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RESEARCH ARTICLE
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SOLID DISPERSION TECHNIQUE TO ENHANCE THE SOLUBILITY AND BIOAVAILABILITY OF TELMISARTAN AND HYDROCHLOROTHIAZIDE

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Abstract

Objectives: The main objective of the present investigation to develop and evaluate solid dispersions of BCS Class II drugs Telmisartan and hydrochlorothiazide employing various polymers, compatible with conventional manufacturing method to enhance solubility of poorly soluble drugs.

Materials and Methods: In this study, Telmisartan and hydrochlorothiazide solid dispersion were prepared using *PEG 6000 and Gelucire 50/13* by solvent evaporation method. Solid dispersions and pure Telmisartan in the form of powder were characterized in comparison with pure drug and corresponding physical mixtures in the same ratios by Fourier transform infrared spectroscopy, differential scanning calorimetry (DSC), powder X-ray diffractogram, and in vitro drug release.

Results: SD formulation of both drug Telmisartan and hydrochlorothiazide was prepared by using two different carrier like PEG 6000 and Gelucire 50/13 in 1:1, 1:3, 1:5 and 1:7 drug to polymer ratio by solvent evaporation method & selected for characterization. The DSC study indicated that the crystalline nature of Telmisartan and hydrochlorothiazide was reduced to amorphous. The diffraction pattern of the solid dispersions in each figure indicates that diffraction peaks at 2ɵ values has less intensity than that of pure drugs. This indicated that the crystalline nature of drug sample was converted to amorphous. Scanning electron microscope photographs of solid dispersion seem to be more porous in nature. From the in vitro drug release profile, it can be seen that formulation PSD3 shows higher dissolution rate i.e. 97.54±2.87% compared with other formulations. It is predicted that, increasing concentration of carrier, increases the drug dissolution rate.\

Conclusion: This study has shown that the solid dispersion of Telmisartan and hydrochlorothiazide using carrier can be promising formulation for solubility and dissolution enhancement. Synthetic polymers used have shown promising results in the modification of drug release from the formulations.

Keywords: Telmisartan and hydrochlorothiazide, solid dispersions, PEG 6000 and Gelucire 50/13

1 INTRODUCTION:

Poorly water-soluble drugs are expected to have dissolution limited absorption. Increasing drug

solubility may contribute substantially to improved drug absorption and consequently drug bioavailability. There are several pharmaceutical strategies available to improve the aqueous solubility of poorly soluble drugs: solid dispersion, solubilization using surfactants, the use of cosolvents, reduction of particle size, hydrotrophy, and the use of aqueous soluble derivative or salts.1,2 Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs.3 One aspect of solid dispersion technology on which most researchers in the field would agree is that the number of marketed products arising from this approach has been disappointing. Indeed, the sheer simplicity of the manufacturing method, the fact that in general only the drug and carrier are required, and the frequently reported improvements in both the dissolution rate and bioavailability would lead one to expect that the transfer to the marketplace would be rapid and widespread. Research for alternative carriers has been increasing to suit the industrial applications as well as to reduce the production cost and toxic effects.

Telmisartan is an angiotensin II receptor blocker (ARB) used in the treatment of hypertension. Generally, angiotensin II receptor blockers (ARBs) such as Telmisartan bind to the angiotensin II type one (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, which leads to a reduction in arterial blood pressure(1). Telmisartan is 2-(4-{[4-methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol 1yl]methyl } phenyl) benzoic acid (figure 1). Studies show that Telmisartan is a partial agonist of PPAR-γ, which is an established target for diabetic persons. This suggests that Telmisartan can improve carbohydrate and lipid metabolism, as well as control insulin resistance without causing the side effects that are associated with full PPAR-γ activators. The absolute bioavailability of Telmisartan is dose- dependent. The bioavailability of Telmisartan increased from 42% to 58%, when the dose was increased from 40 mg to 140 mg respectively[1].The solid dispersion approach can be successfully used in the improvement of solubility of poorly water soluble drugs. Telmisartan has a long duration of action, and has the longest half-life of any ARB (24 hours). The usually effective dose of Telmisartan is 20, 40, 80 mg once daily. In cases where the target blood pressure is not achieved, Telmisartan dose can be increased to a maximum of 80 mg once daily. The pharmacokinetics of orally administered Telmisartan is nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. Telmisartan is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base. The Telmisartan molecule is unusually stable Telmisartan is manufactured and supplied in the free acid form and is has a very poor solubility, and so low bioavailability (~42%). So, in order to enhance oral bioavailability, solubility enhancement can be achieved via solid dispersion formation by using hydrophilic polymers and physical modifications by micronization , cyclodextrin complexation, micellization

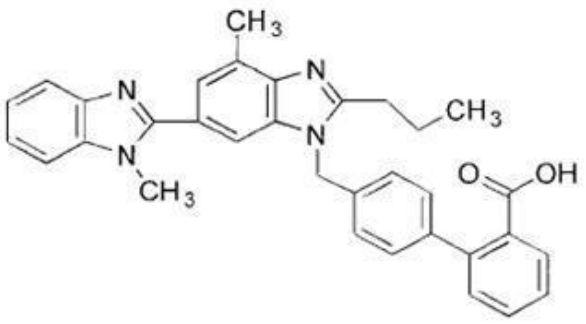

Figure no 1: Structure of Telmisartan

nanoparticle formation and solid dispersion of these methods, the solid dispersion (SD) technique has been widely employed to improve the aqueous solubility and the dissolution rate of poorly

water-soluble drugs. In the present study solvent evaporation method had been used to prepare the solid dispersions. Physical mixture of drug Telmisartan and hydrochlorothiazide was prepared with hydrophilic carrier PEG 6000 and Gelucire 50/13.

2 Materials and Methods

Materials

Depending on the availability and suitability Telmisartan & Hydrochlorothiazide was obtained as a gift sample from Mecleods Pharmaceuticals Ltd, Mumbai. PEG 6000 and Gelucire 50/13 was purchased from Central Drug House Pvt. Ltd., New Delhi, India. All other chemicals and reagents were of analytical grade.

PREFORMULATION STUDY OF SELECTED DRUG

1. Drug Authentication

1.1 Determination of Drug Absorption Maxima (λmax)

Drug absorption maximum was determined by UV spectroscopy. Drug sample of 10 µg/ml solution was scan in the range of 200-400 nm and absorption maxima was recorded.

1.2 Determination of melting point

The capillary method was used to determine the melting temperature of selected drug. The melting point of drug Telmisartan was found to be in range of 266 to 268^{0}C, while melting point of drug hydrochlorothiazide was found in the range of 268 to 270^{0}C, which were furtherconfirmed from the DSC study, which confirmed the etherification and purity of drug sample.\

2. Saturation Solubility Study of Drug

Saturation solubility study of drugs was determined in distilled water, acetate buffer pH 1.2, phosphate buffer pH 6.8 and phosphate buffer pH 7.5. The saturation solubility of a selected drug was determined as per Higuchi and Connor's method. In a glass vial containing 10 ml of study fluid, an excess amount of drug was added. Samples were then shaken for 48 hr at a constant speed on a rotary shaker at 25°±C2°C. After that, the saturated solutions were filtered through a Whatman filter paper no 1. Filtrates were diluted appropriately and spectrophotometrically determined. (Kumar D et al., 1965).

Sr. No	Media	Solubility (µg/ml)
1	Water	4.82 ± 3.06
2	Acetate buffer pH 1.2	84.26 ± 4.16
3	Phosphate buffer pH 6.8	8.16 ± 4.92
4	Phosphate buffer pH 7.5	16.42 ± 3.84

Table 1: Solubility Profile of Telmisartan in different Solvent

Sr. No	Media	Solubility (µg/ml)
1	Water	10.42 ± 1.06
2	Acetate buffer pH 1.2	7.18 ± 1.16
3	Phosphate buffer pH 6.8	18.54 ± 1.52
4	Phosphate buffer pH 7.5	32.31 ± 1.65

Table 2: Solubility Profile of Hydrochlorothiazide in different Solvent

3. Drug Excipient Compatibility study (FTIR Study)

The selected drugs were analyzed using FT-IR for qualitative chemical identification. The FT-IR spectra for selected pure drug was obtained using the KBr disc method, with the spectrum recorded between 4000 cm-1 and 400 cm-1.

Similarly for the identification of any chemical reaction between the APIs and the polymer, FTIR matching technique was applied. A physical mixture of selected APIs and polymer was made in equal ratio and combined with the appropriate amount of potassium bromide and compress the mixture into a pellet. The sample was scanned from 400 cm-1 to 4000 cm-1. The physical mixture's IR spectra was compared to that of pure drug and polymers, and matching was performed.

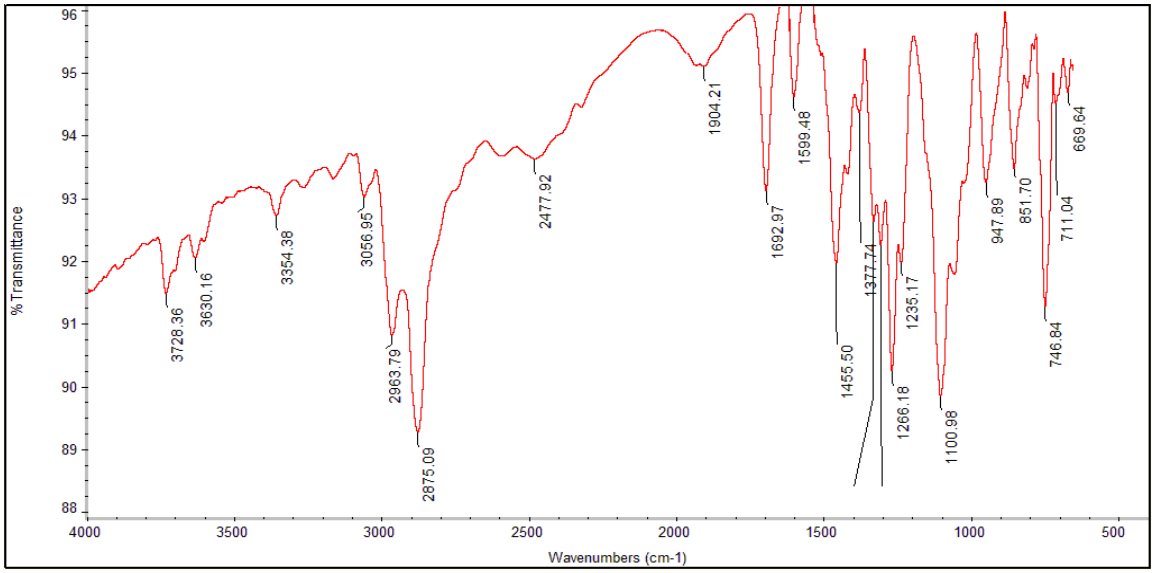

Figure 2: FTIR spectra of pure Drug and polymer Physical mixture(Telmisartan + Hydrochlorothiazide + PEG 6000 + Gelucire 50/13)

4. Preparation of Standard Calibration Curve of Telmisartan and Hydrochlorothiazide

4.1 Preparation of Standard Stock Solution

Standard stock solution both drugs was prepared having the strength of 100µg/ml was prepared. 100 mg drug was taken and dissolved in 100 ml of 0.1 N NaOH. Further 10 ml of above stock solution was pipette out and diluted up to 100 ml with 0.1 N NaOH.

4.2 Calibration Curve of Telmisartan and Hydrochlorothiazide in Distilled Water

From the above standard stock solution, linearity solutions of concentration range 10-50µg/ml for both drugs was prepared by diluting the sample with distilled water. The absorbance of the solution was recorded using UV spectrophotometer at wavelength of 296 nm and 272 nm respectively. (Gangola R et al., 2011).

4.3 Calibration Curve of Telmisartan and Hydrochlorothiazide in Phosphate Buffer pH 7.5

By using standard stock solution, obtained linearity solutions of concentration range 10-50 µg/ml was prepared by dilution with 0.1 N Hcl. At 296 and 272 nm the absorbance of the solution was recorded using UV spectrophotometer (Behera CC et al., 2014).

Table 3: Calibration curve of Telmisartan in Phosphate buffer pH 7.5

Sr. no	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.174
3	20	0.316
4	30	0.511
5	40	0.665
6	50	0.842

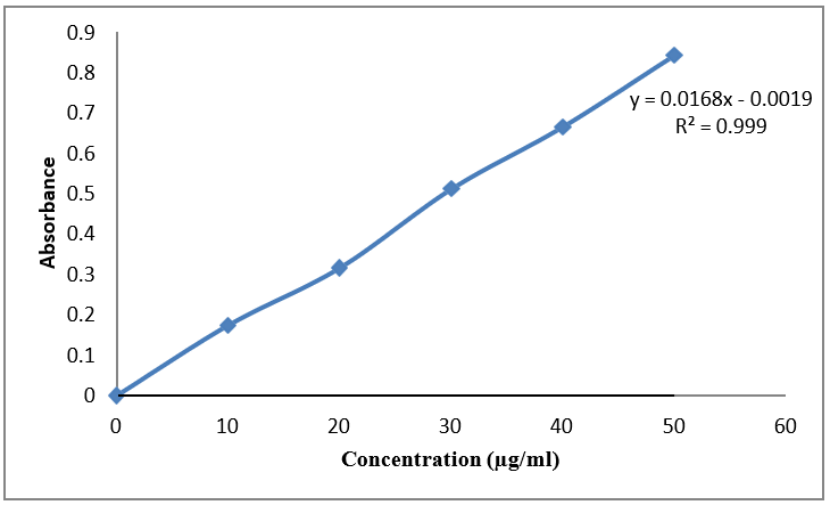

Figure 3: Calibration curve of Telmisartan in Phosphate buffer pH 7.5

Table 4: Calibration curve of Hydrochlorothiazide in Phosphate buffer pH 7.5

Sr. no	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.214
3	20	0.392
4	30	0.567
5	40	0.723
6	50	0.886

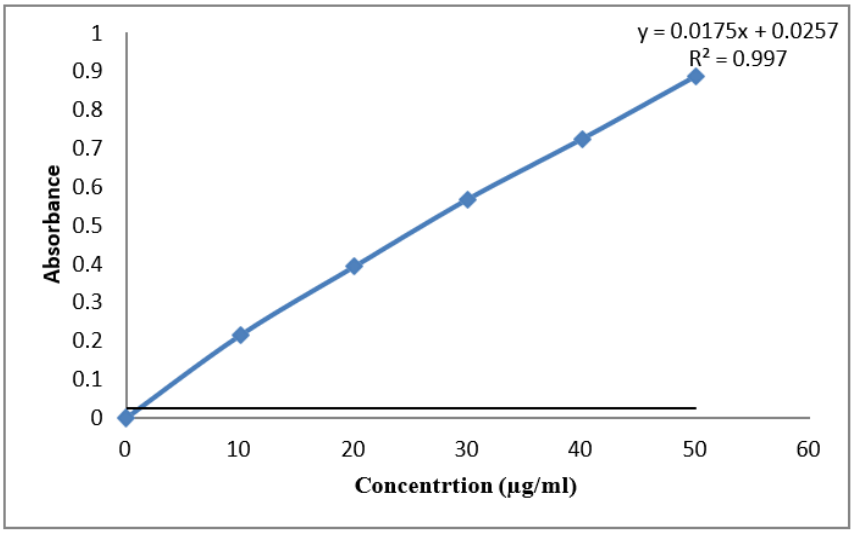

Figure 4: Calibration curve of Hydrochlorothiazide in Phosphate buffer pH 7.5

5. Phase Solubility Study of Drug Telmisartan and Hydrochlorothiazide

Phase solubility study is useful in the determination of the carrier's ability on drug solubilization . The phase solubility study was carried out as per method reported by Higuchi and Connors. An excess quantity of drug (about 100 mg) was taken in to a 10 ml glass vial containing 0.25%, 0.5%, 1%, 1.5% and 2 % aqueous solution of carriers. The mixture was then shaken for 48 hours at a constant temperature of 25^0C $\pm 2^0$C on a rotary shaker. The mixture was then filtered using Whatman filter paper. The concentration of the dissolved drug was determined by analyzing the filtrate using a UV spectrophotometer (Sharma A et al., 2010).

Table 5: Phase Solubility study of Telmisartan in PEG 6000 and Gelucire

Sr. no	Carrier Concentration (% w/v)	Solubility of Telmisartan (µg/ml)	
		PEG 6000	Gelucire 50/13
1	0	4.82±1.45	4.82±1.45
2	0.25	7.24±2.17	6.74±3.54
3	0.5	10.18±1.26	9.24±2.14
4	1	14.18±2.47	12.54±2.74
5	1.5	17.15±3.04	15.14±1.71
6	2	28.31±2.84	25.6±3.21
Stability Constant (Kc)		227.84	229.73

Values are mean ± SD (n = 3)

Table 6: Phase Solubility study of Hydrochlorothiazide in PEG 6000 and Gelucire

Sr. no	Carrier Concentration (% w/v)	Solubility of Hydrochlorothiazide (µg/ml)	
		PEG 6000	Gelucire 50/13
1	0	10.42±1.06	10.42±1.06
2	0.25	13.34±1.64	12.04±2.16
3	0.5	16.25±2.06	14.31±3.12
4	1	21.34±2.36	18.54±2.81
5	1.5	26.17±3.14	23.36±2.25
6	2	31.56±2.71	28.78±2.14
Stability Constant (Kc)		106.14	107.69

6.Gibbs-Free Energy Determination

The Gibbs-Free energy calculation was used to study whether the carrier had a favorable or non-favorable effect on drug solubilization in aqueous media. Gibbs free energy for both drug Telmisartan and Hydrochlorothiazide was calculated from phase solubility study data with carrier PEG and Gelucire. Tables 7 and 8 showed the $\Delta G°$tr of drug at various concentration of PEG and Gelucire. Negative value of Gibbs-free energy indicate better dissolution of drug. Increased in negative $\Delta G°$tr value with increasing proportion of carrier suggests that interaction between drug and polymer was favorable for improving the solubility of drug.

Table 7: Gibbs-Free energy value of Telmisartan with PEG 6000 and Gelucire 50/13

Concentrationof Carrier (%)	Using PEG 6000		Using Gelucire	
	Telmisartan Concentration (µg/ml)	ΔG°tr (J/Mol)	Telmisartan Concentration (µg/ml)	ΔG°tr (J/Mol)
0	4.82±1.45	-	4.82±1.45	-
0.25	7.24±2.17	-1008.19	6.74±3.54	-830.86
0.5	10.18±1.26	-1852.73	9.24±2.14	-1612.65
1	14.18±2.47	-2842.85	12.54±2.74	-2736.11
1.5	17.15±3.04	-3664.73	15.14±1.71	-3417.27
2	28.31±2.84	-4298.16	25.6±3.21	-4137.93

Values are mean ± SD (n = 3)

Table 8: Gibbs-Free energy value of Hydrochlorothiazide with PEG 6000 andGelucire 50/13

Concentrationof Carrier (%)	Using PEG 6000		Using Gelucire	
	Hydrochlorothiazide Concentration (µg/ml)	ΔG°tr (J/Mol)	Hydrochlorothiazide Concentration (µg/ml)	ΔG°tr (J/Mol)
0	10.42±1.06	-	10.42±1.06	-
0.25	13.34±1.64	-612.18	12.04±2.16	-358.09
0.5	16.25±2.06	-1101.17	14.31±3.12	-786.12
1	21.34±2.36	-1776.42	18.54±2.81	-1427.87
1.5	26.17±3.14	-2882.02	23.36±2.25	-2000.54
2	31.56±2.71	-2746.1	28.78±2.14	-2517.6

Values are mean ± SD (n = 3)

a. Preparation of Physical Mixture

Physical mixture of drug Telmisartan and hydrochlorothiazide was prepared with hydrophilic carrier PEG 6000 and Gelucire 50/13. Physical mixture was prepared by simply mixing the drug and carrier together in mortar. Physical mixture of both drug (Telmisartan 40mg and Hydrochlorothiazide 12.5mg dose combination) was created in various drug to carrier ratios (1:1, 1:3, 1:5, and 1:7). In a mortar and pestle, the required amounts of drug and carrier were combined with minimal stirring pressure to make a physical mixture. To achieve a homogeneous size distribution, the mixture was passed through sieved no 60 and place in desiccator until further use (Dubay et al., 2014; Sahoo A et al., 2015). The formulations details are listed in table 9.

Table 9 : Composition of Physical mixture

Formulation	Drug	Carrier	Batch Code	Drug : Carrier Ratio
PhysicalMixture	TemisartanAnd Hydrochlorothiazide	PEG60000	PPM1	1:1
			PPM2	1:3
			PPM3	1:5
			PPM4	1:7
		Gelucire50/13	GPM5	1:1
			GPM6	1:3
			GPM7	1:5
			GPM8	1:7

b. Preparation of Solid Dispersion by Solvent Evaporation Method

Solid dispersion of drug Telmisartan and hydrochlorothiazide in dose combination of 40 mg and 12.5 mg respectively was made using carrier PEG 6000 and Gelucire 50/13 by solvent evaporation method. The drug and polymer were taken in ratio of 1:1, 1:3, 1:5 and 1:7 (SESD1, SESD2, SESD3 and SESD4). The polymer was taken and dissolved in an adequate amount of methanol and then drug was added slowly with stirring. The solvent methanol was then rapidly evaporated with the help of mild heat on water bath to form a uniform solid mass. The precipitate solid mass was then crushed and desiccated for 24 h. The resultant mas was then pulverized and powder was then passed through 60 mesh sieve so as to get uniform size fraction. The product was then kept in suitable container until further use. The details of formulation was shown in table 10 (Shah J at al., 2009; Chen S et al., 2007; Iqbal A et al., 2020)

Table 10: Formulation development of Solid Dispersion

Formulation	Drug	Method	Carrier	Batch Code	Drug : Carrier Ratio
Solid Dispersion	Telmisartanand Hydrochlorothiazide	Solvent Evaporation	PEG6000	PSD1	1:1
				PSD2	1:3
				PSD3	1:5
				PSD4	1:7
			Gelucire50/13	GSD5	1:1
				GSD6	1:3
				GSD7	1:5
				GSD8	1:7

7.IN-VITRO EVALUATION OF SOLID DISPERSION

7.1 Determination of solubility: (Physical Mixture and Solid dispersion)

The solubility of a physical mixture and solid dispersion was determined using the shake flask method in distilled water and 0.1 N Hcl. Excess amount of formulations were placed in a conical flask with 25 ml distilled water and 0.1 N Hcl, which was then agitated for 24 hours at room temperature on a rotary flask shaker. After shaking, undissolved solids dispersed in the test medium were centrifuged at 10000 rpm for 5 minutes, and the clear supernatants were filtered using Whatman filter paper. After that, the sample was diluted appropriately and examined using a UV-Spectrophotometer (Patel B et al., 2012; Sathali AAH et al., 2013).

Table 11: Solubility Study of Telmisartan in PMs and SDs

PM Formulation code	DistilledWater (µg/ml)	PhosphateBuffer pH 7.5 (µg/ml)	SD Formulation code	DistilledWater (µg/ml)	PhosphateBuffer pH 7.5 (µg/ml)
PPM1	16.14 ± 3.47	17.08 ±1.89	**PSD1**	19.36 ± 2.30	21.27 ± 3.16
PPM2	24.35 ± 2.17	27.30 ±1.87	**PSD2**	28.17 ± 2.41	33.16 ± 2.46
PPM3	41.28 ± 2.81	45.21 ±2.65	**PSD3**	47.24 ± 1.84	53.34 ± 1.78
PPM4	43.27 ± 1.93	46.47 ±3.06	**PSD4**	48.61 ± 1.74	54.15 ± 2.21
GPM5	15.12 ± 2.20	16.25 ±2.07	**GSD5**	18.47 ± 3.07	20.15 ± 3.06
GPM6	23.35 ± 1.85	26.16 ±3.14	**GSD6**	27.17 ± 3.11	31.55 ± 2.37
GPM7	38.47 ± 3.04	41.40 ±2.51	**GSD7**	43.34 ± 2.14	47.26 ± 1.94
GPM8	40.10 ± 2.54	42.23 ±2.26	**GSD8**	45.61 ± 1.44	51.15 ± 3.21

Values are mean ± SD (n=3)

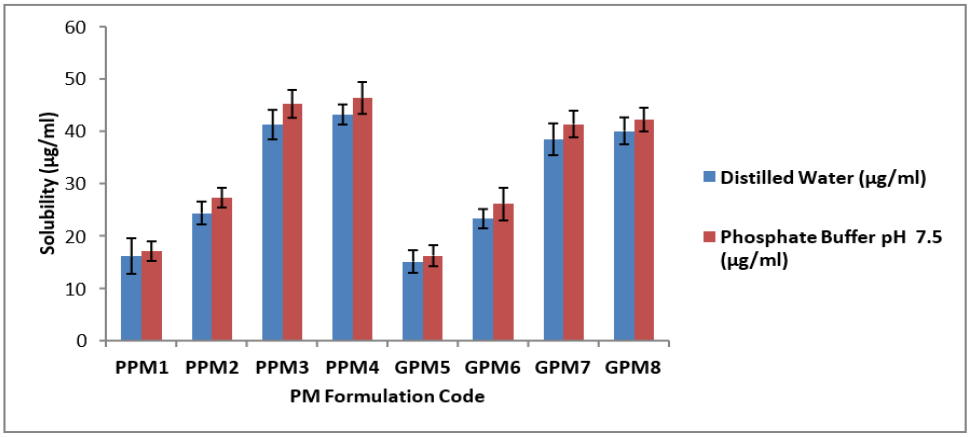

Figure 5 : Solubility profile of Telmisartan in Physical Mixture prepared with PEG6000 and Gelucire 50/13 in different solvent

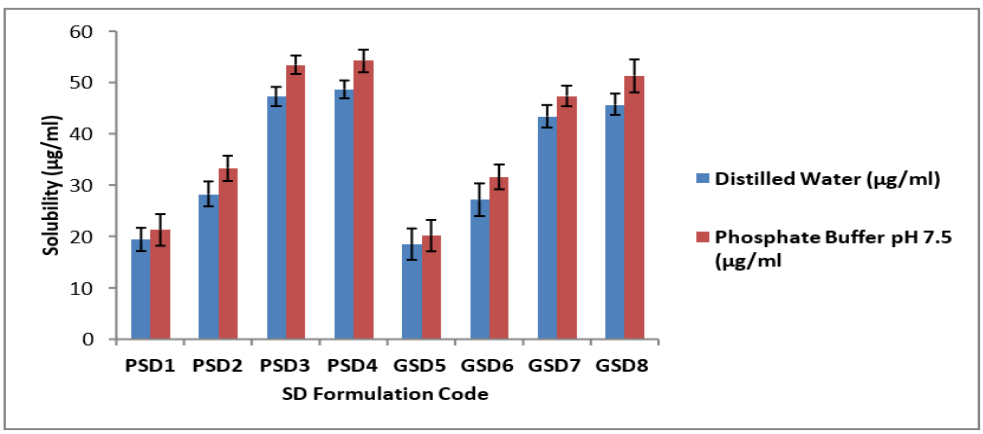

Figure 6 : Solubility profile of Telmisartan in Solid Dispersion prepared with PEG6000 and Gelucire 50/13 in different solvent

Table 12: Solubility Study of Hydrochlorothiazide in PMs and SDs

PM Formulation code	DistilledWater (µg/ml)	PhosphateBuffer pH 7.5 (µg/ml)	SD Formulation code	DistilledWater (µg/ml)	PhosphateBuffer pH 7.5 (µg/ml)
PPM1	19.23 ± 2.47	21.14 ±2.89	**PSD1**	36.40 ± 2.25	38.14 ± 3.10
PPM2	25.54 ± 3.17	28.30 ±1.78	**PSD2**	56.65 ± 2.77	60.33 ± 2.21
PPM3	36.48 ± 3.08	40.47 ±2.15	**PSD3**	83.34 ± 1.90	86.75 ± 2.47
PPM4	38.04 ± 1.86	43.47 ±3.17	**PSD4**	86.31 ± 2.06	89.18 ± 2.63
GPM5	19.02 ± 2.36	22.21 ±2.16	**GSD5**	32.17 ± 3.11	36.40 ± 3.12
GPM6	23.35 ± 2.34	26.52 ±3.26	**GSD6**	47.26 ± 2.87	52.12 ± 2.47
GPM7	34.27 ± 3.10	37.16 ±1.80	**GSD7**	70.34 ± 2.32	74.29 ± 2.46
GPM8	35.48 ± 2.81	37.86 ±2.30	**GSD8**	75.61 ± 2.44	77.17 ± 3.14

Values are mean ± SD (n=3)

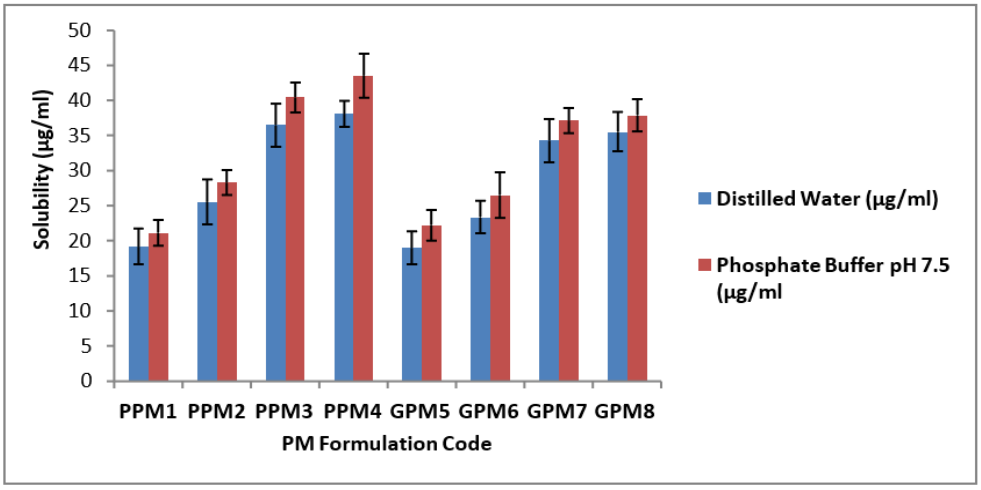

Figure 7: Solubility profile of Hydrochlorothiazide in Physical Mixture preparedwith PEG 6000 and Gelucire 50/13 in different solvent

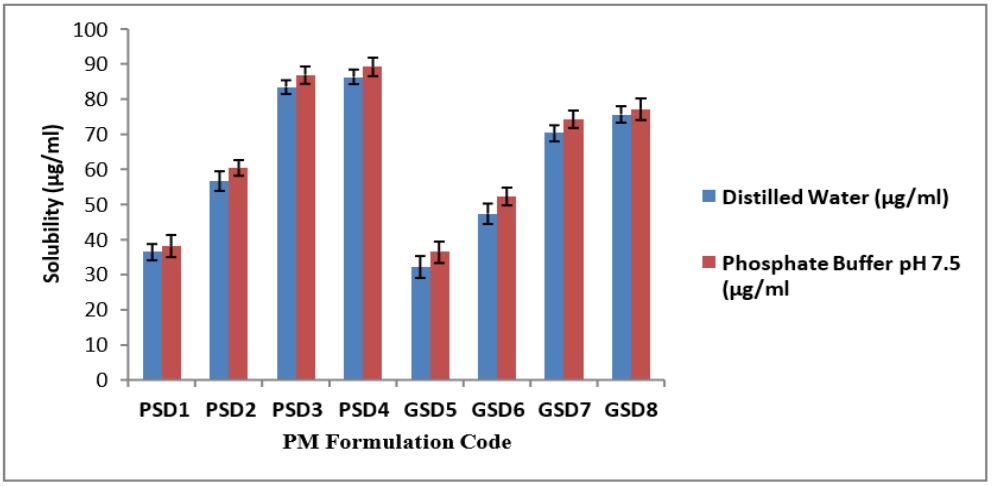

Figure 8 : Solubility profile of Hydrochlorothiazide in Solid Dispersion preparedwith PEG 6000 and Gelucire 50/13 in different solvent

7.2 Fourier Transform Infra-Red Spectroscopy (FTIR)

FTIR spectroscopy was used to determine the drug's compatibility with the selected carrier (Shimadzu FTIR). The FTIR spectrum of a pure drug, a physical mixture, and a solid dispersion was recorded throughout a selected frequency range of 400 to 2000 cm-1. Any kind of incompatibility between drug and selected carrier in the formulation ware observed. (Chittur KK et al., 1998).

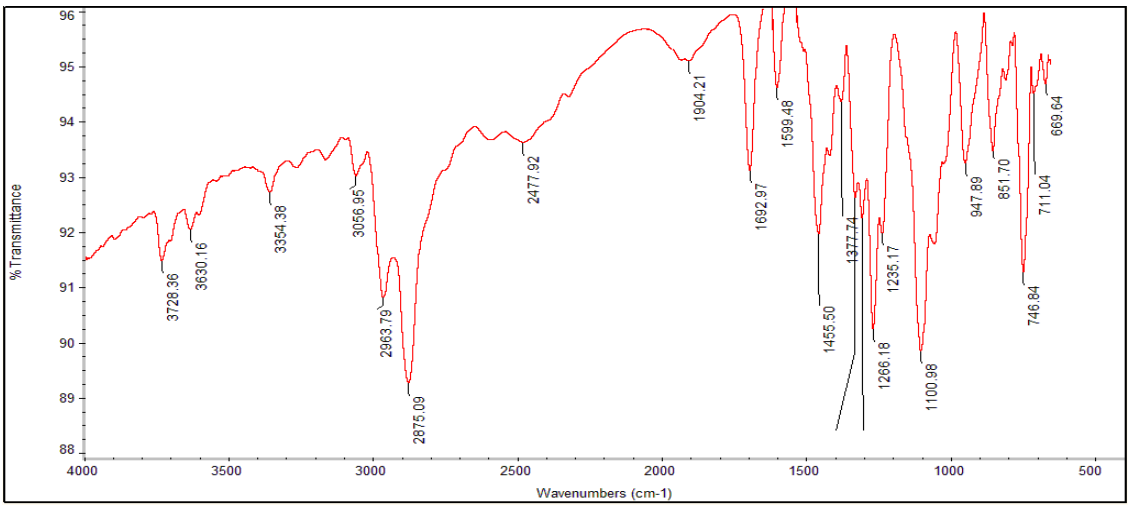

Figure 9: FTIR Spectra of Telmisartan+ Hydrochlorothiazide + PEG 6000 + Gelucire 50/13

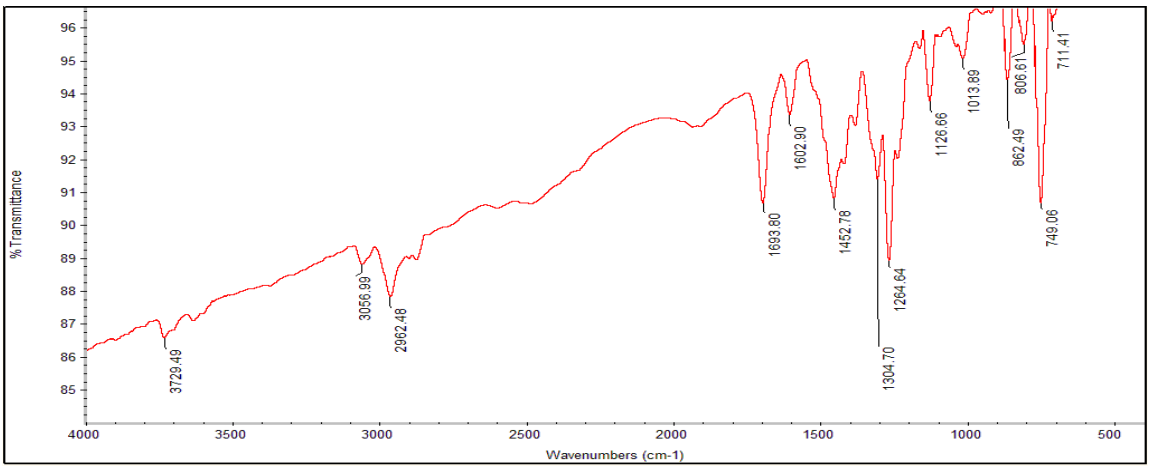

Figure 10: FTIR Spectra of Telmisartan

7.3 Differential Scanning Calorimetry (DSC)

Thermal investigations of solid dispersion were performed by using Shimadzu Thermal Analyzer (Japan). In an aluminum pan, 7–10 mg of sample was placed and crimped with a lidcontaining a pin hole and kept in the differential scanning calorimetry (DSC) unit along with a similar pan as a reference. The sample was heated at the rate of 10°C/min from the temperature range of 30–200°C. Nitrogen was used as a purge gas and flow was adjusted to 50 ml/min. (Altamimi MA at al., 2016)

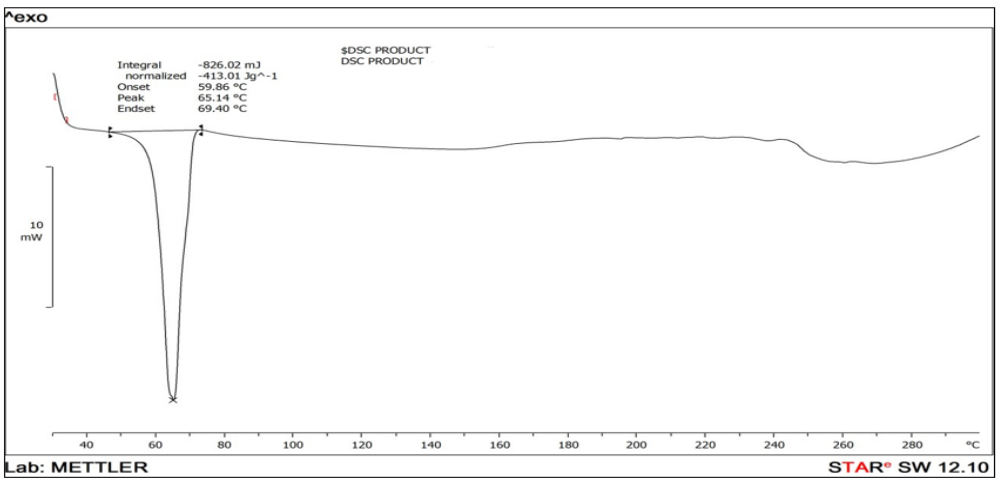

Figure 11: DCS thermogram of solid dispersion PSD3

7.4 Powder X-Ray Diffraction (PXRD)

XRD patterns of selected pure drug, carrier and solid dispersion, were recorded on an X-ray powder diffraction system (Rikagu, Mini Flex 600, Japan), using a copper target, a voltage of 40 Kv, and a current of 30 mA. The scanning was done in a 5^o to 60^o range. For the comparison of crystallinity, the position and intensities of diffraction peaks were taken into account (Tantishaiyakul V et al., 1999; Yamashita K et al., 2003).

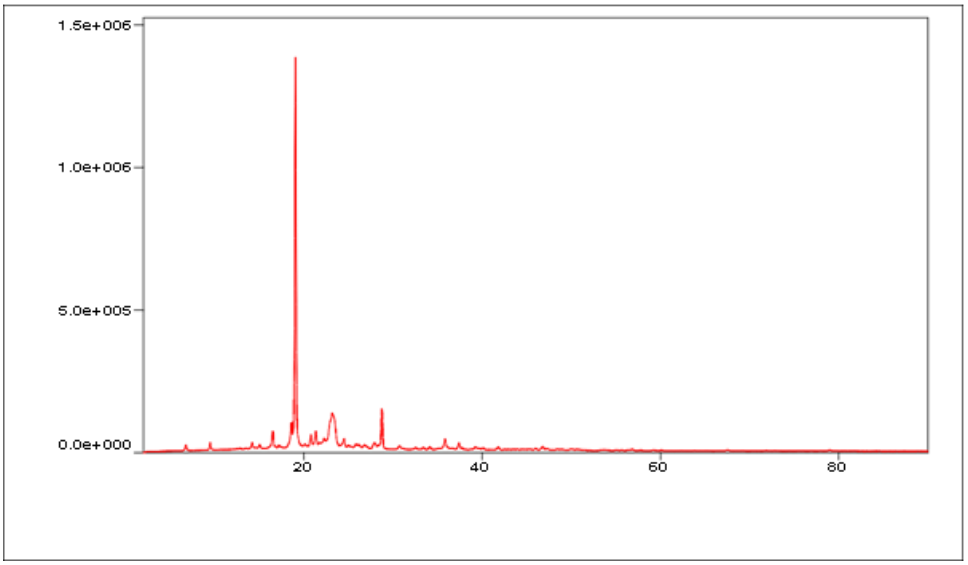

Figure 12: XRD spectra of optimized Solid Dispersion (PSD3)

7.5 Scanning Electron Microscopy

Sample surface morphology was studied by using scanning Electron Microscope (SEM) (ZEISS, Germany) was used to examine for selected pure drug, and solid dispersion formulation. The powder was manually spread onto a carbon tab (double adhesive carbon coated tape) that was glued to an aluminum stub. The POLARON-E 3000 sputter coater was used to coat these sample stubs with a thin coating (30Å) of gold. The samples were examined at various magnification and photographs were taken ((Zidan et al., 2012). Breitenbach J et al., 2002)

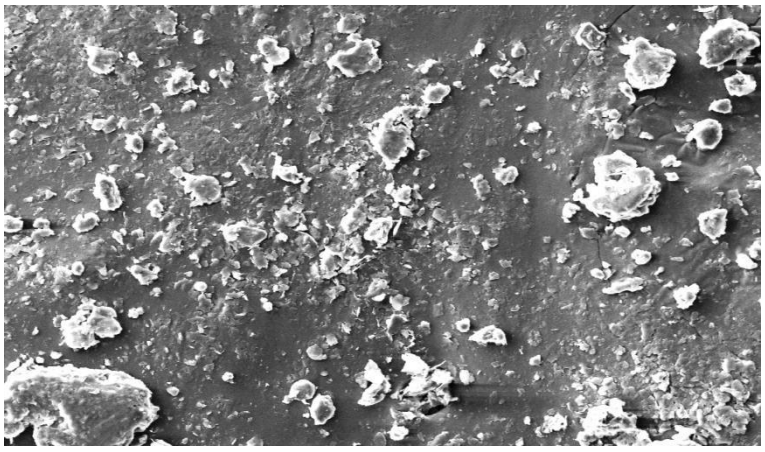

Figure 13: SEM image of Optimized SD formulation (PSD3)

7.6 In vitro drug dissolution study

In vitro drug dissolution study for pure drug, physical mixture and solid dispersion were determined using USP paddle apparatus by dispersed powder technique. Sample equivalent to 40 mg of Telmisartan and 12.5 mg of hydrochlorothiazide was added to 900 ml 0.1N Hcl as dissolution medium at 37 ± 0.5°C and stirred at 50 rpm (Elctrolab). An aliquot of 5 ml was withdrawn at different time intervals with a pipette. The withdrawn volume was replenished immediately with the

same volume of the dissolution medium in order to keep the total volume constant. The filtered samples were suitably diluted, if necessary, and determined spectrophotometrically at 296 and 272 nm for Telmisartan and hydrochlorothiazide respectively. The mean of at least three determinations was used to calculate the drug release.(Chiou WL et al., 1971; Singh B et al., 1997; Leuner C et al., 2000

Table 13: In Vitro Dissolution Data of Pure and SDs of Telmisartan

Time (Min)	0	10	20	30	40	50	60
Pure Tel	0	3.14±2.36	4.25±1.78	6.64±3.45	7.18±2.74	8.26±3.04	9.54±1.26
PSD1	0	54.74±2.20	71.5±0.78	76.3±1.30	81.24±1.47	86.31±3.14	90.14±3.05
PSD2	0	70.61±0.54	82.14±1.78	86.36±135	91.21±3.10	94.04±0.98	94.28±2.21
PSD3	0	81.12±1.87	91.16±3.14	94.25±1.15	96.63±2.21	98.26±2.10	98.58±2.56
PSD4	0	75.84±1.28	85.32±0.57	88.21±2.34	92.57±2.54	94.89±2.36	96.31±1.88
GSD5	0	55.3±3.20	70.14±2.14	76.31±0.85	84.12±1.64	88.5±2.47	91.44±1.60
GSD6	0	61.83±1.63	81.2±2.47	88.2±2.30	90.8±2.11	92.2±0.77	94.6±2.18
GSD7	0	68.35±3.17	85.25±0.47	90.23±3.02	92.44±1.32	95.47±3.11	96.22±2.65
GSD8	0	74.87±0.78	87.26±1.36	91.13±2.47	94.37±3.61	95.62±2.44	97.65±1.26

Values are Mean ± SD, n=3

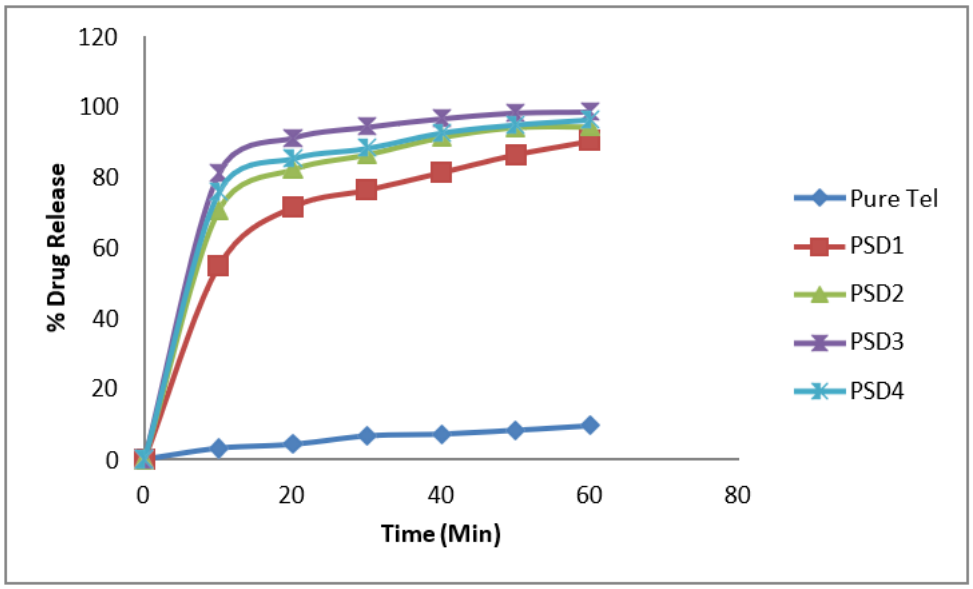

Figure 14: Dissolution profile of pure Telmisartan and its SD prepared with PEG 6000

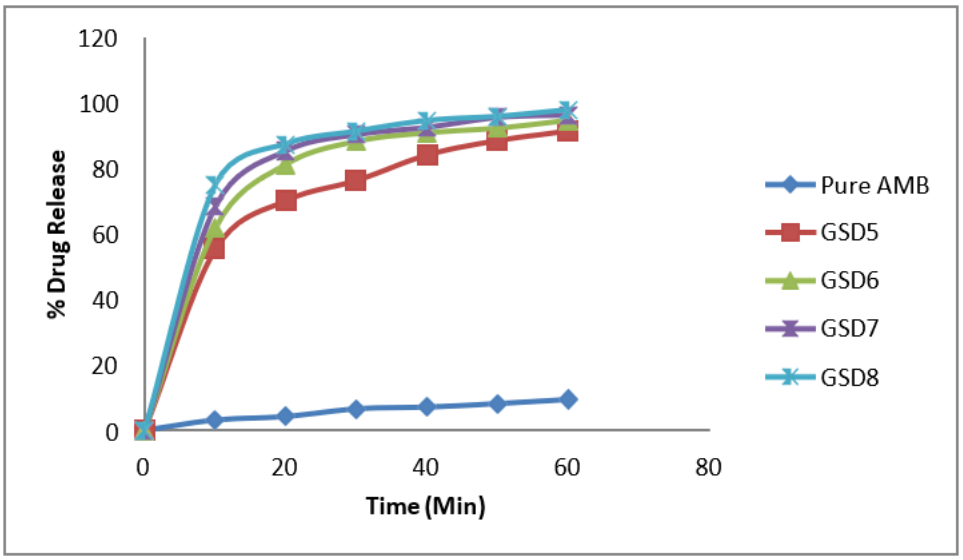

Figure 15: Dissolution profile of pure Telmisartan and its SD prepared with Gelucire50/13

Table 14: In Vitro Dissolution Data of Pure and SDs of Hydrochlorothiazide

Time (Min)	0	10	20	30	40	50	60
Pure HTZ	0	15.74±1.45	20.26±2.56	24.12±0.74	28.14±1.23	34.6±3.04	38.15±1.47
PSD1	0	53.64±2.65	70.3±2.20	75.3±3.47	85.26±2.14	87.31±1.86	90.14±0.55
PSD2	0	70.26±1.33	82.14±0.74	86.36±0.57	88.54±2.34	94.04±3.10	94.28±2.55
PSD3	0	72.54±1.27	91.16±0.77	94.25±2.48	94.52±1.44	97.41±2.67	97.54±2.87
PSD4	0	75.84±2.91	85.32±3.11	88.21±3.47	95.12±1.56	96.04±2.50	96.31±2.47
GSD5	0	50.26±2.41	68.54±1.58	70.14±1.88	80.67±2.07	84.33±3.24	90.21±2.08
GSD6	0	64.74±2.04	72.45±2.44	74.65±0.86	86.21±1.70	90.41±2.40	92.6±2.44
GSD7	0	68.35±2.31	77.25±3.16	81.24±2.14	92.44±2.74	93.47±3.17	94.22±1.77
GSD8	0	74.87±0.56	85.26±1.55	88.13±2.42	94.37±3.21	94.22±2.66	96.6±2.30

Values are Mean ± SD, n=3

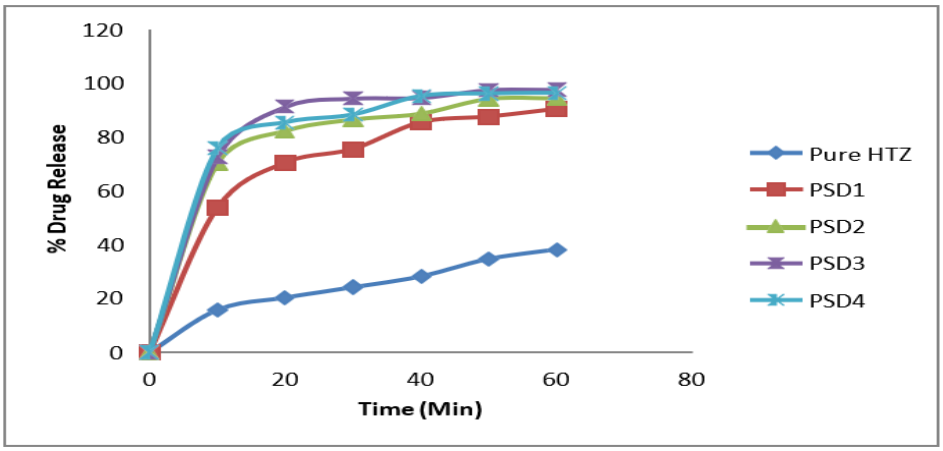

Figure16: Dissolution profile of pure Hydrochlorothiazide and its SD prepared withPEG 6000

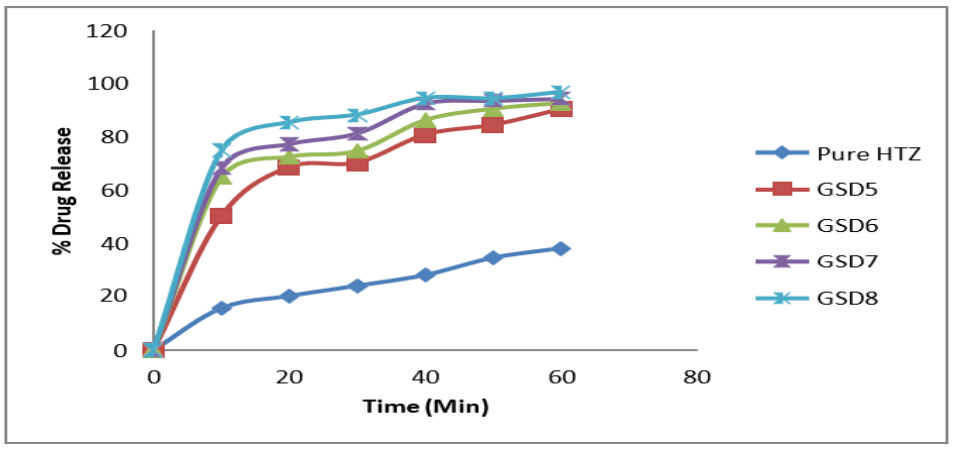

Figure 17: Dissolution profile of pure Hydrochlorothiazide and its SD prepared withGelucire 50/13

7.9 Drug Content and Percentage Practical Yield

Formulations containing equivalent weight of 40 mg of Telmisartan and 12.5 mg of hydrochlorothiazide were accurately weighed and dissolved in 100 ml of methanol. The solution was shaken and then filtered. The drug content was measured using a UV spectrophotometer by taking absorbance of sample at 296 nm and 272 nm for Telmisartan and hydrochlorothiazide respectively, against a blank after appropriate dilution.

The percentage practical yields calculated for all SDs formulation. Practical yield for all the SD formulation formulations were found in the range of 82 to 88 %. The results for percentage yield and drug content for all SDs formulations are shown in table 15.

% Practical Yield = Practical yield / Theoretical yield * 100

Table 15: % Drug Content and Practical Yield of Formulations (ASD1 to ASD10)

Sr. No	Formulation	% Practical Yield	% Drug Content*
1	PSD1	82.21	96.24 ± 0.61
2	PSD2	82.46	97.13 ± 1.60
3	PSD3	88.15	98.47± 1.44
4	PSD4	88.28	97.26 ± 1.22
5	GSD5	78.41	98.14 ± 0.84
6	GSD6	81.30	97.32 ± 1.70
7	GSD7	85.12	98.11 ± 1.16
8	GSD8	85.36	96.31 ± 1.46

*Mean ± SD, n=3

3. RESULT AND DISCUSSION

Telmisartan and hydrochlorothiazide both drugs are BCS class II drug having very low water solubility that resulting in poor bioavailability. The objectives of this research were to increase the solubility, drug dissolution and to enhance the bioavailability of low aqueous soluble drugs Telmisartan and hydrochlorothiazide by solid dispersion techniques. Saturation Solubility study performed on both drug in distilled water and phosphate buffer pH 7.5 showed that both drug have very limited solubility in water, while both drugs showed increased solubility in buffer solution. Both drug showed pH dependent solubility. Phase solubility study performed on both drug to check the carrier's ability on drug solubilization, linear increased in solubility of both drug with increase on carrier concentration was observed that gives A_L type solubility curve showing 1:1 complex formation. The Gibbs-Free energy calculation was used to study whether the carrier had a favorable or non-favorable effect on drug solubilization in aqueous media. Gibbs free energy for both drug Telmisartan and Hydrochlorothiazide was calculated from phase solubility study data with carrier PEG and Gelucire. Both drug showed negative $\Delta G°$tr value which indicate better dissolution of drug. SD formulation of both drug Telmisartan and hydrochlorothiazide was prepared by using two different carrier like PEG 6000 and Gelucire 50/13 in 1:1, 1:3, 1:5 and 1:7 drug to polymer ratio by solvent evaporation method. Compatibility study of drug and excipient indicate that there is no incompatibility was found between the excipient and the drug. DSC and XRD study conducted on SD of both drugs prepared with PEG 6000 and Gelucire confirmed the reduction in crystallinity and amorphous conversion of drugs. Solubility study performed on physical mixture and solid dispersion of both drugs showed multifold increased in solubility as compare to pure form of drug. Solid dispersion formulation prepared with PEG 6000 showed 9.8 and 8-fold increase in water solubility of Telmisartan and hydrochlorothiazide. SEM study conducted on of optimized SD formulation (PSD3) prepared with PEG 6000 shows smooth surface, which may be because of complete miscibility of drug with carrier. In vitro dissolution study showed rise in drug dissolution rate of SD and PM of both drugs compared to its pure form.

4. CONCLUSION

The concept of formulating the solid dispersions of Telmisartan and hydrochlorothiazide with water soluble carriers such as PEG 6000 and Gelucire 50/13 offer a suitable and practical approach in serving desired objective of higher solubility ,faster dissolution rate and improved bioavailability In the place of dissolution of drug. Solid dispersions of the poorly water soluble antihypertensive agents Telmisartan and hydrochlorothiazide with water soluble carriers such as PEG 6000 and Gelucire 50/13 to improving its aqueous solubility and rate of dissolution. The solid dispersions of drug were prepared by solvent evaporation technique. The observed results showed the solid dispersion of drug were found increased in aqueous solubility than pure drug. Evaluation of the dispersions were performed using aqueous solubility and dissolution studies, the results obtained showed that the aqueous solubility and rate of dissolution of fixed dose combination Telmisartan

and hydrochlorothiazide was significantly improved when formulated in solid dispersions as compare to pure drugs.

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