 shows that all values of ΔG°_{tr} were negative at all levels of carriers, demonstrating

Phase Solubility Studies: Fig. 2 and 3 represent the phase solubility of Telmisartan in the presence of mannitol and PEG 6000 respectively. The plots of drug solubility against the polymer concentration indicate a linear relationship in the investigated polymer concentration range.

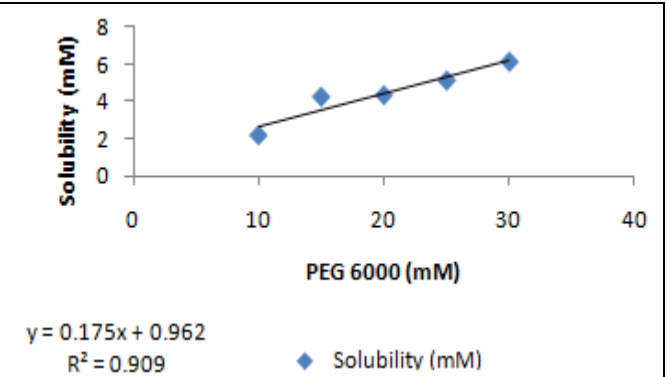


FIG. 3: PHASE SOLUBILITY DIAGRAM OF TELMISARTAN IN DIFFERENT CONCENTRATION OF PEG 6000 IN DISTILLED WATER AT 37 ± 0.5 °C

spontaneity of drug solubilization process. The values show a declining trend with increase in the carrier concentration too construing that the process is more favorable at higher carrier levels.

It also indicates that Telmisartan-PEG 6000 interaction has a higher K_a value. The higher K_a value indicates that the binding affinity between Telmisartan-PEG 6000 is more than that of Telmisartan-mannitol.

Physical Mixtures and Solid Dispersions: Altogether 12 formulations were prepared with 6 physical mixtures and 6 solid dispersions containing drug and carriers in different ratios as shown in Table 2.

TABLE 2: PHYSICAL MIXTURES AND SDS WITH DIFFERENT DRUG: MANNITOL AND DRUG: PEG 6000 RATIOS

S. no.	Physical Mixtures	Ratio	Solid Dispersions
	Mannitol		Mannitol
1	PMM1	1:1	SDM1
2	PMM2	1:3	SDM2
3	PMM3	1:5	SDM3
PEG 6000		1:1 1:3 1:5	PEG 6000
4	PMP1		SDP1
5	PMP1		SDP2
6	PMP3		SDP3

Drug Contents: All the formulations were within the range as required by IP, 2010 as shown in Table 3.

TABLE 3: LIST OF DRUG CONTENTS OF DIFFERENT PHYSICAL MIXTURES AND SOLID DISPERSIONS

Physical mixtures			Solid dispersions		
Formulation code	Drug content	Std. dev Dev.	Formulation code	Drug contents	Std. Dev.
PMM1	100.13	±0.56	SDM1	98.13	±0.38
PMM2	97.89	±0.89	SDM2	99.70	±0.58
PMM3	98.76	±0.78	SDM3	102.46	±0.49
PMP1	97.72	±1.20	SDP1	103.22	±1.30
PMP2	99.58	±0.23	SDP2	104.12	±0.60
PMP3	103.78	±0.45	SDP3	105.55	±0.8

In-vitro Dissolution Study: Solubility study suggests that Telmisartan has slightly better solubility in PEG 6000 than mannitol, but contrarily from dissolution data, we can clearly observe that formulation SDM2 containing drug: mannitol in the ratio of 1:3 shows highest dissolution profile. Because of higher dissolution

profile of SDM2 containing mannitol and toxic character of PEG 6000, this formulation was taken as optimized solid dispersion and was subjected to central composite design.

The results of dissolution studies have been tabulated below:

TABLE 4: DISSOLUTION STUDIES OF DIFFERENT PHYSICAL MIXTURES AND SOLID DISPERSIONS

Physical mixtures			Solid dispersions		
Formulation code	Dissolution	Std. Dev.	Formulation code	Dissolution	Std. Dev.
PMM1	75.67	±0.53	SDM1	94.05	±1.22
PMM2	89.91	±0.78	SDM2	100.23	±1.80
PMM3	91.82	±0.98	SDM3	95.64	±0.77
PMP1	63.04	±0.67	SDP1	85.22	±0.56
PMP2	77.43	±0.89	SDP2	83.70	±0.54
PMP3	74.38	±1.34	SDP3	80.26	±0.68

Central Composite Design: Formulation SDM2 was further optimized by response surface methodology using Minitab 16. Neusilin US2 as an adsorbent and Croscopovidone as a superdisintegrant were used as two factors that contribute in drug release in varying concentrations. Two level full factorial central composite design with 4 cube points ($\alpha=1.41421$), 5 centre point and 4 axial points with 1 replication resulting in a total of 13 experiments were used to optimize the chosen key factors that affects drug release.

Based on CCD chart developed by software, working chart was developed and used for the study. There were altogether 13 formulations; the composition is summarized on **Table 5**.

Evaluation of Powder Blend: Details of the pre-compression properties of the lubricated granules of Telmisartan tablets are given in **Table 6**.

The bulk density of granule was between 0.25 of formulation CCDF1 and 0.37 of formulation CCDF13. The tapped density of granule was between 0.31 of formulation CCDF10 and 0.50 of formulation CCDF13. Formulations CCDF4, CCDF6, CCDF7, CCDF8, CCDF9, CCDF11 and

CCDF12 showed good flow properties with CI values of 17.78, 15.79, 15.79, 13.89, 16.67 and 15.79 respectively.

The value of Hausner's ratio of formulations CCDF4, CCDF6, CCDF7, CCDF8, CCDF9, CCDF11 and CCDF12 showed below 1.25 which indicates better flow property. Other formulation value were higher than 1.25.

Evaluation of Tablets: Compressed tablets of all formulation had uniform weight due to uniform die fill which were within acceptable limit i.e. % deviation was within $\pm 5\%$ as per IP. The physicomachanical properties of the formulations are detailed in **Table 7**.

In-vitro Dissolution Study: Results of *in-vitro* dissolution time at 10, 20, 30 and 45 min of all formulations are detailed in Table VIII. Comparison was made between all thirteen CCD formulations for dissolution time as shown in **Fig. 4** and **5**. All the formulation showed similar kind of drug release pattern i.e immediate release at earlier and constant at later phase. From the **Fig. 4** and **5**, at 10 min F4 showed the highest drug release and F1 showed the lowest.

Similarly at 20 min also, F4 showed highest whereas F1 showed lowest. In 30 minutes and 45 minutes, similar pattern was seen where F1 showed slowest where as F4 showed highest. Therefore, drug release from F1 was less than other formulation and F4 showed best release profile. Immediate release of Telmisartan from tablet can be ascribed to several factors, such as lack of

crystallinity of Telmisartan after Solid dispersion preparation, reduction of aggregation and agglomeration by incorporating Crospovidone in solid dispersion, reduction of interfacial tension between hydrophobic drug and dissolution medium, increased wettability due to Neusilin US2 and effective surface adsorption of drug on hydrophilic carrier.

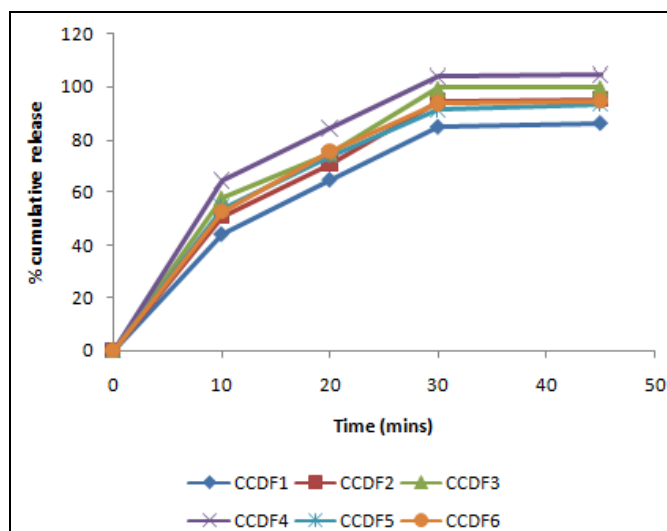


FIG. 4: SHOWING DISSOLUTION PROFILE OF CCDF1 TO CCDF6

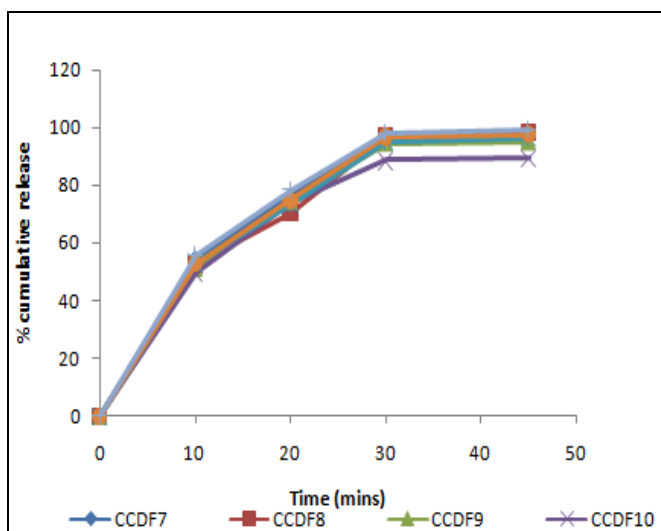


FIG. 5: SHOWING DISSOLUTION PROFILE OF CCDF7 TO CCDF13

Optimization of Formulation: For the optimization, distance based optimality in Minitab 16 was used, which gave CCDF4 as optimum point. 40 mg Neusilin and 14 mg Crospovidone

concentration of CCDF4 was flagged in contour plot and surface plot **Fig. 6** and **Fig. 7** and showed the desired target dissolution i.e. 100-110%. Therefore CCDF4 was chosen as optimized batch.

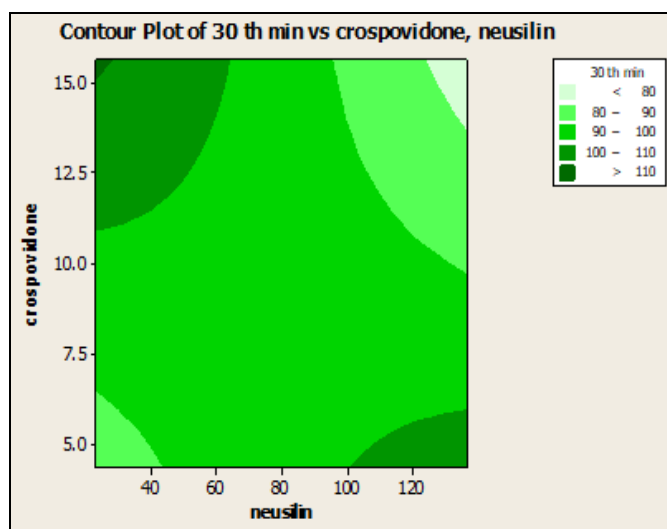


FIG. 6: CONTOUR PLOT OF DISSOLUTION IN 30 MINUTES VS CROSPVIDONE, NEUSILIN

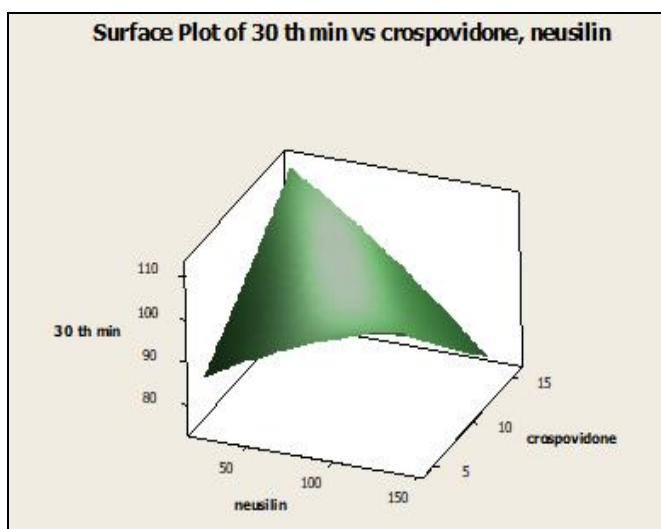


FIG. 7: SURFACE PLOT OF DISSOLUTION IN 30 MINUTES VS. NEUSILIN, CROSPVIDONE

Comparison of Dissolution Profile of Optimized Formulation with Market Product: Comparison of dissolution profiles of market product M and optimized formulation is shown in **Fig. 8** which

shows that the dissolution profile of M (market product) and the optimized formulation have similar pattern of drug release with the later having slightly better result.

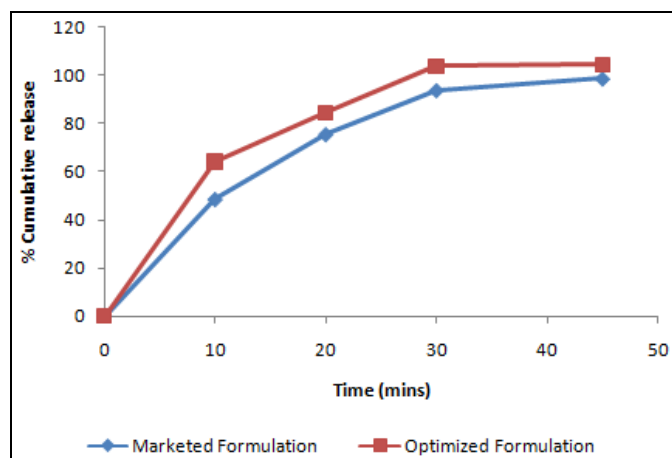


FIG. 8: SHOWING DISSOLUTION PROFILE OF M (MARKET PRODUCT) AND OPTIMIZED FORMULATION

Similarity and Dissimilarity Factors: All 13 formulations were similar to the market product M. The values of the similarity and dissimilarity factor of the formulations are given in **Table 4** which clearly indicates that the drug release profile of M market product and these formulations are identical as the range of F_s value is 50 to 100 and the range of F_d is 0 to 15

Release Kinetics: The best fitted model was selected upon coefficient of regression R^2 . The coefficient of regression R^2 for zero order was obtained within a range of 0.6134 to 0.7416 when cumulative percentage drug release against time up to 45 minutes was plotted for 13 batches with 0.6134 for optimized batch. The R^2 for first order release kinetics was within 0.9848 to 0.9956 when

log cumulative percent drug remaining was plotted against time for all formulated batches with 0.9848 for optimized batch. R^2 for Higuchi model was within 0.9532 to 0.9799 when cumulative percentage drug release was plotted against square root of time with 0.9532 for optimized batch.

The regression coefficient (R^2) of zero order, first order and Higuchi model are tabulated in **Table 5**.

Telmisartan release from the immediate release tablet of the optimized formulation follows the First Order Kinetics with $R^2 > 0.98$.

FT-IR Study: FTIR spectrum of pure Telmisartan is shown in **Fig. 9**.

The spectrum of Telmisartan showed characteristic bands at

- 1695 cm^{-1} (C=O stretching vibrations)
- 1350-1000 cm^{-1} (C-N stretching vibrations) and
- 1455 and 1381 (CH₃ bending vibrations)
- 743 cm^{-1} (Aromatic out plane bending for C-H)
- 2926 cm^{-1} (C-H Stretching)
- 1462 cm^{-1} (Aromatic ring stretch)
- 1657 cm^{-1} (C=C stretch)

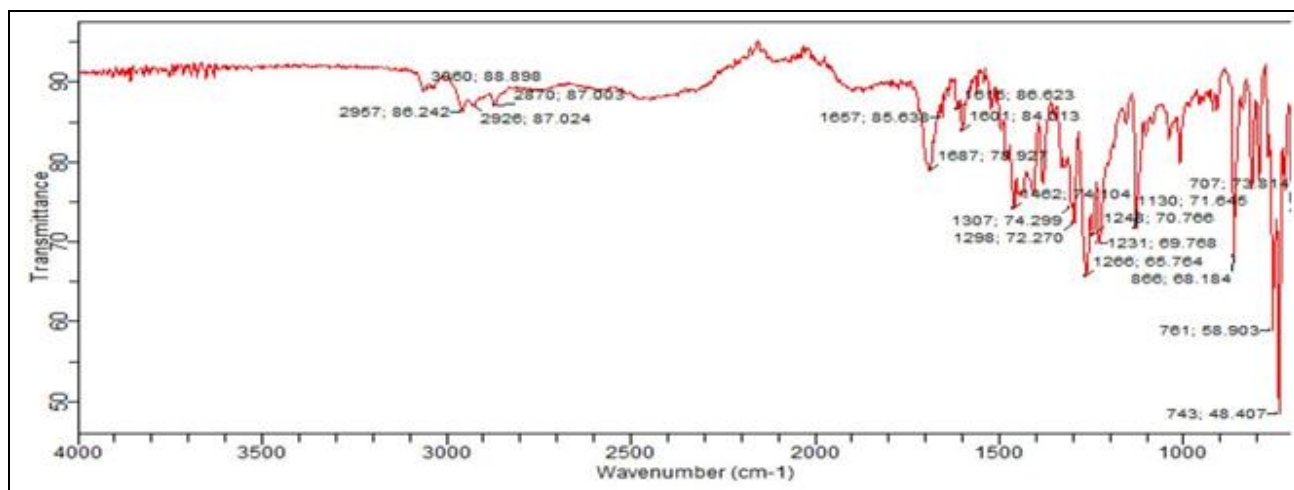


FIG. 9: IR SPECTRUM OF TELMISARTAN

These peaks were also shown by all physical mixtures containing different polymers. These confirm the stability of the drug. The overlaid FTIR

spectra for physical mixtures kept in oven and refrigerator for all polymers mannitol, PEG 6000, Crospovidone and Neusilin US2 have been shown

in Fig. 10, 11, 12 and 13 respectively. These spectra show that there is no significant change in the prominent functional groups responsible for

therapeutic activity of Telmisartan which confirms that these polymers have sufficient compatibility with the drug.

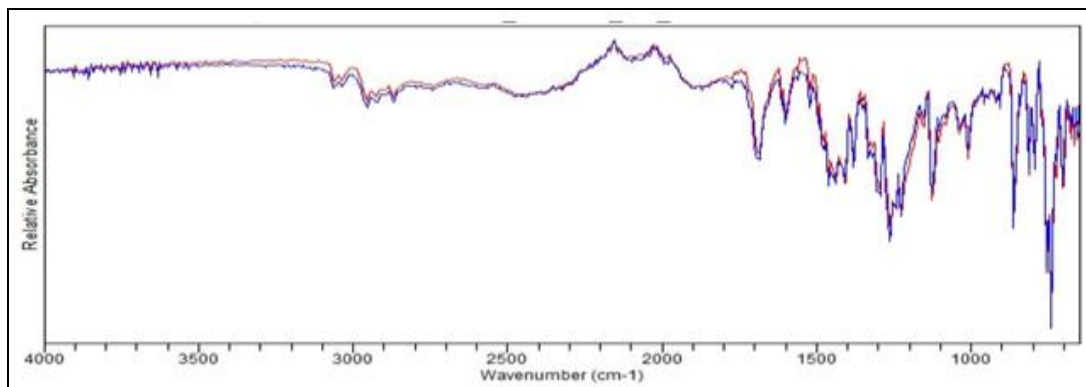


FIG. 10: IR SPECTRUM OF TELMISARTAN IN MANNITOL

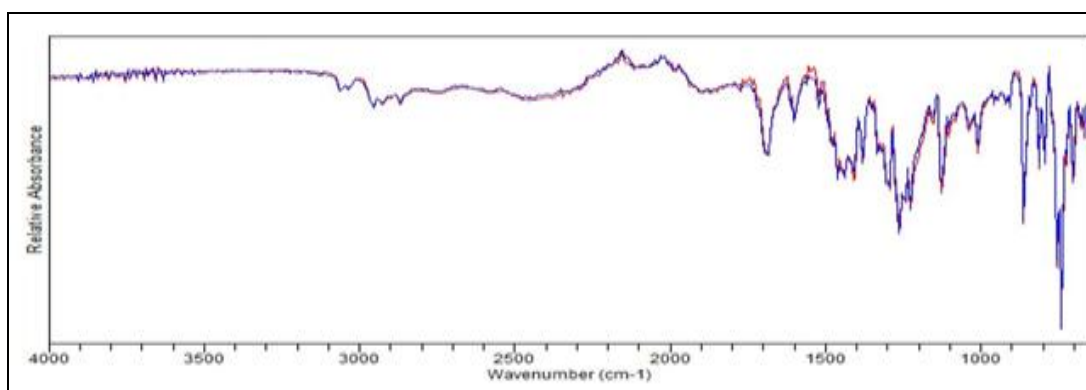


FIG. 11: IR SPECTRUM OF TELMISARTAN IN PEG 6000

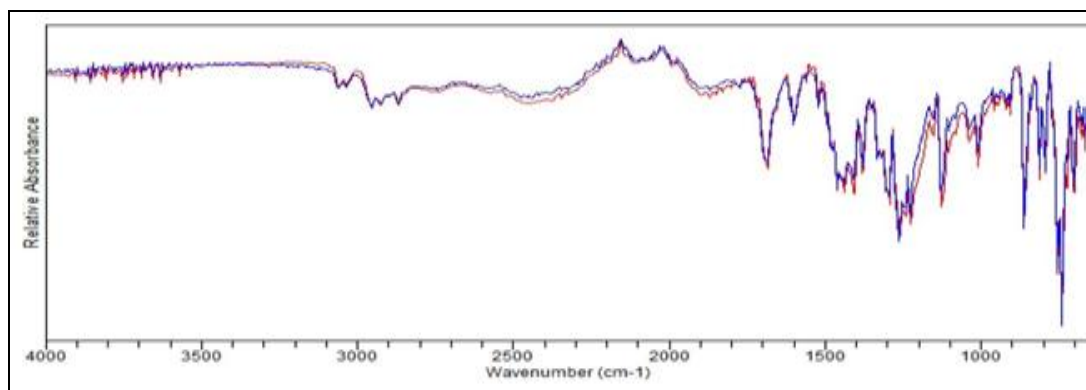


FIG. 12: IR SPECTRUM OF TELMISARTAN CROSPVIDONE

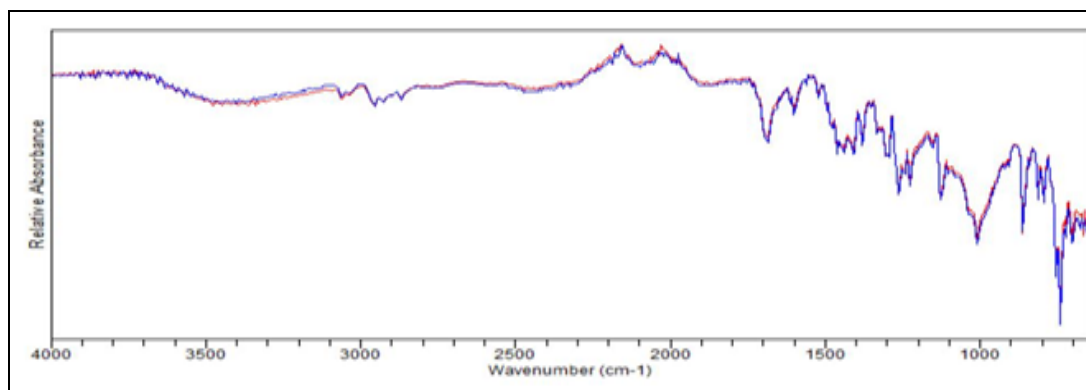


FIG. 13: IR SPECTRUM OF TELMISARTAN IN NEUSILIN

CONCLUSION: Among all formulations, formulation CCDF4 containing solid dispersion (drug: mannitol in the ratio 1:3), Crospovidone and Neusilin at concentration of 80 mg(60 mg mannitol+20 mg drug), 14 mg and 40 mg respectively was optimized batch. Thus, it can be concluded that combination of carrier and superdisintegrant and further adsorption with ternary agent like Neusilin to solid dispersion of drug is promising approach to enhance dissolution of tablet of poorly water soluble drug Telmisartan and other BCS class II drugs.

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