Research Article

Preparation and Evaluation of Telmisartan Solid Dispersion Using Skimmed Milk

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ABSTRACT

Telmisartan is Angiotensin II Receptor Antagonist, belongs to class II drug in BCS classification i.e. low solubility and high permeability. To improve aqueous solubility of drug and its dissolution rate, solid dispersion with skimmed milk was prepared by solvent evaporation and spray drying method. No chemical interaction was observed between Telmisartan and skimmed milk, indicated by FT-IR studies. Twelve different formulations were prepared by different methods with varying drug: carrier ratios viz.1:1- 1:3.5 and the corresponding physical mixtures were also prepared. The formulations were characterized for solubility parameters, drug release studies and drug-polymer interactions by using phase solubility studies, dissolution studies; XRD analysis, After comparison of solubility and dissolution profile it was found that solid dispersions such as TMS:SD_{SD5} showed desired dissolution profile of Telmisartan in terms of % cumulative release i.e. 84.10% and 90.70% respectively. Reduction in crystallinity was indicated by XRD studies due to less number presence of peaks in XRD pattern.

Key words: Telmisartan, skimmed milk, spray drying, aqueous solubility.

INTRODUCTION

The solubility behaviour of a drug is a key determinant of its oral bioavailability. Insufficient solubility has presented a challenge to the development of a suitable formulation for oral administration of many drugs[1].Aqueous solubility of a drug can be used as first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and hence suffer oral bioavailability problems[2]. So if the solubility of the drug is less than desirable, steps are to be taken to improve its solubility. There have been numerous reports of the work done for the improvement of the solubility and dissolution behaviour of drugs[3]. Several techniques have been developed concerning the optimization of the dissolution rate of poorly water-soluble drugs. Such methods include particle size reduction, solubilisation, salt formation etc., but there are several disadvantages and limitations in use of these techniques[4].

The solid dispersion technique for water insoluble drugs developed by Chiou and Reigelman provides an efficient method to improve the dissolution rate of a drug[5]. Solid dispersions can be prepared by various methods depending on the conditions and need like Melting method, Solvent evaporation method, Melting solvent method, Supercritical fluid process, Kneading method, Freeze drying etc.[6-7]. Solid dispersion are classified on the basis of their release mechanism into two major types, i.e. Sustained release type solid dispersion &Fast release type solid dispersion. Characterization of Solid Dispersion by Thermal analysis i.e. Cooling curve method, Thermo microscopic method, Differential thermal analysis, Differential scanning calorimetry; X-ray diffraction method; Spectroscopic method; Microscopic method. Drug dissolution is the dynamic process by which solid material is dissolved in a solvent and solubility describes an equilibrium state where the maximal amount of drug per volume unit is dissolved[8, 9]. Solid dispersion of drug in proper carriers is the most promising approach for enhancing solubility because of the fact that, drug as a molecular or near to molecular dispersion thus giving the both benefits of a local increase in its solubility (within the solid solution) and offering the maximum surface area. Telmisartan is Angiotensin II Receptor Antagonist, which is used in the prevention and treatment of Hypertension.Telmisartan belongs to class II drug in BCS classification i.e. low solubility and high permeability. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. The solubility of

Telmisartan in aqueous medium was very low i.e. 0.078 mg/ml in water. Absolute bioavailability of the Telmisartan was 42-58% and biological half-life is only 24 hours that results into poor bioavailability after oral administration. Poor solubility of Telmisartan leads to poor dissolution and hence variation in bioavailability. Thus increasing aqueous solubility and dissolution of Telmisartan is of therapeutic importance.[10]

MATERIALS AND METHODS

MATERIALS

Telmisartan was obtained as a gift sample from Verdant life sci. Pvt. Ltd. Skimmed Milk obtained from Nestle India Ltd., All the reagents and materials were of analytical or pharmacopoeia grade.

Preparation of Solid dispersion[11]

The solid dispersion of drug and polymers were prepared by two methods.

Solvent evaporation method-

Telmisartan and skimmed milk are were weighed accurately in the ratio of 1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5 and triturated in a morter pestle for 5 minutes and then were dissolved in 1 ml of methanol with constant titration. Solvent was evaporated at 40^0c and dried in a desicator for 4 hrs and pass through sieve no 80.

Table 1: Preparation of Solid dispersion by different method.

Solvent evaporation method		Spray drying method	
Batches	**Drug: Polymer ratio**	**Batches**	**Drug: Polymer ratio**
$TMS:SM_{SD1}$	1:1	$TMS:SM_{SD7}$	1:1
$TMS:SM_{SD2}$	1:1.5	$TMS:SM_{SD8}$	1:1.5
$TMS:SM_{SD3}$	1:2	$TMS:SM_{SD9}$	1:2
$TMS:SM_{SD4}$	1:2.5	$TMS:SM_{SD10}$	1:2.5
$TMS:SM_{DS5}$	1:3	$TMS:SM_{DS11}$	1:3
$TMS:SM_{SD6}$	1:3.5	$TMS:SM_{SD12}$	1:3.5

Spray drying method

Telmisartan and skimmed milk powder were dissolved in chloroform (1%w/v) six different ratios of drug: carrier from 1:1,1:1.5,1:2,1:2.5,1:3,1:3.5 were prepared and correspondingly the batches were named as $TMS\text{-}SM_{SD1}$ upto $TMS\text{-}SM_{SD6}$ the clear solution were spray dried using a spray dryer (labultima,LU-222,Mumbai,india) The operating parameters like inlet & outlet temperature were 120^0 c and 100^0 c respectively whereas inlet and outlet high were at 160^0c and 140^0 c. Aspirator flow rate was kept at 30 Nm^3/hr. and feed pump speed was 1 ml/min. Spray–dried products were obtained as free flowing off–white powders.

Evaluation of Solid Dispersions

Phase Solubility Studies[12]

The Phase Solubility Studies were carried out according to Higuchi and Connors and the known amount of drug was added to the different concentrations of polymers for 1-5% w/v respectively and the vials were equilibrated until 24 hrs of centrifugation Orbital shaking incubator (CIS-24, Remi International) and then filtered using Whatman filter paper (0.45µ) and suitably diluted and analyzed using UV spectrophotometer (LAB INDIA UV 3000+) at 296 nm in triplicate.

Determination of Percentage Yield[13]

Percentage practical yields of all the formulations were calculated to know about percent yield or efficiency of the method chosen for the formulations. The formed solid dispersions were collected and weighed to determine the respective practical yields (PY) and Percentage yields were determined

Determination of Drug Content[14]

The drug content was calculated by dissolving drug, physical mixtures and solid dispersion equivalent to 10 mg in a 100 ml volumetric flask with minimum quantity of methanol and volume was made up to the mark with phosphate buffer pH 7.4. The solution was filtered through 0.45µ filter membrane and assayed further by using UV double beam (Lab India UV3000+) spectrophotometer at 275 nm. Three replicates were prepared, and the average drug contents were estimated in the prepared solid dispersion.

In-Vitro Dissolution Studies[15]

The Dissolution of pure drug and SDs were carried out by using USP XXIV Apparatus 2 (paddle) method. The dissolution media 0.1 N HCL, paddle speed 50 RPM, UV analysis was done at 296 nm. 10 ml of aliquots were collected periodically and replaced with fresh dissolution medium. Aliquots, after filtration through Whatman filter paper (No. 41), were analyzed at 296 nm by UV double beam (Lab India UV3000+). The samples were wrapped in muslin cloth and cumulative releases were calculated by using PCP-Disso Software-V2.08 and dissolution data of Telmisartan & SDs.

FTIR STUDIES

The Pure drug Telmisartan (TS), Polymer Skimmed milk (SM) and their mixtures were mixed separately with IR grade KBr in the ratio of 1:300 in mortar and pestle and placed in metallic superceeds by pressing with metallic rod and pellets were obtained. The pellets were individually prepared for drug and polymers and were scanned over a wave number range of 4000 to 400 cm^{-1} by Diffuse Reflectance System in FTIR instrument Shimadzu, Japan (IR Affinity -1).[16,17]

X-Ray Diffraction studies[18]

The X-ray diffractograms were taken for the physical mixtures and the solid dispersions. X-ray diffractograms were obtained using the X-ray diffractometer Philips diffractometer (PW 1729) and Cu-kα radiation, diffractograms were run at a scanning speed of 2°/mm and a chart speed of 2°/2 cm per 2ø.

Accelerated Stability Studies[19]

Stability study of formulation was carried out to point out any visual physical or chemical changes made in the formulation after storing it at elevated temperature and humidity conditions. Chemical and physical stability of SDs formulation was assessed at 40 ± 2 °C and 75 ± 5% RH as per ICH Guidelines. SDs formulation was filled in sealed vial with aluminum foil and stored for 3 month in stability chamber (CIS-24 REMI Instruments Ltd, India). Samples were analyzed for physical parameters and drug content during time period of 3 months.

RESULT AND DISCUSSION

Phase Solubility Studies

The phase solubility data according to Higuchi and Connor was showed below and based on the data the selection of the ratios for final formulations was done. The criterion observed was increment of drug solubility with polymer concentration.

Table 2: Effect of Concentrations of SM on Solubility of Telmisartan by solvent evaporation method

Concentration of SM (% w/v)	Concentration of Telmisartan (µg/ml) at 37 °C	Concentration of SM (% w/v)	Concentration of Telmisartan (µg/ml) at 37 °C
SD_1 (0)	27.61±0.810	SD_7 (0)	25.53
SD_2 (1)	29.88±0.473	SD_8 (1)	28.43
SD_3 (2)	33.27±0.512	SD_9 (2)	32.57
SD_4 (3)	36.54±1.452	SD_{10} (3)	36.19
SD_5 (4)	41.43±0.991	SD_{11} (4)	40.52
SD_6 (5)	49.44±0.775	SD_{12} (5)	47.93

The trial ratios were selected and evaluated for phase solubility studies. From Table No. 2 it was seen that solubility of telmisartan was increased up to 2.07 folds in case of 1.79 folds in case of SM. The phase solubility was found to be linear in a wide range of polymer concentrations and best results were obtained in case of SM.

Percentage yield

The Percentage yields of various formulations of solid dispersions were determined and it was observed that solvent evaporation method yielded higher % yields than Spray drying. The highest yield was observed in TMS: SM_{SD6}.

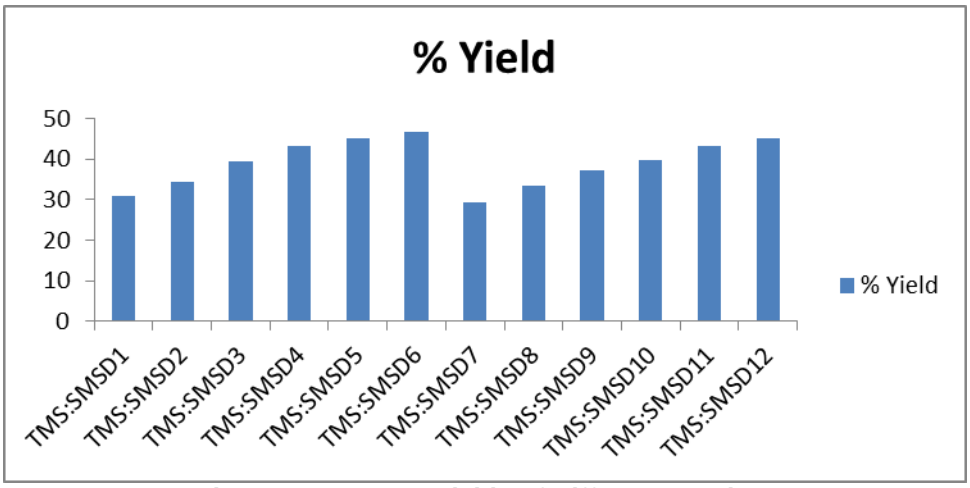

Fig. 1: Percentage Yields of Different Batches

Drug Content

The solid dispersions or physical mixtures equivalent to 10 mg of Telmisartan were used to determined drug content. The drug content of solid dispersions and physical mixtures was found to be in range of 93.51% showed below.

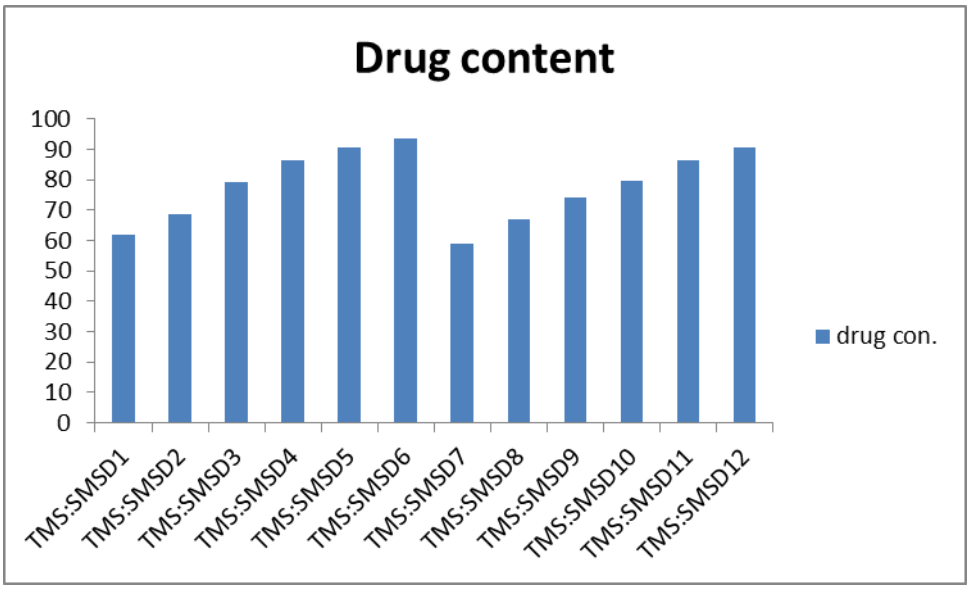

Fig. 2: Drug content of Different Batches

In-Vitro Dissolution Studies

Telmisartan solid dispersions presented better dissolution performance over corresponding physical mixtures and the pure drug. It may be due to an improved wettability of drug particles, a significant reduction in particle size during the formation of solid dispersion, and the intrinsically higher rate of dissolution of the soluble polymer component of the solid dispersion. The PMs of Telmisartan with SM showed a marked increase in the cumulative % drug release from 8.03 to 61.90% whereas SDs showed increase from 18.38 to 84.10%.

Table 3: *In-vitro* Dissolution Profile of Solid Dispersions of TMS, in 0.1 N HCL

Sr.No	Batches	Cumulative % Release at Different Time Intervals in min*							
		15	30	45	60	90	120	150	180
1	TMS	1.135 ±0.45	3.143 ±0.53	4.871 ±0.62	6.443 ±0.92	14.12 ±0.69	17.02 ±0.34	20.25 ±0.59	27.71 ±0.42
2	TMS:SM_{SD1}	8.16 ±0.38	9.98 ±0.36	12.27 ±0.44	15.46 ±0.80	19.90 ±0.43	23.70 ±0.34	25.35 ±0.45	33.67 ±0.42
3	TMS:SM_{SD2}	18.38 ±0.36	20.92 ±0.54	22.21 ±0.18	25.83 ±0.52	28.23 ±0.55	33.88 ±0.34	36.20 ±0.35	39.27 ±0.17
4	TMS:SM_{SD3}	25.23 ±0.38	28.89 ±0.68	32.85 ±0.44	34.98 ±0.61	39.95 ±0.61	42.63 ±0.69	43.81 ±0.42	45.01 ±0.58
5	TMS:SM_{SD4}	35.40 ±0.38	38.34 ±0.47	39.61 ±0.44	40.38 ±0.36	43.41 ±0.36	47.09 ±0.51	51.55 ±0.51	56.06 ±0.76
6	TMS:SM_{SD5}	40.84 ±0.45	42.69 ±0.54	44.67 ±0.35	46.85 ±0.53	48.65 ±0.78	51.77 ±0.34	56.75 ±0.35	60.42 ±0.51
7	TMS:SM_{SD6}	44.97±0 .21	46.69±0 .27	48.32±0 .64	51.75±0 .37	53.87±0 .39	56.74 ±0.47	61.11 ±0.12	64.88 ±0.26
8	TMS:SM_{SD7}	20.01 ±0.48	22.16 ±0.63	24.09 ±0.54	26.56 ±0.79	28.10 ±0.61	30.95 ±0.61	33.51 ±1.18	38.87 ±0.84
9	TMS:SM_{SD8}	22.95 ±0.63	25.26 ±0.57	29.38 ±0.73	32.12 ±1.22	33.34 ±1.21	36.37 ±1.28	41.96 ±0.59	48.67 ±0.84
10	TMS:SM_{SD9}	24.70 ±0.65	25.37 ±0.27	27.21 ±0.57	29.74 ±0.44	31.07 ±0.95	47.34 ±0.51	51.16 ±0.67	57.37 ±0.44
11	TMS:SM_{SD10}	40.86 ±0.65	43.95 ±0.71	48.38 ±0.44	52.42 ±0.82	55.05 ±0.53	59.41 ±0.71	64.77 ±0.67	71.85 ±0.76
12	TMS:SM_{SD11}	48.77 ±0.45	53.40 ±0.63	56.20 ±0.67	62.92 ±0.44	66.70 ±0.43	71.13 ±0.51	77.27 ±0.76	81.60 ±0.92
13	TMS:SM_{SD12}	54.97 ±0.31	61.69 ±0.17	66.32 ±0.64	70.75 ±0.37	75.87 ±0.69	82.74 ±0.47	89.11 ±0.22	92.88 ±0.34

Effect of Concentration of Carrier on Dissolution Rate of Telmisartan

As examined in all cases, the increase in weight fraction of the polymer significantly increased the rate and extent of drug dissolution. All the PMs showed increased dissolution profiles as compared to Telmisartan and SDs showed remarkable increase overall. Amongst all of the batches, SM shows best dissolution profile in 0.1 N HCL with highest % Cumulative drug release of 90.70±0.84 % at t_{180} mins as compared to Telmisartan which showed only 27.71±0.42 % release. The possible reasons for this trend include facilitation of Telmisartan dissolutions by dissolved amounts of the carrier and a decrease in the particle size of the drug in the carrier, with an increase in carrier concentration.

Effect of the Type of Polymer used on Dissolution Rate of Telmisartan

It was clearly understood that Solid dispersions of Telmisartan prepared with SM showed better dissolution profiles.

Effect of Different Methods of Preparation

Solid dispersions of Telmisartan were prepared with Skimmed milk powder by Spray drying and Solvent evaporation method. It is clearly indicated that SDs formulated by Solvent evaporation method exhibited better dissolution profiles than Spray drying method. The reason attributed to reduction in particle size and thereby increasing the surface area for dissolution.

FTIR Studies

The FT-IR spectra of the pure Telmisartan and physical mixture of drug and polymers were recorded. The characteristic peaks of Telmisartan were appeared, some were shifted slightly, and some disappeared due to the formation of complex with polymers. It indicated that there was no chemical interaction between Telmisartan and polymers.

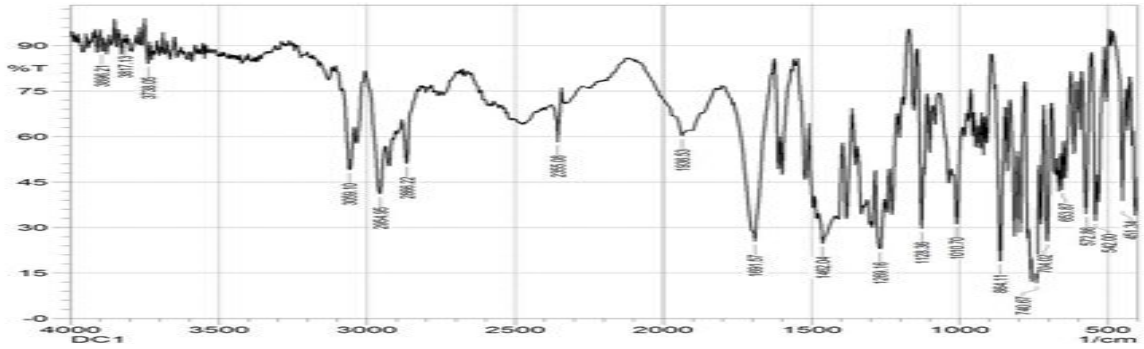

Fig. 3: FTIR Spectrum of Telmisartan

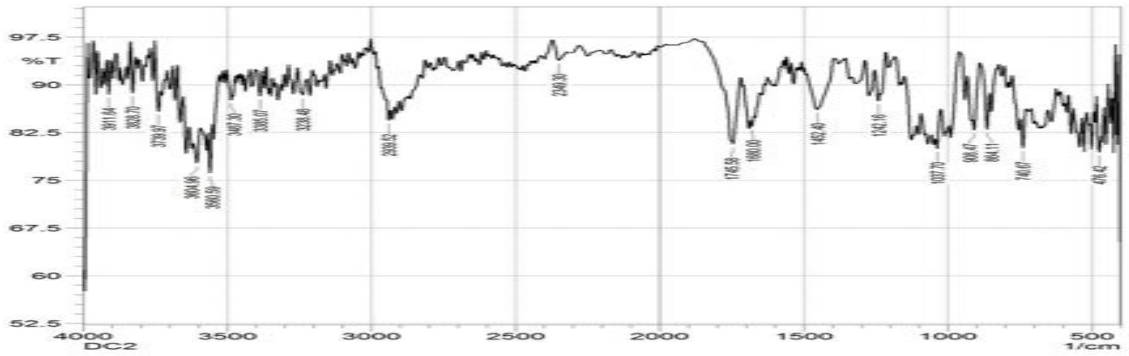

Fig. 4: FTIR Spectrum of SM

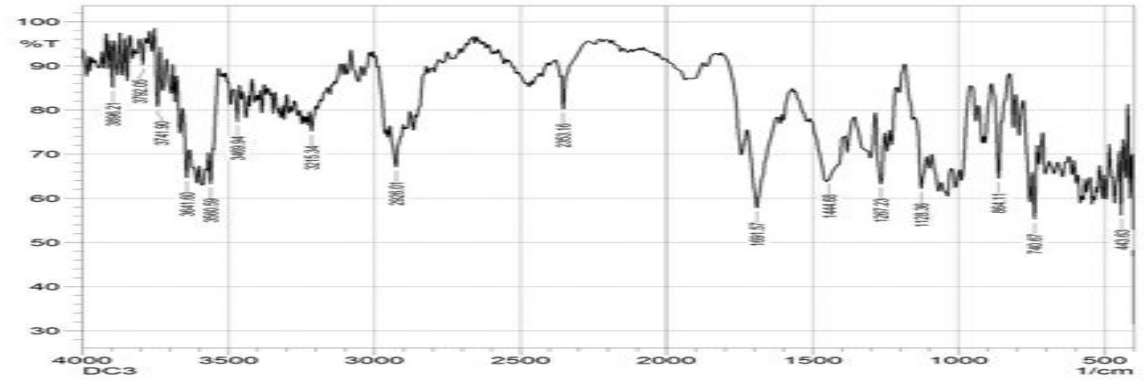

Fig. 5: FTIR Spectrum of Physical Mixture of TMS:SM

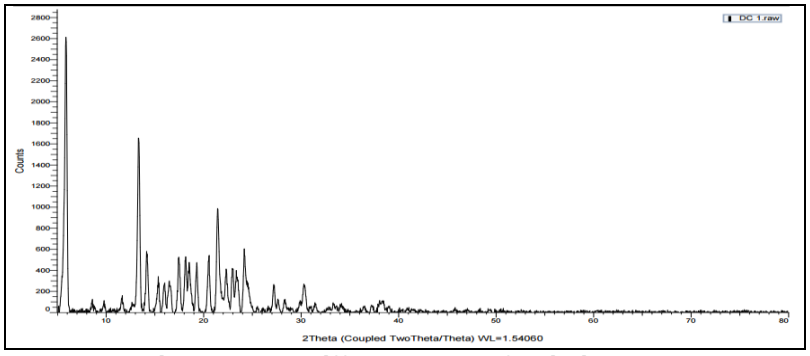

Fig. 6: X-ray-Diffractogram of Telmisartan

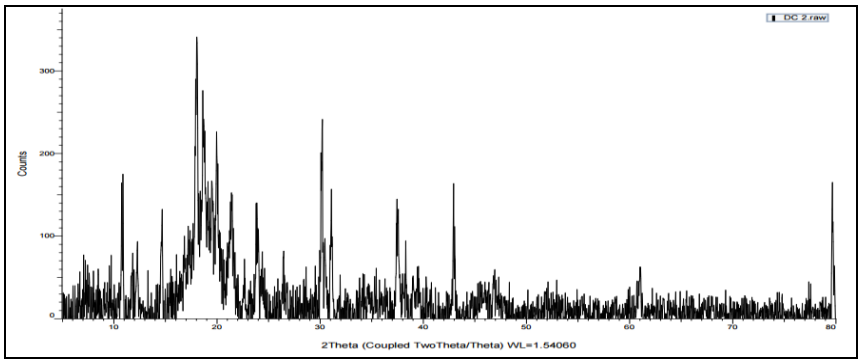

Fig. 7: X-ray-Diffractogram of SM

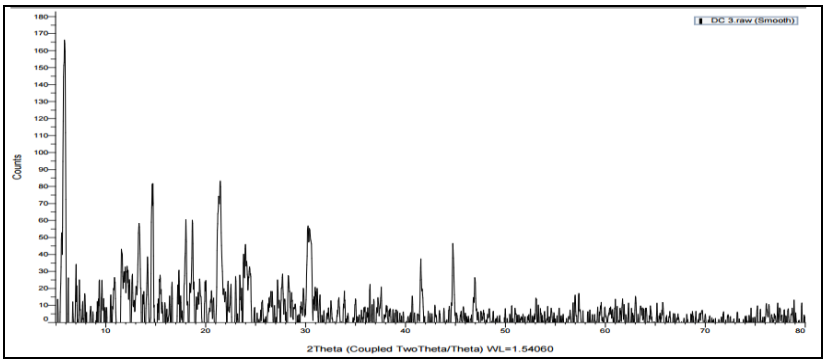

Fig. 8: X-ray-Diffractogram of Physical Mixture of TMS: SM

Accelerated Stability Studies

The Solid Dispersions TMS:SM_{SD6}, TMS:SM_{SD12}, were subjected to stability studies as per ICH guidelines Various physical parameters (appearance, color change and grittiness) and drug content were measured of stability. Result of Accelerated Stability Studies showed there was no significant change in parameters after stability studies. Thus it can be proved from stability studies that the prepared SDs is stable and not much affected by elevated humidity and temperature condition.

Table No 4: Stability Studies of SDs

Days	Drug Content	
	TMS:SM_{SD6}	MS:SM_{SD12}
0	99.50± 0.23	100.31± 1.21
30	98.85± 0.31	98.70± 0.54
60	97.86± 0.72	97.86± 0.56
90	97.25± 0.98	97.15±1.42

(n = 3)

CONCLUSION

From the above study it was concluded that by using the skimmed milk the solid dispersion can be prepared to enhance the solubility of insoluble drug to increase the bioavailability. Also the solid dispersion prepared by using skimmed milk was stable for a period of 60 days.

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