International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Design Development and Optimization of Telmisartan's Ternary Solid Dispersion with Its Formulation

D. R. Powar[*1], A. V. Desai[2], V. Y. Rohile[3], M. V. Bhosale[4], N. R. Inamdar[5]
[*1,2,3,4]Assistant Professor Ashokrao Mane Institute of Pharmacy, Ambap, Kolhapur, MH, India
[5]Assistant Professor Annasaheb Dange College of B. Pharmacy, Ashta, Sangli, MH, India

***Abstract*—** *The current study was conducted to address issues related to the solubility, dissolution, and oral bioavailability of telmisartan, a poorly water-soluble ionizable drug (TMS). The primary goal of this study is to improve Telmisartan solubility using the Solvent evaporation method. To study effect of adsorbents carrier on solubility of drug. Enhancement in dissolution is very crucial for the development of of BCS Class II drugs formulation. This was achieved by use of solvent evaporation method. By Thermal analysis and PXRD it is confirmed that the release rate of Telmisartan by solid dispersion technique using solvent evaporation method is amorphous structure. Furthermore, the weak interactions detected by FTIR spectroscopy between the porous carrier and Telmisartan in solid dispersion contribute to the drug's rapid desorption from the carrier surface upon contact with the dissolution media. This research work concludes that porous carrier particles aid in increasing dissolution rate, including stability studies.*

***Keywords*—** *Telmisartan, Ternary Solid Dispersion, Box Behnken, Stability, Neusilin*.

I. INTRODUCTION

Drugs with low water solubility frequently have low oral bioavailability due to low levels of absorption, so their dissolution rate can be increased by micronisation or size reduction, but this causes particle aggregation, which leads to poor wettability. The advantages of previous approaches were overcome by the development of solid dispersions of poorly bioavailable drugs. The first drug whose rate and extent of absorption were significantly increased by using solid dispersion was sulfathiazole by sekiguchi and obi, who formed a eutectic mixture of sulfathiazole with urea as the inert carrier. [1] Solid dispersion prepared by melting (fusion), solvent, or melting solvent method of dispersing one or more active ingredients (hydrophobic) in an inert carrier (hydrophillic). The resulting product contains various components, including a hydrophillic matrix and a hydrophobic drug. [2]

Many pharmaceutical applications include improved absorption, homogeneous distribution of a small amount of drug in solid form, stabilisation of unstable drugs, protection against decomposition.[3], conversion of liquid compounds into solid formulations, masking of unpleasant taste and odour.[4]

Solubility is one of the most important parameters in achieving the desired drug concentration in systemic circulation for the desired (anticipated) pharmacological response. More than 40% of new chemical entities developed in the pharmaceutical industry are water-insoluble. For formulation scientists, solubility is a major challenge. [5]

Drug absorption from the GI tract can be limited by a number of factors, the most significant of which are the drug molecule's poor aqueous solubility and membrane permeability.[6]

II. MATERIALS AND METHODS

Antihypertensive drug Telmisartan is used in preparation of Solid Dispersion. Different alkalizers Sodium Carbonate, Magnesium Oxide and Sodium Hydroxide were used. Solubilizers like Soluplus, Poloxamer, PVP K30 etc. were screened. Distilled water was used as an aqueous system.

Experimental Study

Preformulation Study Carried out by performing tests like identification, purity and physicochemical nature with the help of Infrared spectrum, U.V. spectra, melting point, physical state, Color and odor. Solubility of Telmisartan in different solvents was determined as per USP and BP by adding 2mg of solute into 10 ml solvent. Crystalline nature of Telmisartan was determined by Scanning Electron Microscopy micrographs. A single beam UV-Visible spectrophotometer (Agilent 1800) with matched quartz cells of 1 cm width was used. 10 ppm of Telmisartan solution was taken and carrying the UV spectrum was recorded in wavelength range 200-400nm for the determination maximum wavelength.

Telmisartan calibration curve was determined by taking solutions with concentrations of 1,2,3,4,5,6,7,8,9,10g/ml and measuring absorbance at 290 nm. Telmisartan calibration curves can also be obtained using 0.1N HCL, Phosphate Buffer (6.8), and Water.

Preparation of Ternary Solid Dispersion with Alkalizer: (A)

To prepare amorphous powder by adsorbent using solvent evaporation. Each alkalizer was suspended in 12.5 ml of Telmisartan solutions in methanol in different ratios of 1:1, 1:0.5, and 1:2:1, and 300 mg of Neusilin was adsorbed on the petri plate. The obtained suspensions were evaporated in a hot

D. R. Powar, A. V. Desai, V. Y. Rohile, M. V. Bhosale, N. R. Inamdar, "Design Development and Optimization of Telmisartan's Ternary Solid Dispersion with Its Formulation," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 6, Issue 1, pp. 21-31, 2022.

air oven at 40°C. The dried mass was crushed and passed through a glass tube for further testing.

Table 1 Batches of Pure Telmisartan with Alkalizer ratios

Sr. No.	Batch Code	Content	Ratio
1	AA1	TMS:Sodium Carbonate:Neusilin	1:1:1
2	AA2	TMS:Sodium Carbonate:Neusilin	1:0.5:1
3	AA3	TMS:Sodium Carbonate:Neusilin	1:2:1
4	AB1	TMS:Sodium Hydroxide:Neusilin	1:1:1
5	AB2	TMS:Sodium Hydroxide:Neusilin	1:0.5:1
6	AB3	TMS:Sodium Hydroxide:Neusilin	1:2:1
7	AC1	TMS:Magnesium Oxide:Neusilin	1:1:1
8	AC2	TMS:Magnesium Oxide:Neusilin	1:0.5:1
9	AC3	TMS:Magnesium Oxide:Neusilin	1:2:1

Preparation of Ternary Solid Dispersion with Solubilizer: (S)

To prepare amorphous powder by adsorbent using solvent evaporation. A different ratio of each solubilizer, 1:1:1, 1:0.5:1, and 1:2:1 was suspended in 12.5 ml of Telmisartan solutions in methanol, and 300 mg of Neusilin was adsorbed on the petri plate. The obtained suspensions were evaporated in a hot air oven at 40°C. The obtained dried mass was crushed and passed through a glass tube before being studied for evaluation tests.

Table 2 Batches of Pure Telmisartan with Solubilizer ratios.

Sr. No.	Batch Code	Content	Ratio
1	BA1	TMS:Soluplus:Neusilin	1:1:1
2	BA2	TMS: Soluplus:Neusilin	1:0.5:1
3	BA3	TMS: Soluplus:Neusilin	1:2:1
4	BB1	TMS: Lutrol:Neusilin	1:1:1
5	BB2	TMS: Lutrol:Neusilin	1:0.5:1
6	BB3	TMS:Lutrol:Neusilin	1:2:1
7	BC1	TMS:PVP K30:Neusilin	1:1:1
8	BC2	TMS: PVP K30:Neusilin	1:0.5:1
9	BC3	TMS: PVP K30:Neusilin	1:2:1

Determination of Percent yield:

The formula Percentage Yield= Practical Yield/Therotical Yield x100 was used to calculate the percentage yield of batches.

Determination of Drug content of prepared batches:

Dissolving dried prepared powder batches was used to determine drug content. Ten milligrammes of TMS in ten millilitres of methanol the solution was filtered through Whatman filter paper, diluted, and spectrophotometrically analysed at 290 nm. Each sample was prepared and analysed three times.

Determination of Saturation Solubility:

Determination of Saturation Solubility of prepared batches in water:

Separately, the known excess amount of sample was mixed with 10ml of water. Shaken for 48 hours with a rotary shaker, then filtered through Whatman paper. Diluted and spectrophotometrically examined at 296nm.

Determination of pH dependent Saturation Solubility of prepared batches:

A known excess amount of sample was added to 10ml of phosphate buffer 7.4 and shaken with a rotary shaker for 48 hours before being filtered through Whatman paper and spectrophotometrically measured at 296nm.

In vitro dissolution Study of prepared Batches:

The dissolution tests of Telmisartan (amorphous powder) mixture were carried out using the United States Pharmacopoeia (USP) dissolution apparatus II at 50 rpm. The formulations were placed in a dissolution vessel with 900 ml of pH 6.8 buffer in purified water kept at 37 ± 0.5^0c. At regular intervals, samples from the dissolution medium were taken and the concentration was measured spectrophotometrically at 290 nm.

Following the pre-formulation of prepared batches, we proceed to test parameters for their physicochemical properties such as FTIR, XRD, DSC, and SEM.

Formulation of TMS SD fast dissolving tablet:

Preparation of mixture/ powder blend

First croscarmellose sodium and HPMC with drug mixed well by dry mixing. Then Magnesium stearate and lactose were added to above blend. Angle of repose, Bulk density, Tapped density, Hausners ratio, and Carr's index were all evaluated for Powder Blend.

Method of TMS SD fast dissolving tablet preparation:

Direct compression

Required quantity of raw material of each were weighed and were mixed for 30 min. After preparation of primary powder mixture passed through the appropriate mesh and these were mixed together for 5 min. The tablets were created on an 8-station rotary tablet machine using punches with 8 mm flat edges.

Experimental Design Using Box Behnken

A Box Behnken Experimental Design is more efficient than a 32 factorial design because it requires fewer experiments. Multiple regression was used to generate a second polynomial equation from the all-selected variables obtained at various levels of the three independent variables (X1, X2, X3) and dependent variables (Y1, Y2). The experimental design (experimental design) generates the polynomial equation as follows:

$$Yi = b0 + b1\ X1 + b2\ X2 + b3\ X3 + b4\ X1\ X2 + b5\ X1\ X3 + b6\ X2\ X3 + b7\ X12 + b8\ X22 + b9\ X32$$

Where Yi is the dependent variable, b0 is the intercept, and b1 to b9 are the regression coefficients calculated from the observed experimental Y values from the experiment runs.

The independent variables X1, X2, and X3 were chosen from preliminary experiments. X1= (A-XO)/X; X1 is the coded value of the variable A; X0 is the value of A at the centre point; X=Step change, and so on, where A, B, and so on are the input variables. The amount of disintegrants used is an independent variable in the study. The hardness (kg/cm-1) and disintegration time are the dependent variables (seconds). Checkpoint analysis, Statistical analysis, Optimization data analysis by Reliasoft DOE was performed for the same.

Preparation of Telmisartan SD fast dissolving tablets:

Based on its superior dissolution properties in pH 6.8, telmisartan solid dispersion tablet of solubilizer was prepared

D. R. Powar, A. V. Desai, V. Y. Rohile, M. V. Bhosale, N. R. Inamdar, "Design Development and Optimization of Telmisartan's Ternary Solid Dispersion with Its Formulation," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 6, Issue 1, pp. 21-31, 2022.

by solvent evaporation and incorporated into the fast-dissolving tablets. Croscarmellose was added as a tablet super disintegrant, and HPMC was added as a binder, and mixed with the above mixture in a glass mortar with a pestle for 15 minutes. The above mixture was then lubricated with magnesium stearate for another 30 minutes. The resulting powder blend was then compressed under constant pressure into 40 mg tablets containing a total of 20mg Telmisartan using a multi-punch rotary tableting machine.

Table 3 Compositions of Telmisartan fast dissolving tablet

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
TMS SD (mg)	20	20	20	20	20	20	20	20	20
HPMC (mg)	10.9	9.9	10.7	10.3	10.6	9.8	10.5	10.8	10.9
Crosscarmellose(mg)	6.6	7.5	6.3	7.3	7.1	6.9	6.2	6.1	6.3
Lactose(mg)	2	2	2.6	2.1	2	2.5	2.6	2.4	2.2
Magnesium Stearate(mg)	0.5	0.6	0.4	0.3	0.3	0.8	0.7	0.7	0.5
Total weight	40	40	40	40	40	40	40	40	40

Evaluation of prepared fast dissolving tablets as per USP:

Wetting Time

Wetting time was determined by placing five circular tissue papers of 10 cm diameter in a petri dish with 0.2%w/v methylene orange solution (3ml). A tablet was carefully placed on the surface of the tissue paper. The wetting time was determined by observing the time required for the development of orange colour on the upper surface of the tablet.

Water absorption ratio

In a small petridish containing 6ml of water, a small piece of tissue paper folded twice was placed. The time required for complete wetting was measured using a tablet placed on the paper. After that, the wetted tablet was reweighed. The water absorption ratio, R, was calculated using the following formula:

$$R=100xWa-Wb/Wb$$

Wb denotes the weight of the tablet before water absorption, while Wa denotes the weight of the tablet after water absorption.

Friability, Hardness and dimension

Friability tests were performed using a Roche friabilator test apparatus, hardness was measured using a Pfizer hardness tester, and tablet thickness and diameter were measured using a vernier calliper.

Disintegration test:

To determine the disintegration time, one tablet was placed in each tube of the USP disintegration apparatus, and the basket rack was set in a one-liter beaker of 0.1N HCL, at 37ºC $\pm$2ºC

Comparative in vitro dissolution profile of prepared fast dissolvingTablet and marketed tablets of Telmisartan:

The dissolution tests of TMS SD prepared fast dissolving tablets and TMS marketed tablets were performed at 75 rpm using the USP dissolution apparatus II. TMS tablets were placed in a dissolution vessel with 900mL of pH 6.8 kept at 37ºC $\pm$5ºC. TMS concentrations were determined spectrophotometrically at 290 nm by withdrawing and filtering samples from the dissolution medium at appropriate intervals.

Stability study of Telmisartan & optimized batches of amorphous powder

The optimised amorphous powder batch was kept at 40^0C±2°C/75 ±5% RH Drug content was studied for 1 month in a stability chamber and the effects of storage conditions on the preparation.

III. RESULTS AND DISCUSSION

Preformulation Study

Identification Test

Telmisartan identification tests were carried out using the appropriate methods. The outcomes are listed below, and the values observed are within the range. The results show that the Telmisartan is in its purest form.

Table 4 Identification tests of Telmisartan

Sr. No.	Physical properties and test	Methods	Description
1.	Physical state	Visual observation	Solid
2.	Color	Visual observation	White or off- white crystalline powder
3.	Odor	Smelling by nose	Odorless
4.	Melting point	Capillary Method	265-272^{0}C
5.	U. V. Spectra	U.V visible Spectrophotometer	UV spectra were obtained atstandard condition and it shows λ max of 290 nm in Methanol
6.	Infra-Red Spectra	IR Spectroscopy	The infra-red absorption spectrum is concordant with the reference spectrum

Solubility

Telmisartan soluble in methanol and phosphate buffer 7.4, Slightly soluble in ethanol, acetone, chloroform and 0.1 N HCL, practically insoluble in water

Results of Analytical Methods

Determination of λ max

The λ max of Telmisartan by UV-spectrophotometer in methanol, phosphate buffer 6.8, 0.1 N HCL, Water was found to be 290, 289, 288, 286 nm respectively and it is very close to standard λ max. The UV-Visible spectrum of Telmisartan is shown inFig.8.2

D. R. Powar, A. V. Desai, V. Y. Rohile, M. V. Bhosale, N. R. Inamdar, "Design Development and Optimization of Telmisartan's Ternary Solid Dispersion with Its Formulation," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 6, Issue 1, pp. 21-31, 2022.

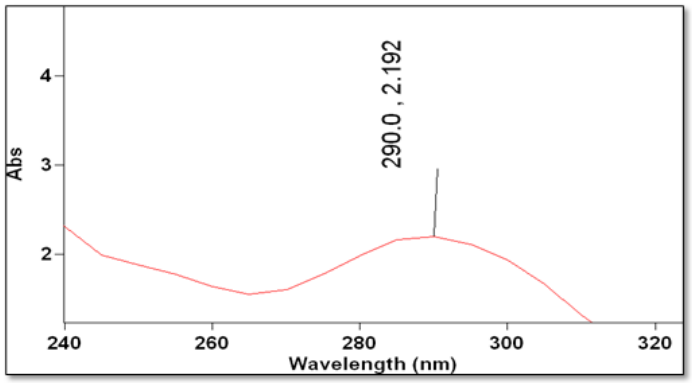


Fig. 1 UV- Visible absorption spectrum of Telmisartan with Methanol

Calibration curve for Telmisartan:

At 290 nm, the absorbance vs. concentration graph for pure Telmisartan was found to be linear in the concentration range 1-10µg/ml it follows Beer-Lamberts law.

Table 5 Calibration curve values of Telmisartan in different solvents

Sr. No.	Solvent	Slope	Intercept	R square value
1.	Methanol	0.0478	0.0064	0.9987
2.	Phosphate Buffer 6.8	0.0420	0.1437	0.9555
3.	Water	0.054	0.035	0.998

Saturation solubility of Telmisartan:

Table 6 Saturation solubility of Telmisartan in water and Phosphate Buffer 7.4

Solvent	Solubility(µg/ml)
Distilled Water	0.0684±0.005
Phosphate Buffer 7.4	0.0534±0.017
Mean ± S.D., n=3	

Fourier Transform Infrared of Telmisartan

The FTIR spectrum of Telmisartan was recorded using FTIR (cary-630 Agilent technology). The spectrum was recorded over the range of wave no. 4000 to 400 cm^{-1}.

Table 7 FTIR Interpretation of Telmisartan

Sr. no.	Functional Group	Peak (wave number) cm^{-1} (observed)	Peak (wave number) cm^{-1} (standard)
1	Aromatic CH stretching	3058.72	3059cm^{-1}
2	AliphaticCH stretching	2957cm^{-1}	2957cm^{-1}
3	H O H bending	1600cm^{-1}	1652cm^{-1}
4	COOH stretching	1694cm^{-1}	1699cm^{-1}
5	C O C bending	1447cm^{-1}	1459cm^{-1}

Experimental Study

PART I

Solid Dispersion Preparation using adsorbent carrier

The formulated batches have been found in form of free-flowing powder without any agglomeration of particles within the batches, this powder batches are then stored at in well-sealed container for its further characterization like percentage yield, drug content, saturation solubility and dissolution study etc.

Percentage Yield of Batches:

The prepared formulation was poured in the petri plate and weighed accurately. Further this petri plate was kept in Oven for 30 min and weighed.

Table 8 Percentage Yield of Batches

Sr. No.	Batch Name	% Yield	Batch Name	% Yield
1	AA1	94.55±0.44	BA1	89.17±0.38
2	AA2	95.05±0.84	BA2	95.03±0.27
3	AA3	98.11±0.21	BA3	96.88±0.94
4	AB1	74.48±0.01	BB1	96.68±0.64
5	AB2	96.11±0.67	BB2	90.41±0.84
6	AB3	98.82±0.24	BB3	97.64±0.39
7	AC1	94.65±0.39	BC1	90.55±0.77
8	AC2	97.60±0.57	BC2	96.41±0.54
9	AC3	89.05±0.28	BC3	98.82±0.68

Drug Content determination using UV spectroscopy.

Table 9 % Drug Content of Batches

Sr. No.	Batch Name	% Drug Content	Batch Name	% Drug Content
1	AA1	90.01±0.84	BA1	88.34±0.11
2	AA2	96.45±0.22	BA2	94.38±0.36
3	AA3	95.31±0.38	BA3	93.01±0.74
4	AB1	86.07±0.67	BB1	98.34±0.16
5	AB2	94.27±0.94	BB2	89.76±0.74
6	AB3	93.21±0.33	BB3	97.35±0.31
7	AC1	93.34±0.54	BC1	90.14±0.20
8	AC2	98.17±0.71	BC2	97.34±0.34
9	AC3	91.94±0.36	BC3	98.68±0.14

Saturation solubility of Telmisartan:

Telmisartan saturation solubility was tested in distilled water and phosphate buffer 7.4 here. The table below shows the saturation solubility of pure Telmisartan and powder batches with diluents in water and phosphate buffer 7.4. According to the findings, Telmisartan has a much lower solubility in water than phosphate buffer 7.4.

Table 10 Saturation solubility of Telmisartan in distilled water and phosphate buffer after 48 hrs

Sr. No.	Batches	Saturation Solubility in water(mg/ml)	Saturation Solubilty in Phosphate Buffer 7.4 (mg/ml)
1	AA2	0.3184 ±0.001	0.2144 ±0.003
2	AA3	0.5175 ±0.009	0.4820 ±0.007
3	AB2	0.3384 ±0.004	0.2934 ±0.001
4	AB3	0.6418 ±0.002	0.5610 ±0.004
5	AC1	0.3942 ±0.001	0.2183 ±0.001
6	AC2	0.8647 ±0.003	0.6447 ±0.008
7	BA2	0.3573 ±0.001	0.2108 ±0.003
8	BA3	0.6541 ±0.004	0.5401 ±0.007
9	BB1	0.7624 ±0.002	0.6210 ±0.002
10	BB3	0.2179 ±0.003	0.1174 ±0.004
11	BC2	0.5348 ±0.001	0.4127 ±0.006
12	BC3	0.8831 ±0.002	0.6608 ±0.001

In vitro Dissolution study

The USP dissolution test apparatus was used to conduct an in vitro dissolution study of prepared powder batches and Telmisartan. The dilution media was chosen to be Phosphate Buffer pH6.8.

D. R. Powar, A. V. Desai, V. Y. Rohile, M. V. Bhosale, N. R. Inamdar, "Design Development and Optimization of Telmisartan's Ternary Solid Dispersion with Its Formulation," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 6, Issue 1, pp. 21-31, 2022.

International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Table 11 % Cumulative drug release 0f TMS Powder and Batches AA3, AB3, AC2

Time (min)		% Cumulative drug release		
	Telmisartan	Batch AA3	Batch AB3	Batch AC2
0	0	0	0	0
10	8.12±0.104	38.28±0.305	35.01±0.064	39.74±0.025
20	10.41±0.062	51.32±0.015	49.25±0.032	58.30±0.050
30	21.39±0.010	63.33±0.035	60.27±0.084	68.94±0.036
40	28.31±0.015	74.94±0.078	64.99±0.011	79.64±0.060
50	36.01±0.032	81.83±0.025	69.84±0.061	87.89±0.025
60	44.68±0.436	89.48±0.030	84.38±0.034	94.91±0.017
	Mean ± S.D., n=3			

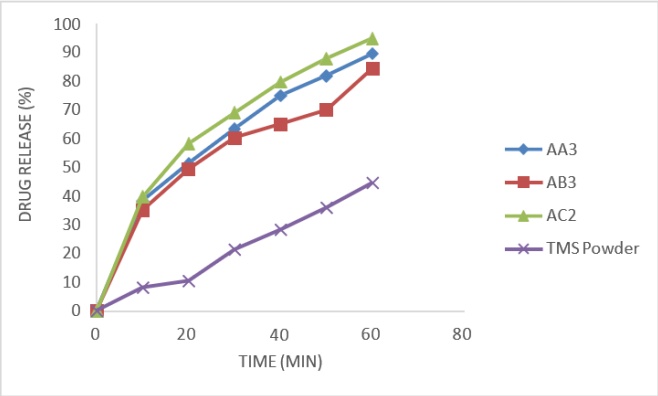


Fig. 2 % Cumulative drug release of TMS powder and batches AA3, AB3, AC2

Table 12 % Cumulative drug release 0f TMS Powder and Batches BA3, BB1, BC3

Time (min)		% Cumulative drug release		
	Telmisartan	Batch BA3	Batch BB1	Batch BC3
0	0	0	0	0
10	8.12±0.104	38.17±0.021	36.84±0.071	40.35±0.084
20	10.41±0.062	47.64±0.028	48.66±0.020	50.84±0.026
30	21.39±0.010	54.38±0.084	59.67±0.047	63.90±0.047
40	28.31±0.015	67.38±0.034	68.33±0.095	71.67±0.033
50	36.01±0.032	74.57±0.030	71.24±0.047	79.35±0.074
60	44.68±0.436	84.31±0.031	83.67±0.022	89.67±0.039
	Mean ± S.D., n=3			

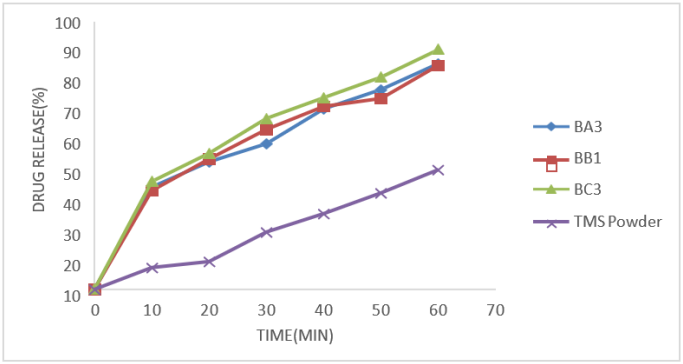


Fig. 3 % Cumulative drug release of TMS powder and batches BA3, BB1, BC3

Drug Excipients compatibility study:

It is well known that interactions between the active substance and excipients can influence the pharmacological properties and behavior of drugs in biological systems. In this study, Alkalizer and solubilizer with drug Telmisartan were ground together and analyzed by FTIR, DSC, XRD and SEM in the formulation.

Fourier Transform Infrared Analysis FTIR of Optimized Batches

Data from the Experimental Study were studied for FTIR Analysis, taking into account the percentage yield, drug content, and dissolution study among the batches Batch AC2 and Batch BC3.

Table 13 FTIR Interpretation of Batch AC2 and Batch BC3

Sr. no.	Functional Group	Peak (wave number)cm^{-1} (standard)	Batch AC2 Peak (wave number) cm^{-1} (observed)	Batch BC3Peak (wave number) cm^{-1} (observed)
1	Aromatic CH stretching	3059 cm^{-1}	3055cm^{-1}	3068 cm^{-1}
2	AliphaticCH stretching	2957cm^{-1}	2957cm^{-1}	2955 cm^{-1}
3	H O H bending	1652cm^{-1}	1655cm^{-1}	1599 cm^{-1}
4	COOH stretching	1699cm^{-1}	1695cm^{-1}	1690 cm^{-1}
5	C O C bending	1459cm^{-1}	1447cm^{-1}	1410 cm^{-1}

Powder X-Ray Diffraction (PXRD)

Less diffused peaks in the X-Ray diffraction spectrum may be seen in the X-Ray diffraction pattern of pure telmisartan, which suggests that telmisartan is present as a crystalline substance. The creation of the drug's amorphous nature form is demonstrated by X-ray diffraction of formulations of batches AC2 and BC3 since there is a drop in the intensity of the API.

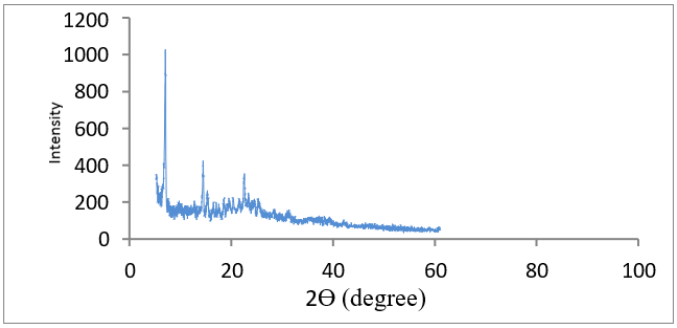


Fig. 4 XRD of Telmisartan

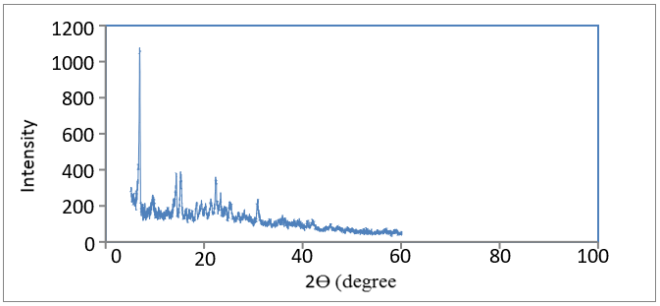


Fig. 5 XRD Pattern of Batch AC2

D. R. Powar, A. V. Desai, V. Y. Rohile, M. V. Bhosale, N. R. Inamdar, "Design Development and Optimization of Telmisartan's Ternary Solid Dispersion with Its Formulation," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 6, Issue 1, pp. 21-31, 2022.

International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

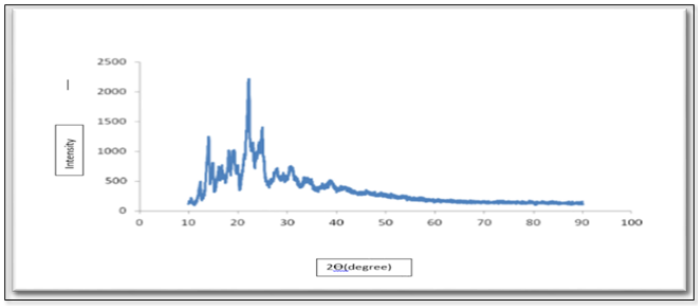


Fig. 6 XRD Pattern of Batch BC3

Differential Scanning Calorimetry (DSC)

A quick and reliable method to check for drug-excipient compatibility, differential scanning calorimetry (DSC) offers the most details on potential interactions. A DSC interaction ends when endothermic peak(s) are eliminated, new peak(s) form, peak shape and onset, peak temperature/melting point, and relative peak area or enthalpy are changed.

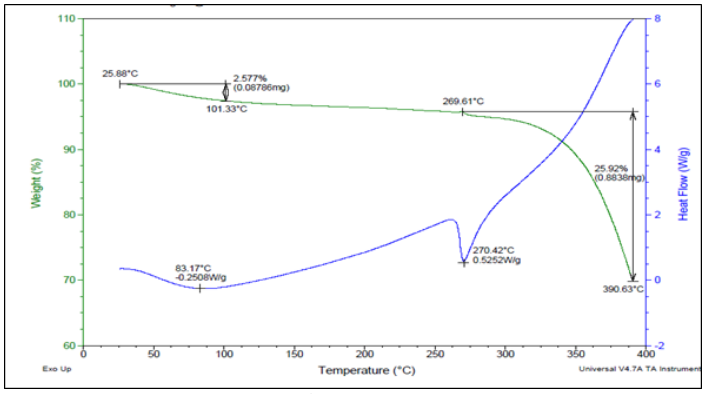


Fig.7 DSC of Telmisartan (TMS)

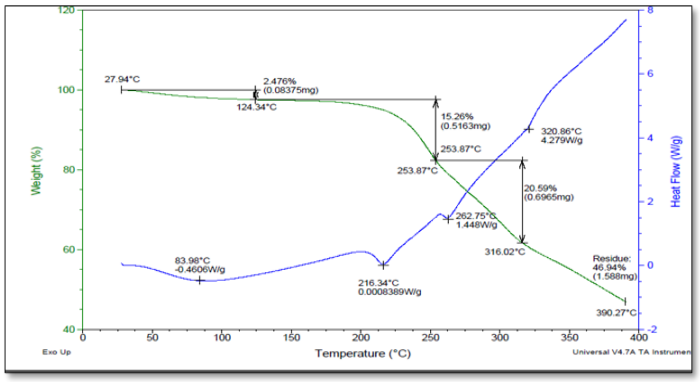


Fig. 8 DSC of Batch AC2

DSC thermogram over the temperature range 270°C and the DSC thermogram of TMS and Magnesium Oxide (AC2) and TMS and PVP (BC3) were observed at 262°C and 265°C respectively. DSC was used to confirm the synthesis of the complex of TMS with magnesium oxide and PVP in the solid state. The endodermic peaks of the complex and the individual components are compared. The data shows an endodermic peak of TMS at 270.42°C near to its melting point (272°C). The endodermic peaks characteristic of TMS with a significant shift in batch AC2 and BC3 endodermic peaks at 262°C and 265°C respectively.

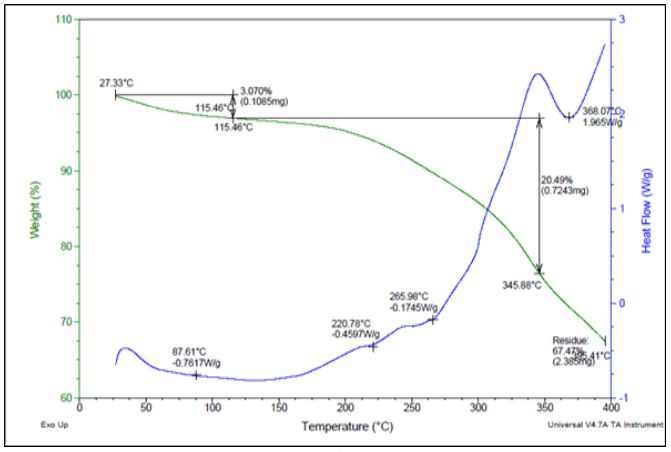
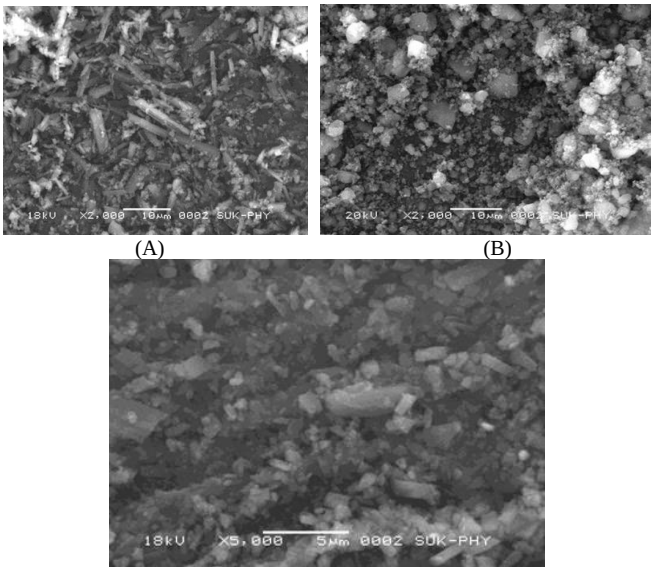


Fig.9 DSC of Batch BC3

Scanning Electron Microscopy (SEM):

From Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD) study two batches AC2 and BC3 were optimized. (A) depicts SEM images of pure TMS and prepared batches AC2 and BC3.. The bar on the pictures indicates the degree of magnification (5µm, 10µm).The SEM micrograph of pure TMS revealed irregular shape crystals of TMS with rough surfaces (B,C). SEM image of prepared powder (batch AC2, BC3) observed in the form of hollow spherical particles (B,C) and not asingle crystal of TMS has observed. SEM images confirmed that uniformity and fine naturepowder which might be contributing for rapid drug release from powder



(A) (B)

(C)

Fig. 10 SEM of Telmisartan and Batches AC2 and BC3

Formulation of TMS SD fast dissolving tablet

D. R. Powar, A. V. Desai, V. Y. Rohile, M. V. Bhosale, N. R. Inamdar, "Design Development and Optimization of Telmisartan's Ternary Solid Dispersion with Its Formulation," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 6, Issue 1, pp. 21-31, 2022.

Table 14 Evaluation of Powder Blend

Sr. No.	Precompression properties	Batch AC2	Batch BC3
1	Angle of Repose(Θ)	26	27
2	Bulk Density(gm/cm^3)	0.13	0.15
3	Tapped Density(gm/cm^3)	0.82	0.89
4	Hausner's ratio	1.08	1.27
5	Carr's index	9.67	9.78

Box - Behnken design

When the conventional step-by-step approach is utilised, the adoption of an experimental design prevents the usage of an enormous number of independent runs and allows for the testing of many factors at once. The concentrations of crosscarmellose, microcrystalline cellulose, and sodium stearate were optimised using the Box-Behnken design.

Data analysis:

Data Analysis for TMS SD Tablet

Three components and three levels make up this Box-Behnken design, and 15 runs were acquired from the nine runs that were conducted to examine the impact on the dependent variables. All of the manufactured powder batches used in the experimental plan produced tablets, which were then assessed for their hardness, disintegration speed, and friability. The table displayed the values for the batches.

Table 15 Compositions of Telmisartan fast dissolving tablet

Ingredient	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
TMS (mg)	20	20	20	20	20	20	20	20	20
HPMC (mg)	10.9	9.9	10.7	10.3	10.6	9.8	10.5	10.8	10.9
Crosscarmellose(mg)	6.6	7.5	6.3	7.3	7.1	6.9	6.2	6.1	6.3
Lactose(mg)	2	2	2.6	2.1	2	2.5	2.6	2.4	2.2
Magnesium Stearate(mg)	0.5	0.6	0.4	0.3	0.3	0.8	0.7	0.7	0.5
Total weight	40	40	40	40	40	40	40	40	40

Table 1 6 Box Behnken experimental design for independent factor and dependentresponse:

Run order	**X1 HPMC**	**X2 Microcrystalline cellulose**	**X3 Magnesium Stearate**	**Y1 Disintegration Time(sec)**	**Y2 Hardness (kg/cm^2)**
1	1	0	1	21±0.6	4.6±0.2
2	-1	0	-1	14±0.5	4.7±0.3
3	0	0	0	22±0.8	5.0±0.4
4	-1	0	1	20±0.6	4.9±0.8
5	-1	-1	0	22±0.4	4.2±0.6
6	0	-1	-1	32±0.7	4.8±0.4
7	0	0	0	32±0.1	5.0±0.7
8	1	0	-1	30±0.3	4.6±0.6
9	0	1	1	29±0.7	4.3±0.6

Where , X1, X2, X3= Independent variables and Y1, Y2 = Dependent variables

Probability Plots

Normal likelihood Disintegration time and hardness graph It explains that in the event that the residuals have a normal distribution, the points will follow a straight line. With typical data, there is still some scatter. Only when the curve is clearly "S-shaped," indicating that a response transformation might improve the study. This leads us to conclude that the disintegration and hardness plot is accurate. This leads us to the conclusion that the blue patch in the normal probability distribution represents a non-significant influence on the variables scattered around the straight line.

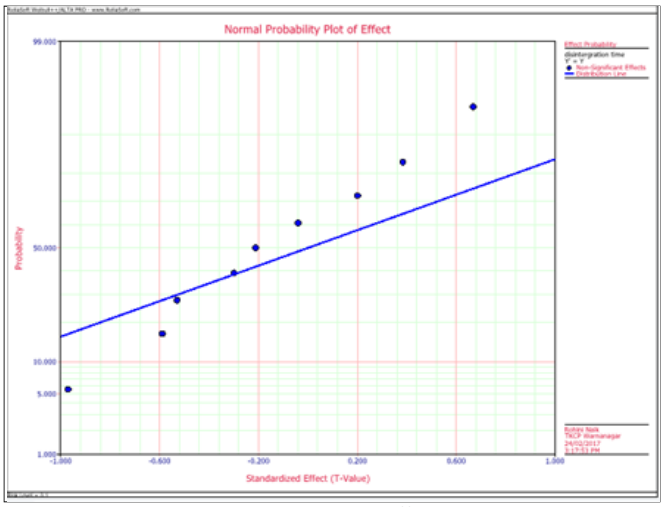


Fig. 11 Normal probability plot showing effect on disintegration time

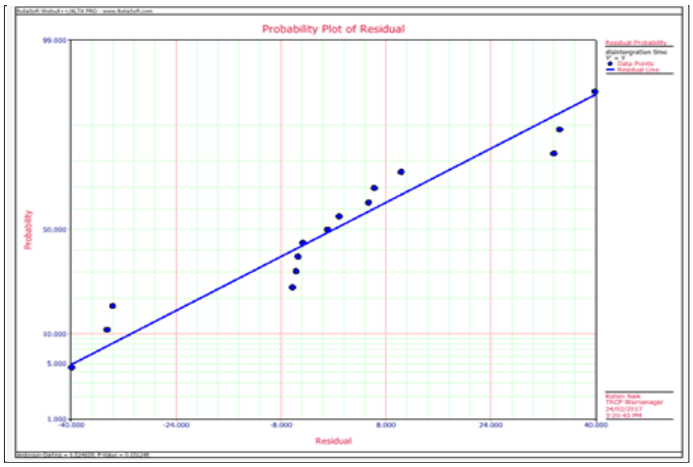


Fig. 12 Normal probability plot showing effect on hardness

ANOVA, Pure error and Lack of fit

The ANOVA results reveal that the model was significant for each and every dependent variable listed in the table. The regression co-efficient was calculated using regression analysis. For every answer variable, it was discovered that every independent variable was significant. Y1 and Y2 results for the quadratic model were determined to be non-significant. For Y1, it was determined that the linear model was not significant. Therefore, the aforementioned conclusion suggests that both aspects are crucial in the creation of an AC tablet. The table illustrates the data of pure mistake and lack of fit. This can offer an estimate of the pure experimental uncertainty as well as the mean response. The residuals are the discrepancy between actual values and predictions.

The dependent variable's ANOVA shows that our model was significant for each of the response variables. For all dependent variables, the effects of crosscarmellose quantity, HPMC, and sodium stearate, as well as their quadratic and interaction terms, were found to be non-significant. Therefore, based on the aforementioned findings, we can conclude that the binder concentration plays a significant influence in fast-dissolving tablet disintegration time as well as efficient hardness and friability during packaging and handling. A

D. R. Powar, A. V. Desai, V. Y. Rohile, M. V. Bhosale, N. R. Inamdar, "Design Development and Optimization of Telmisartan's Ternary Solid Dispersion with Its Formulation," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 6, Issue 1, pp. 21-31, 2022.

mean response and an estimate of experimental hesitation are provided by the data of pure error and lack of fit.

Table 17 Polynomial equation values in terms of actual values:

Terms	Disintegration time	Hardness
Intercept	32	5.0
A:Crossccarmellose	0.5070	-0.088
B: HPMC	1.79	0.0074
C: Sod. Stearate	0.458	-0.0162
AB: Interaction	1.34	-0.20
AC: Interaction	3.59	0.041
BC: Interaction	5.73	0.051
A:Crossccarmellose (r^2)	-1.55	-0.2292
B: MCC (r^2)	-1.67	-0.1797
C:Mag. Stearate (r^2)	1.60	+3.1111

Table 18 ANOVA for Disintegration Time and Hardness

Terms	Disintegration time		Hardnesss	
	F-value	P-value	F-value	P-value
Intercept (DT= 12), (Hardness=5.1)	0.7657	0.5145	-	-
A: Crossccarmellose	1.2530	0.4353	1.7879	0.17523
B: HPMC	1.7294	0.3182	0.6473	0.5890
C: Sod. Stearate	0.1312	0.5452	1.2035	0.4994
AB: Interaction	0.5517	0.8377	0.3017	0.7965
AC: Interaction	0.6968	0.5016	1.7873	0.2056
BC: Interaction	1.5487	0.3678	0.2442	0.4674
A2	1.4466	0.2018	0.5512	0.5225
B2	2.7524	0.294	0.2481	0.1912
C2	0.3752	0.7411	4.0481	0.3567
Lack of fit	-	-	-	-
Pure error	-	-	-	-
Cor total	PRESS =14180.00		Cor total	PRESS =13495.62
R- sq= 39.45%	R-sq (adj) =0%		R- sq= 38.42%	R-sq (adj) =0%
R-sq (pred)=0%			R-sq (pred)=0%	

Interaction Plot

This figure makes it simple to understand how the concentration of disintegrants changed in relation to the reaction. As a result, they will display two non-parallel lines, suggesting that the effect of one element is independent of the response, as illustrated in fig. This leads to the conclusion that the response is unaffected by the disintegration time and hardness.

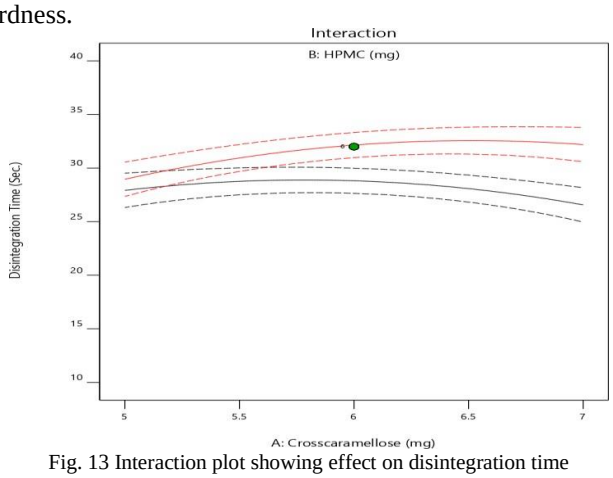


Fig. 13 Interaction plot showing effect on disintegration time

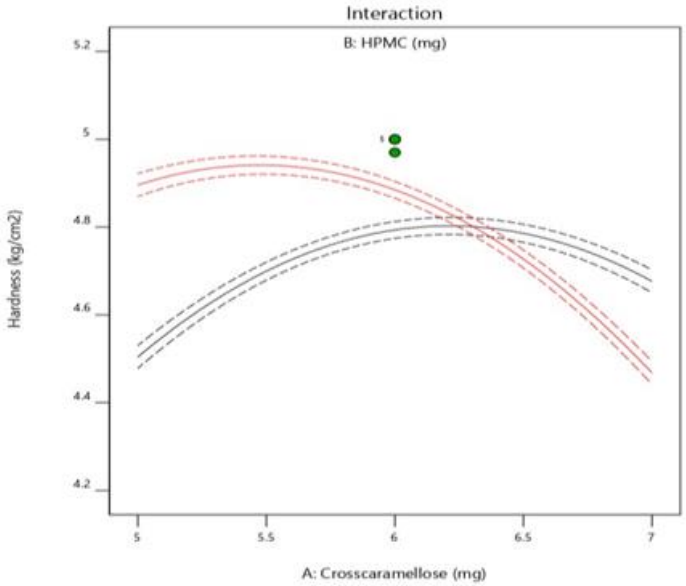


Fig. 14 Interaction plot showing effect on hardness

Contour Plot

Figures 15 and 16 exhibit two-dimensional (2D) contour plots, which are excellent for seeing how a component interacts with the responses. These kinds of plots are helpful for examining the simultaneous impacts of two factors on the answer, and in all of the plots that were given, the third factor's value was held constant. All of the correlations between the three variables are linear up to a specific range where X1, X2, and X3's effect on disintegration time at a particular level is unaffected by their interactions. The graphs' linear behaviour up to 25% suggests that X1 and X2 have a linear connection. All of the values were treated as dependent variables in a similar manner. According to the contour plot, X1 level range of 30 to 25% and X2 at 4.8 to 5% might yield the best value of disintegration time. The contour plot clearly shows that the greater level of X1, X2, and X3 favours the formulation.

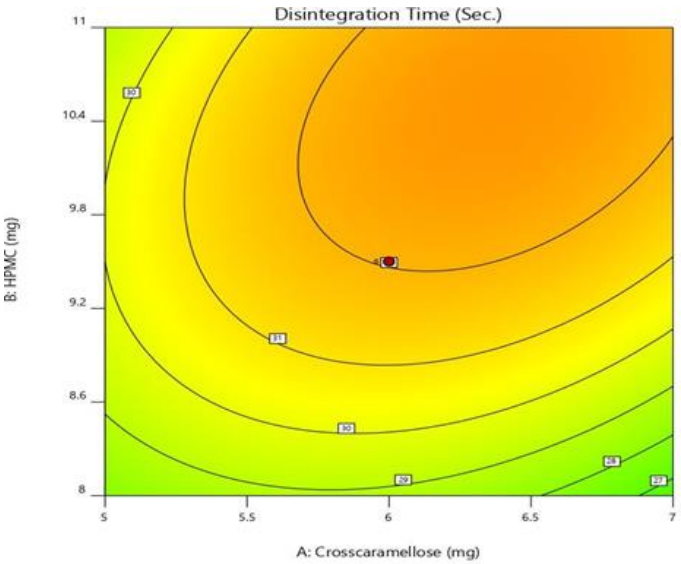


Fig. 15 Contour plot showing effect on disintegration time

D. R. Powar, A. V. Desai, V. Y. Rohile, M. V. Bhosale, N. R. Inamdar, "Design Development and Optimization of Telmisartan's Ternary Solid Dispersion with Its Formulation," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 6, Issue 1, pp. 21-31, 2022.

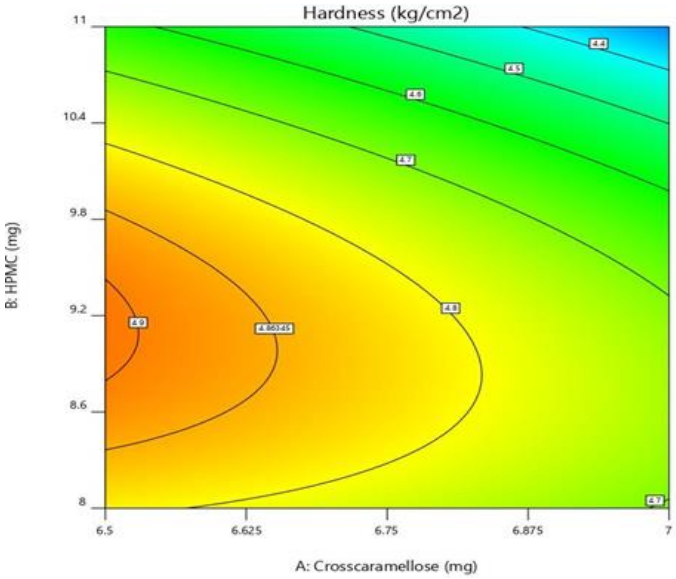


Fig. 16 Contour plot showing effect on hardness

Response Surface Plot

A graphical representation of the potential relationship between three variables is a response surface (3D) plot. The response (z) variable is represented by a smooth surface (3D) plot, and it is obtained by plotting two independent variables on the x and y axes. Similar to contour plots, but with more accuracy, 3D surface plots are helpful for determining the response values.

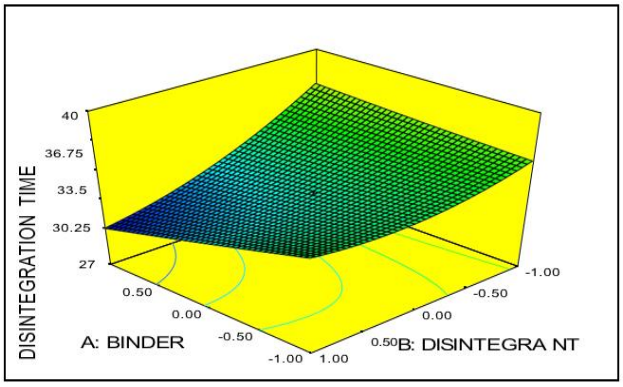


Fig. 17 3D surface plot showing effect on disintegration time

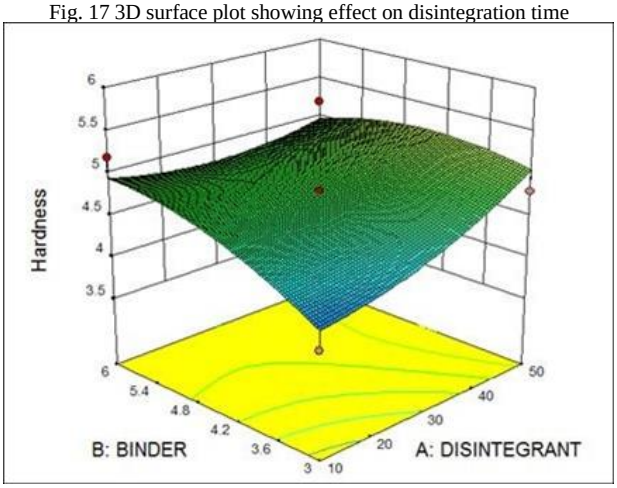


Fig. 18 3D Surface Plot graph showing effect on hardness

Evaluation of fast dissolving tablet of TMS SD of batch BC3

Considering TMS SD Batch AC2 was carried further for data analysis. Here the 9 batches were obtained by use of Box-Behnken design.The further evaluation of physical properties as well as wetting time and water absortion ratio was done as follows:

Table 19 Physical properties of fast dissolving tablet batch AC2

Properties	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness (kg/cm^2)	4.7	4.1	5.2	4.5	4.1	4.9	5.1	4.2	4.4
Disintegration time (s)	20	24	25	21	38	15	20	47	38
Friability (%)	0.45	0.61	0.39	0.52	0.34	0.25	0.25	0.58	0.47

Depending upon the physical properties of batches F1 to F9, batch F6 was selected as finalbatch for tablet formulation.

Table 20 Formula for the fast dissolving tablet (F6)

Sr.No	Ingredient	Quantity (mg)
1	TMS SD (mg)	20
2	Crosscarmellose(mg)	6.9
3	HPMC(mg)	9.8
4	Lactose (mg)	2.5
5	Magnesium Stearate(mg)	0.8
7	Total weight	40

Table 21 Properties of F6 batch tablets

Sr. no.	Tablet properties
Hardness(kg/cm^2)	5.2±0.068
Friability (%)	0.27±0.023
Disintegrationtime(sec)	27.91±0.87
Thickness(mm)	2.9±0.04
Diameter (mm)	2.8±0.058

Wetting Time

The wetting time for all the formulated tablets was in the range of 12±1.2 to 24±1.0 sec

Water Absorption ratio:

Water absorption ratio ranged from 056.64±0.433 to 58.46±0.230%

In vitro Dissolution study.

An essential factor in figuring out the cumulative drug release in the dilution media is the in vitro dissolution study. The USP dissolution test apparatus was used to conduct an in vitro dissolution investigation on improved batches of the drug formulation for TMS and telmisartan. The dilution medium in the jar was chosen to be Phosphate Buffer pH6.8.

Table 22 % Cumulative drug release 0f Marketed formulation and Batches BC

Time	Marketed Formulation	Batch BC3
0	0	0
10	35.88±0.324	39.89±0.617
20	45.17±0.641	56.94±0.524
30	57.09±0.926	67.39±0.321
40	65.21±0.741	74.61±0.924
50	78.09±0.364	83.27±0.751
60	87.06±0.951	92.17±0.624

D. R. Powar, A. V. Desai, V. Y. Rohile, M. V. Bhosale, N. R. Inamdar, "Design Development and Optimization of Telmisartan's Ternary Solid Dispersion with Its Formulation," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 6, Issue 1, pp. 21-31, 2022.

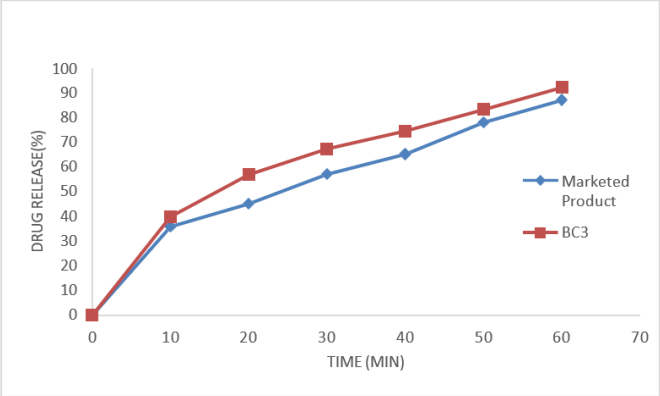


Fig. 19 Dissolution study of prepared tablet of batch F8 of BC3 and marketed product 40 mg

According to the aforementioned graphs, SD formulation and commercial product showed an increasing trend in the dissolving profile of TMS when the pH of the medium increased. According to observations, the amounts of medication released from the SD after 60 min at pH 6.8 for batch BC3 and commercial product, respectively, were 92.17% and 87.06%. The greater modulation of the drug supplied by the solubilizer, the smaller particle size, the better wettability, and the solubilization impact of the carrier may be the causes of the improvements in dissolution rate at higher pH. As a result, it was determined that SD increased the rate of TMS dissolution that was poorly water-soluble. The optimized batch of amorphous powder was stored at 40^0C±2°C/75 ±5% RH for 1 month in a stability chamber and the effects of storage condition on the preparation were studied by Drug content & In vitro dissolution studies.

Experimental Study.

% Drug content after stability

Stability study of optimized batches carried out as per ICH guidelines for safe, stable and effective dosage forms,at temperature 40^0C /75%RH for 1 month.

Table 23 % Drug content of Stability batches reading at 40^0C for 0 months & 1month.

Period	% Drug Content
	Batch BC3
0 Month	98.68%
1 Month	91.83%

From the present work of stability study, it was observed that, stored tablet has not shown so much change in the percentage of drug content. Thus, the tablet was stable over the period ofone month at accelerated storage conditions.

IV. CONCLUSION

The goal of this research was to increase Telmisartan's solubility, rate of dissolution, and extent of dissolution. The increase in surface area has resulted in a small rise in the solubility of TMS particles. The amount and rate of the medicine Telmisartan's minor water solubility have been slightly improved by the SD powder. Additionally, the compressibility and flowability also increased. According to the research, the introduction of an absorbent carrier increased the surface area of Telmisartan, which led to an increase in solubility with an increase in dissolution rate.

This study used the solvent evaporation approach to successfully create a new SD of TMS that is poorly water-soluble but is ionizable. The final, ideal formulation had TMS, magnesium oxide, and neusilin with a weight ratio of 1/0.5/1 taking alkalizer into account. TMS/PVP K30/Neusilin were combined in Solubilizer's optimal formulation at a weight ratio of 1/2/1. TMS-loaded SD, in contrast to other typical SD systems, uses substantially less organic solvent and a lower carrier to drug ratio, which has several positive economic and environmental effects. Additionally, TMS-loaded SD produced a markedly larger drug release than TMS powder or commercial products, indicating improved oral bioavailability.

REFERENCE

1. Sekiguchi K., Obi.N; Studies on absorption of eutectic mixtures: A comparison of the behaviour of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man; Chem. Pharm. Bull; 1961; 9;866–872
2. Singh et al; A review on solid dispersion; IJPLS; 2011; 2(9);1078-1095
3. B Kapoor; Kaur, R Kour; S Behl; H Kour; S. *Int J Recent Advances in PharmRes*., 2012, 2(2),1-16.
4. T Tachibana; NA Nakamaru. *Kolloid Z- Polymer*., 1965, 203,130-133.
5. D Sharma; M Soni; S Kumar; GD Gupta. *Research J. Pharm Tech*., 2009, 2(2),220-224.
6. Mladen Milovi, Jelena Djuri, Ljiljana Djeki, Dragana Vasiljevi, Svetlana Ibric. Characterization and evaluation of solid self-micro emulsifying drug delivery systems with porous carriers as systems for improved carbamazepine release. IntJ Pharm 2012; 436:58–65.
7. M Bi; SJ Hwang; KR Morris. *Thermo ChimicaActa*., 2003, 404,213-226.
8. S.G Avula; K Alexander; A Riga. *J thermal analysis calorimetry*.,2010,99,655-658.
9. Huda N.H., Saffoon N., Sutradhar K.B., Uddin R; Enhancement of Oral Bioavailability and Solid Dispersion: A Review; Journal of Applied Pharm Sci;2011; 1;13-20.
10. Dixit AK., Singh RP; solid dispersion – A strategy for improving the solubility of poorly soluble drugs; IJRPBS; 2012; 3(2);960-966.
11. Jain C.P., Sharma A; Solid dispersion: A promising technique to enhancesolubility of poorly water soluble drug; Int. J of Drug Delivery; 2011; 3;149- 170.
12. praveenkumar; solid dispersion – A review; Journal of pharmaceutical and scientific innovation; 2012; 1(3); 27-34 Dixit AK., Singh RP; solid dispersion – A strategy for improving the solubility of poorly soluble drugs; IJRPBS; 2012; 3(2);960-96
13. S Patro; AA Choudhary. *Ind J Pharm Sci*., 2005, 67,334-341.
14. A Karatas; Y Nilufer; T Baykara. *IL Farmaco*.,2005, 60,777-782.
15. Navnit Shah, Harpreet Sandhu, Wantane Phuapradit, Rodolfo Pinal, RamanIyer, Antonio Albano, Ashish Chatterji, Shalini Anand, Duk Soon Choi,Kin Tanga, Hung Tian .Development of novel microprecipitated bulk powder (MBP) technology for manufacturing stable amorphous formulations of poorly soluble drugs. Int J Pharm 2012; 438:53– 60.
16. Yohei Kawabata, Koichi Wada, Manabu Nakatan, Shizuo Yamada, Satomi Onoue. Mini review on Formulation design for poorly water-soluble drugs based on Biopharmaceutics classification system: Basic approaches and practical applications. Int J Pharm 2013; 420:1– 10.
17. T Vasconcelos; BP Sarmanto Costa. *J Pharm Sci*., 2007, 12,1068-1075.
18. Peng Zhang, Johan Forsgren, Maria Stromm. Stabilization of amorphous ibuprofen in Upsalite a mesoporous magnesium carbonate, as an approach to increasing the aqueous solubility of poorly soluble drugs. Int J Pharm 2014; 472:185–191.
19. Hiroshi Miura a, Makoto Kanebako a , Hiroyuki Shirai a , Hiroshi Nakao a , Toshio Inagi a , Katsuhide Terada. Enhancement of dissolution rate and oral absorption of a poorly water-soluble drug, K-832, by adsorption onto porous silica using supercritical carbon dioxide. European Journal of Pharmaceutics and Biopharmaceutics 76 (2010) 215.

20. M Vasanthavada; WQ Tong; Y Joshi; MS Kislalioglu. *Pharm Res.*, 2004,21(9),1598-1606.
21. Peng Zhang, Johan Forsgren, Maria Stromm. Stabilization of amorphous ibuprofen in Upsalite a mesoporous magnesium carbonate, as an approach to increasing the aqueous solubility of poorly soluble drugs. Int J Pharm 2014; 472:185–191.
22. Navnit Shah, Harpreet Sandhu, Wantane Phuapradit, Rodolfo Pinal, Raman Iyer, Antonio Albano, Ashish Chatterji, Shalini Anand, Duk Soon Choi, Kin Tanga, Hung Tian. Development of novel microprecipitated bulk powder (MBP) technology for manufacturing stable amorphous formulations ofpoorly soluble drugs.Int J Pharm 2012; 438:53– 60.
23. Yohei Kawabata, Koichi Wada, Manabu Nakatan, Shizuo Yamada, Satomi Onoue. Mini review on Formulation design for poorly water-soluble drugs based on Biopharmaceutics classification system: Basic approaches and practical applications. Int J Pharm 2013; 420:1– 10.
24. Mladen Milovi, Jelena Djuri, Ljiljana Djeki, Dragana Vasiljevi, Svetlana Ibric. Characterization and evaluation of solid self-micro emulsifying drug delivery systems with porous carriers as systems for improved carbamazepine release. Int J Pharm 2012; 436:58– 65.
25. Riikka Laitinena, Korbinian Lobmanna, Clare Strachana, Holger Grohganz, Thomas Rades. Review on Emerging trends in the stabilization of amorphous drugs. Int J Pharm 2013; 453:65– 79.
26. Aled D. Roberts, Haifei Zhang. Pharmaceutical nanotechnology poorly water- soluble drug nanoparticles via solvent evaporation in water-soluble porouspolymers. Int J Pharm 2013; 447:241– 250.
27. Toshiyuki Niwa, Hiroko Shimabara, Masahiro Kondo, Kazumi Danjoet. Design of porous microparticles with single-micron size by novel spray freeze- drying technique using four-fluid nozzle. Int J Pharm 2013; 382: 88–97.
28. Dinesh Kumar, S.V. Sailaja Chirravuri, Nalini R. Shastri. Impact of surface area of silica particles on dissolution rate and oral bioavailability of poorly water soluble drugs: A case study with aceclofenac. Int J Pharm 2014; 461:459– 468.
29. Nirmal Marasini, Tuan, Bijay, Hyuk, Fabrication and evaluation of pH-modulated solid dispersion for telmisartan by spray-drying technique, International Journal of Pharmaceutics,2012: 426-432.
30. Choon Lian Ng, Sang-Eun, Joon-Kyung, Tae-Hyeon, Solubilization and formulation of chrysosplenol C in solid dispersion with hydrophilic carriers, International Journal of Pharmaceutics,2016:314-321.
31. Jin-Seok Choi, Jeong-Sook Park, Design of PVP/VA S-630 based tadalafil solid dispersion to enhance the dissolution rate, European Journal ofPharmaceutical Sciences,2016:1-30.
32. Ha, N.S., Tran, T.T., Tran, P.H., Park, J.B., Lee, B.J., 2011. Dissolution-enhancing mechanism of alkalizers in poloxamer-based solid dispersions and physical mixtures containing poorly water-soluble valsartan. Chem. Pharm.Bull. (Tokyo) 59:844–850.
33. Li, J., Liu, P., Liu, J.P., Zhang, W.L., Yang, J.K., Fan, Y.Q., 2012a. Novel Tanshinone IIA ternary solid dispersion pellets prepared by a single-step technique: in vitro and in vivo evaluation. Eur. J. Pharm. Biopharm. 80, 426– 432.
34. Craig, D.Q.M., 2002. The mechanisms of drug release from solid dispersionsin water soluble polymers. Int. J. Pharm. 231, 131–144.
35. Hao, K., Chen, Y.C., Cao, Y.G., Yu, D., Liu, X.Q., Wang, G.J., 2007.
36. Pharmacokinetic–pharmacodynamic modeling of TMS using an indirect response model in spontaneously hypertensive rats. Acta. Pharmacol. Sin 28, 738–743.
37. Janssens, S., Van den Mooter, G., 2009. Review: physical chemistry of solid dispersions.J. Pharm. Pharmacol. 61, 1571–1586.
38. Peng Zhang, Johan Forsgren, Maria Stromm. Stabilization of amorphous ibuprofen in Upsalite a mesoporous magnesium carbonate, as an approach to increasing the aqueous solubility of poorly soluble drugs. Int J Pharm 2014; 472:185–191.
39. Martins, R.M., Siqueira, S., Tacon, L.A., Freitas, L.A.P., 2012. Microstructured ternary solid dispersions to improve carbamazepine e solubility. Powder Technol. 2012(215–216), 156–165.
40. Dinesh Kumar, S.V. Sailaja Chirravuri, Nalini R. Shastri. Impact of surface area of silica particles on dissolution rate and oral bioavailability of poorly water-soluble drugs: A case study with aceclofenac. Int J Pharm 2014; 461:459– 468.
41. Pallavi Bassi, Gurpreet Kaur, pH modulation: a mechanism to obtain pH-independent drug release, Expert Opin. Drug Deliv.2010,845-857.
42. Nam Sung, Thao Truong, Phuong Ha, Jun-Bom, Dissolution-Enhancing Mechanism of Alkalizers in Poloxamer-Based Solid Dispersions and Physical Mixtures Containing Poorly Water-SolubleValsartan, *Chem. Pharm. Bull.2011* 844—850
43. Kumar K. V., Arunkumar N., Verma P. R. P., Rani C., Int. J. Pharm-Tech. Res2009., 431—437.
44. Mingda Bi, Ali Kyad, Fernando Alvarez-Nunez,1and Francisco Alvarez, Enhancing and Sustaining AMG 009 Dissolution from a Bilayer Oral Solid Dosage Form via Microenvironmental pH Modulation and Supersaturation, AAPS Pharm Sci Tech, Vol. 12, No. 4, December 2011,1401-1406
45. L A. Nikghalb, G. Singh, Gaurav Singh and K. F. Kahkeshan, Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs, Journal of Applied Pharmaceutical Science Vol. 2 (10), pp. 170-175, October, 2012