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EFFECT OF TELMISARTAN ON THE SOLUBILITY OF HYDROCHLOROTHIAZIDE BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Drugs having poor aqueous solubility present one of the major confronts better absorption for good bioavailability of such drugs. Solid dispersion of Hydrochlorothiazide and Telmisartan in a fixed dose combination was prepared. The major problem with these drugs is their low aqueous solubility, which results into poor bioavailability after oral administration. The purpose of this study was to prepare and characterize solid dispersions of the poorly water soluble antihypertensive agent. Hydrochlorothiazide and Telmisartan with water soluble carriers such as PEG-4000 to improving its aqueous solubility and rate of dissolution. The solid dispersions of drug were prepared by solvent evaporation technique and evaluated by FTIR, X-ray diffraction and DSC analyses and in-vitro dissolution characteristics. The data were compared with that of physical mixture of hydrochlorothiazide and Telmisartan and of pure hydrochlorothiazide. The results showed reduction in particle size, change from crystalline form to amorphous form and enhanced the dissolution rate of hydrochlorothiazide from solid dispersion as compared to physical mixture as well as pure hydrochlorothiazide. The findings of the present study propose that the novel drug-drug solid dispersion approach is beneficial for fixed dose combinations of poorly soluble and soluble drugs to improve bioavailability of poorly soluble drugs.

Keywords: Hydrochlorothiazide, Telmisartan, PEG 4000, Dissolution Enhancement, Solid Dispersion

1. INTRODUCTION:

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

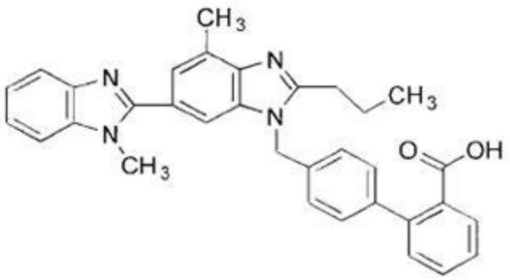


Figure 1: Structure of Telmisartan

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. Methanol was used as the solvent. PEG 4000 were used as the hydrophilic carriers. The samples were prepared at different drug: carrier weight ratios. PEG 4000 have been successfully used to improve the water solubility and dissolution (hence bioavailability) of several drugs.

2. MATERIALS AND METHODS

Materials

Telmisartan was obtained as a gift sample from Amneal Pharmaceutical PVT.LTD. Hydrochlorothiazide (USP) was obtained from Mecleods Pharmaceuticals Ltd, Mumbai. Ahemedabad, (India). PEG 4000 was purchased from Central Drug House Pvt. Ltd., New Delhi, India. All other chemicals and reagents were of analytical grade.

Estimation of Pure drugs, Physical mixtures and Solid dispersions:

Method 1:

Pure sample of Telmisartan were analyzed by Spectrophotometer method 100mg of Telmisartan and hydrochlorothiazide standard solution were prepared using methanol and used in the mixed standards. The concentrations of two components in the mixed standards were taken as 10-50µg/ml. All the mixed standard solutions were scanned in the range of 200-400 nm using the sample points 236 and 270nm for Telmisartan and Hydrochlorothiazide respectively. A standard curve was constructed by plotting the absorbance vs. concentration of the drug taken.

Method 2:

This method was adapted to pure hydrochlorothiazide.100mg hydrochlorothiazide was accurately weighed and dissolved in methanol in standard flask and diluted to 100ml with methanol. Further, dilutions were made to get 1-5µg/ml HCT and this solution was scanned at 270nm to obtain absorbance. Standard curve was constructed by plotting absorbance vs. concentration of drug.

Preparation of Physical Mixture and Solid Dispersion:

Physical Mixture:

Hydrochlorothiazide and Telmisartan were accurately weighed at the ratio of 1:1, 1:2, 1:4 (12.5:12.5 mg, 12.5:25 mg, and 12.5:50 mg) Pulverized, and then drug and polymer mixed thoroughly in a glass mortar with

pestle until homogeneous. The mixtures were passed through a 250µm sieve.

Solid Dispersion: Solid dispersion of Hydrochlorothiazide and Telmisartan at three ratios of 1:2, 1:4, 1:8 (12.5:25mg, 12.5:50mg, and 12.5:100mg) was prepared by solvent method. Hydrochlorothiazide and Telmisartan were dissolved in methanol and PEG 4000 polymer was dissolved in water. Both solutions were mixed in beaker with magnetic stirring. Solvent was evaporated at reduced pressure a 40ºC in a rotatory evaporation apparatus. Subsequently solid dispersion was stored vacuum over silica gel for 12hrs at room temperature. After dried solid dispersion was passed through a 250µm sieve. Sample was stored in a desiccator and used for further investigation.

Table 1: Formulation ratio of physical mixtures and solid dispersions of drugs Hydrochlorothiazide- Telmisartan

Sr.no	Physical mixture -PM (HCT:TLM)		Solid dispersion -SD (HCT:TLM)	
1	1:1	B1PM	1:1	B1SD
2	1:2	B2PM	1:2	B2SD
3	1:4	B3PM	1:4	B3SD

B1PM, B2PM, B3PM are batches of physical mixture from Batch 1-3 respectively: B1SD, B2SD, B3SD are batches of solid dispersion from Batch 1-3 respectively

3. Characterizations of Prepared Solid dispersion of Telmisartan-Hydrochlorothiazide

3.1 Solubility Study

Excessive amount of pure Hydrochlorothiazide was added to 100mL of 0.1N HCL containing varying concentrations of Telmisartan (0020%, 0.060%, 0.0200% w/v) in stoppered flasks. These suspensions were equilibrated by intermittent shaking for 72hrs maintained at 37±2oC. These suspensions were filtered through a Whatman filter. To determine the impact of Telmisartan (TLM) on the solubility properties of Hydrochlorothiazide (HCT), a phase solubility experiment was carried out and the findings are given in Table. In presence of TLM in 0.1N HCL at a concentration of 0.02 percent w/v, the solubility of HCT enhanced by about eight times. These findings suggest that TLM in 0.1N HCL functioned as a novel vehicle and significantly improved HCT solubility, presumably as a result of the solvent effect of TLM.

Table 2: Table showing Values observed in solubility study

Sr.no.	Telmisartan concentration (%w/v)	Solubility of Hydrochlorothiazide (mg/ml)
1	0	0.2126
2	0.0020	0.3645
3	0.0060	0.5445
4	0.0200	1.6529

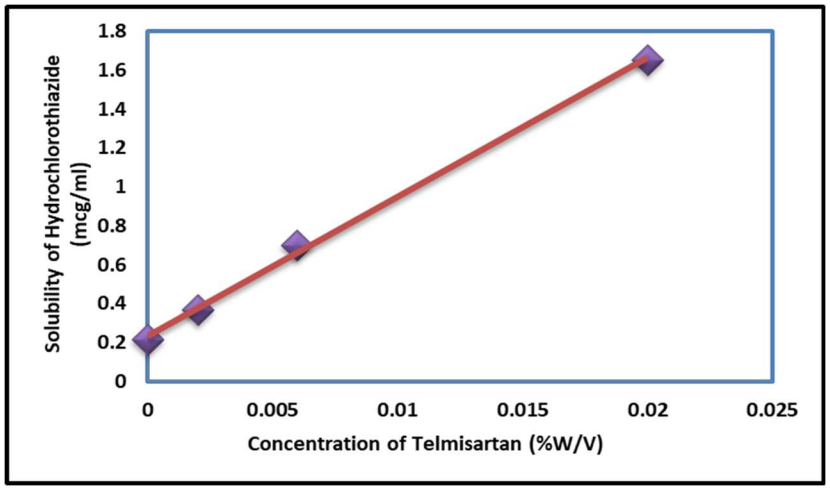


Figure 2: Effect of concentration of Telmisartan on the solubility of Hydrochlorothiazide

Calibration Curve

Table 3: Shows Calibration curve data for Hydrochlorothiazide-Telmisartan combination

Sr. no.	Drug Concentration (µg/mL)	Absorbance of Hydrochlorothiazide 270nm	Absorbance of Telmisartan 234nm
1	0	0.015	0.001
2	10	0.814	0.720
3	20	1.594	1.37
4	30	2.46	2.10
5	40	3.18	2.77
6	50	3.92	3.48

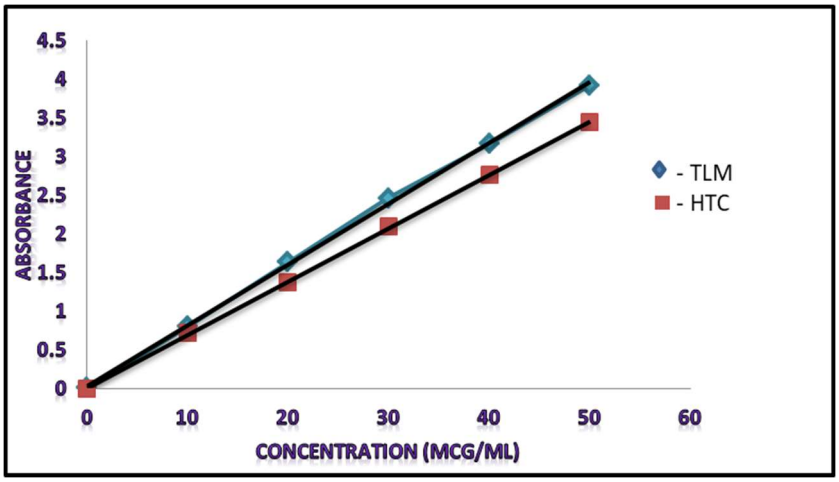


Figure 3: Calibration Curve of Telmisartan and Hydrochlorothiazide

3.2 FTIR study

In the tables and figures, the FTIR spectra of pure Hydrochlorothiazide and Telmisartan along with their physical mixtures and solid dispersions are displayed. There were the typical drug peak appearances in the spectra, this indicates that no chemical interaction there was between the drugs in the physical mixture and solid dispersion.

Table 4: FTIR Spectra of Hydrochlorothiazide in Physical mixture (PM) and Solid dispersion (SD)

Characteristics	HCT	B1 PM	B2 PM	B3 PM	B1 SD	B2 SD	B3 SD
NH(Stretching)	3372.04-3183.01	3372.04-3184.94	3372.04-3175.79	3370.97-3190.65	3370.11	3360.18	3361.11
Aromatic(CH Stretching)	2948.33	2945.04	2957.97	2959.97	2959.90	2960.97	2957.97
NH (bending)	1612.90-1528.03	1604.76-1514	1615.76-1507.46	1618.69-1508.46-	1600-1526	1601.97-1520.10	1601.97-1507.46
S=O(stretching)	1470.16	1470.16	1463.09	1463.09	1463.09	1472.09	1406.16
Aromatic(CH Bending)	868.35-738.41	842.92-764.84	850.99-765.91	842.99-762.91	819.85-760.98	825.70-760.98	880.57-760.98
C-Cl (Stretching)	679.04-609.60	679.04-607.60	676.11-610.53	676.11-610.53	679-609	679.18-608.67	672.25- 60

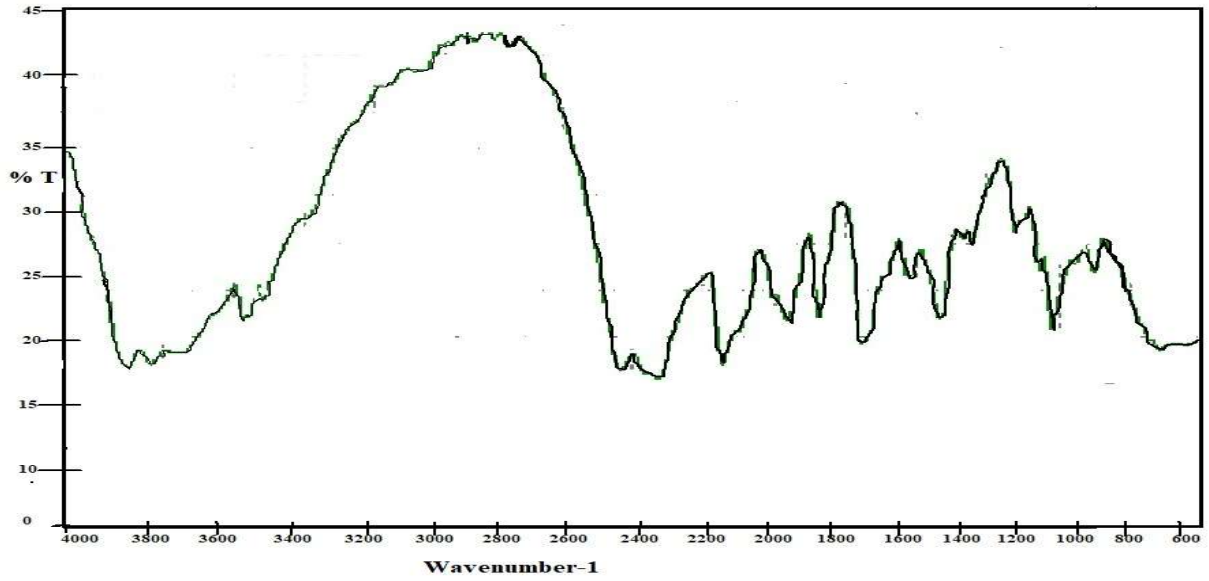


Figure 4: FTIR Spectra of Hydrochlorothiazide and Telmisartan Mixture (1:1) (B1 SD)

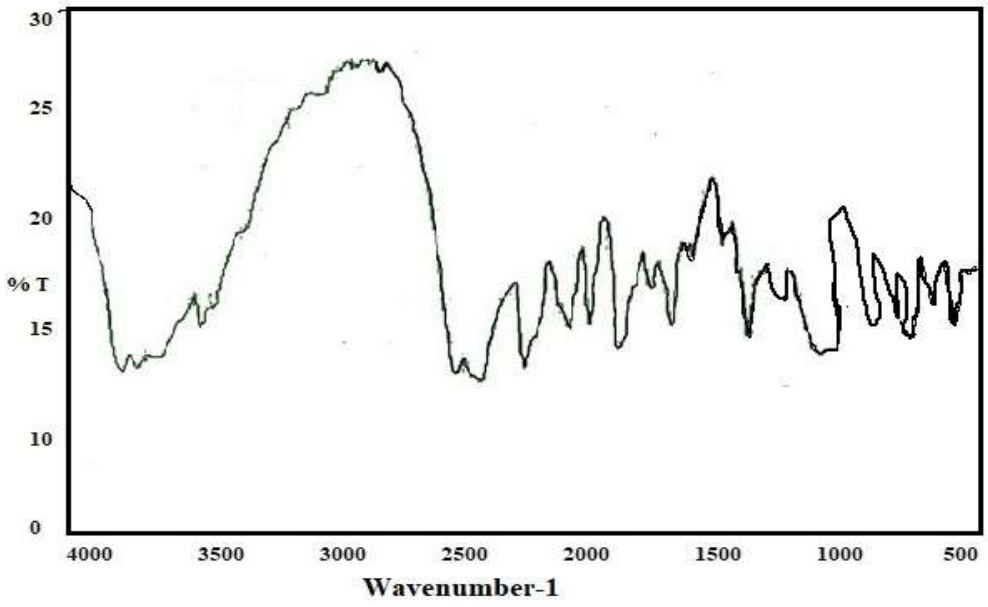


Figure 5: FTIR Spectra of Hydrochlorothiazide and Telmisartan Mixture (1:2) (B2 SD)

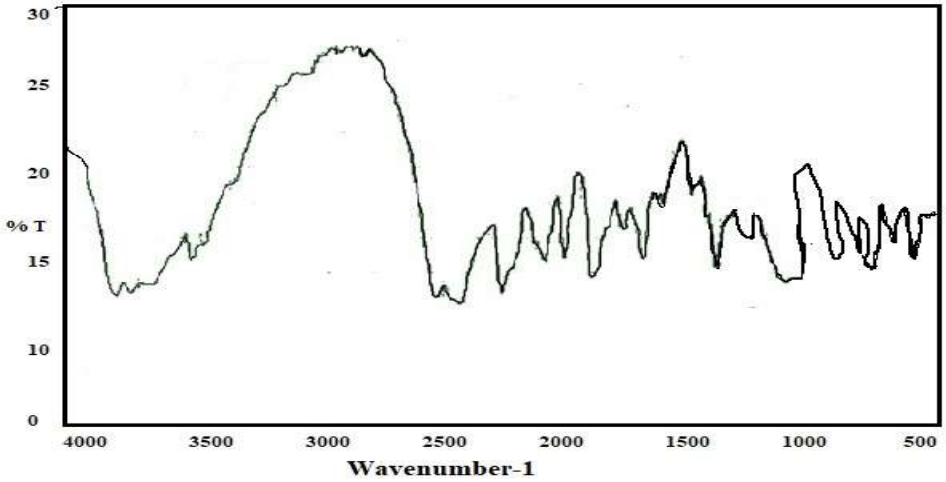


Figure 6: FTIR Spectra of Hydrochlorothiazide And Telmisartan Mixture (1:4) (B3 SD)

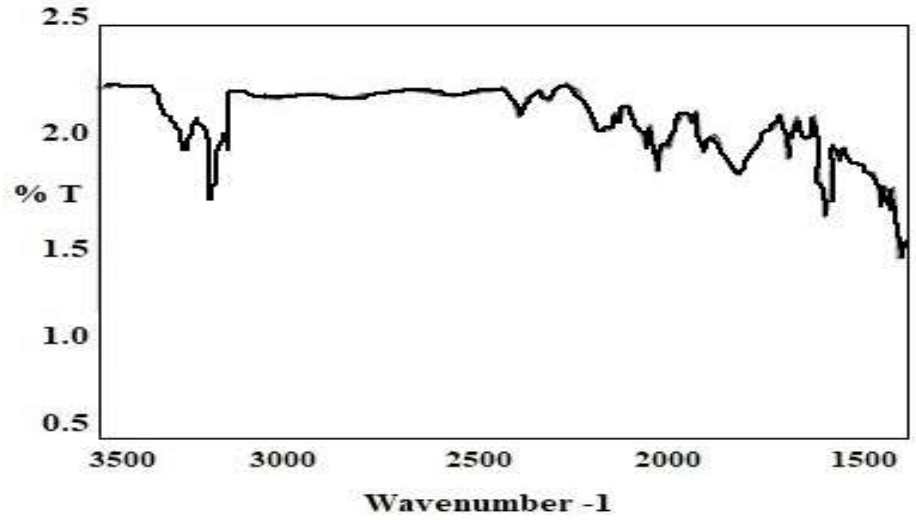


Figure 7: FTIR Spectra of Hydrochlorothiazide and Telmisartan Mixture (1:1) (B3 PM's)

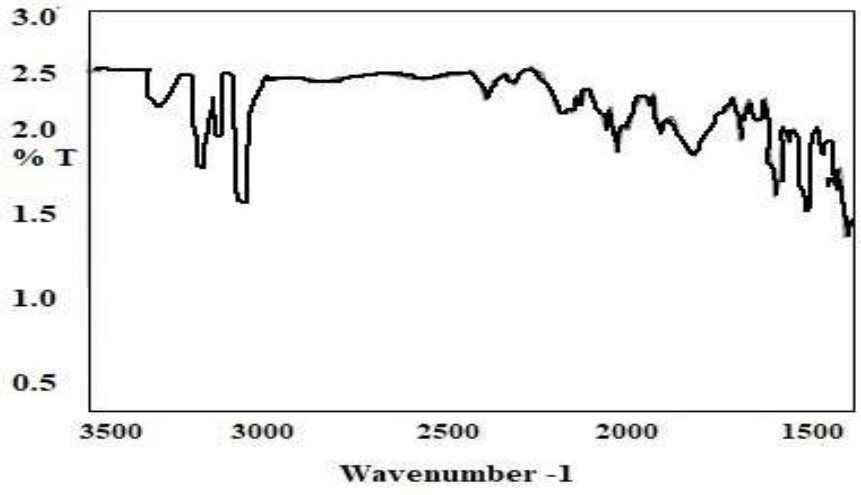


Figure 8: FTIR Spectra of Hydrochlorothiazide and Telmisartan Mixture (1:2) (B3 PM's)

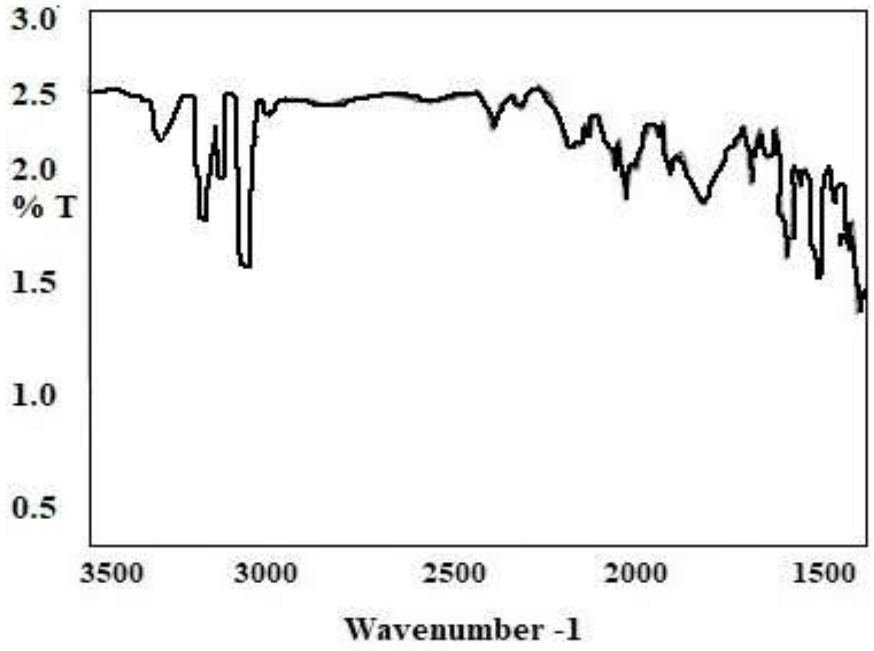


Figure 9: FTIR Spectra of Hydrochlorothiazide And Telmisartan Mixture (1:4) (B3 PM's)

3.3 Differential scanning calorimetry (DSC)

Tables and Figures illustrate the DSC thermo gram of Hydrochlorothiazide, Telmisartan, P.Ms, and S.Ds. TLM and HCT both had a sharp endothermic peak at 241.93°C and 274.35°C, respectively. These peaks correspond to their melting point at their crystalline nature. Endothermic peak of HCT in P.Ms was moved to lower melting temperatures of 236.25°C, 245.12°C, and 239.51°C for B1 P.M, B2 P.M, and B3 P.M, respectively as well as widening the peaks. The endothermic peak of HCT was moved to a lower melting temperature in S.Ds, , at 211.41°C, 229.53°C, and 229.57°C which were B1 S.D, B2 S.D, and B3 S.D formulations, respectively. Additionally, S.Ds peaks were wider than P.M peaks. P.M. and S.D. changes were equivalent, according to TLM's thermo gram. For the B1 PM, B2 PM, and B3 PM formulations the endothermic peak of TLM was detected at 241.93°C; however it was moved to a lower melting temperature of 161.75°C, 212.78°C, and 185.65°C. and shifted to further lower melting temperature141.43°c,187.60°c and 166.53°c for B1 S.D, B2 S.D, B3 S.D for solid dispersion respectively and the endothermic peak in S.Ds were more broader than in P.Ms.

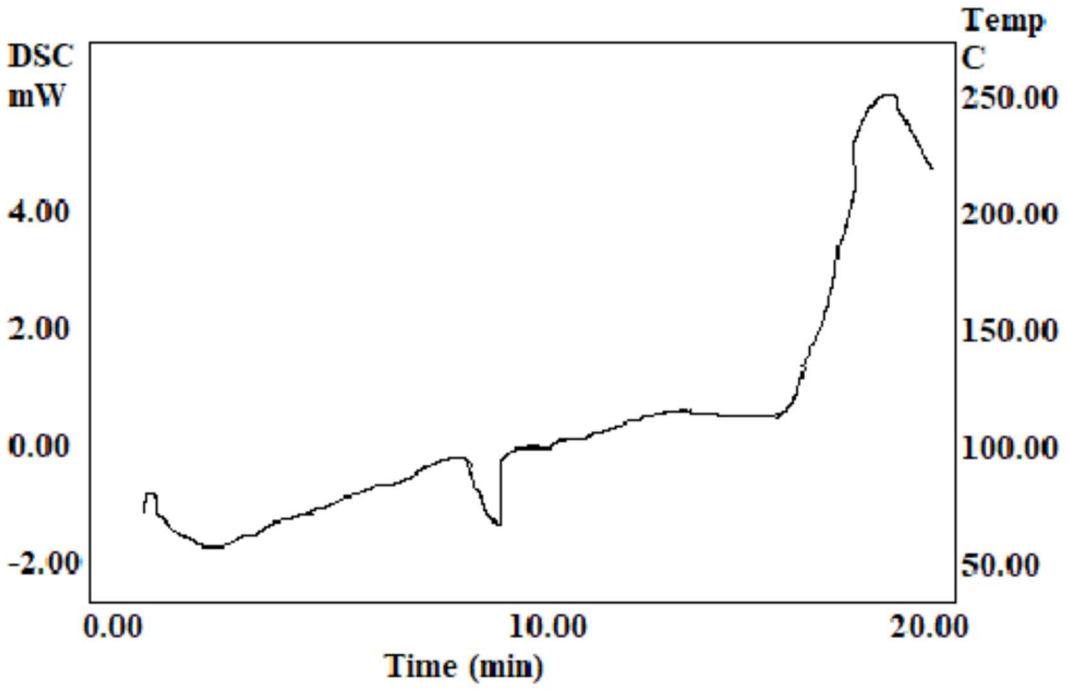


Figure 10: DSC of Hydrochlorothiazide and Telmisartan SD mixture B1 (1:1)

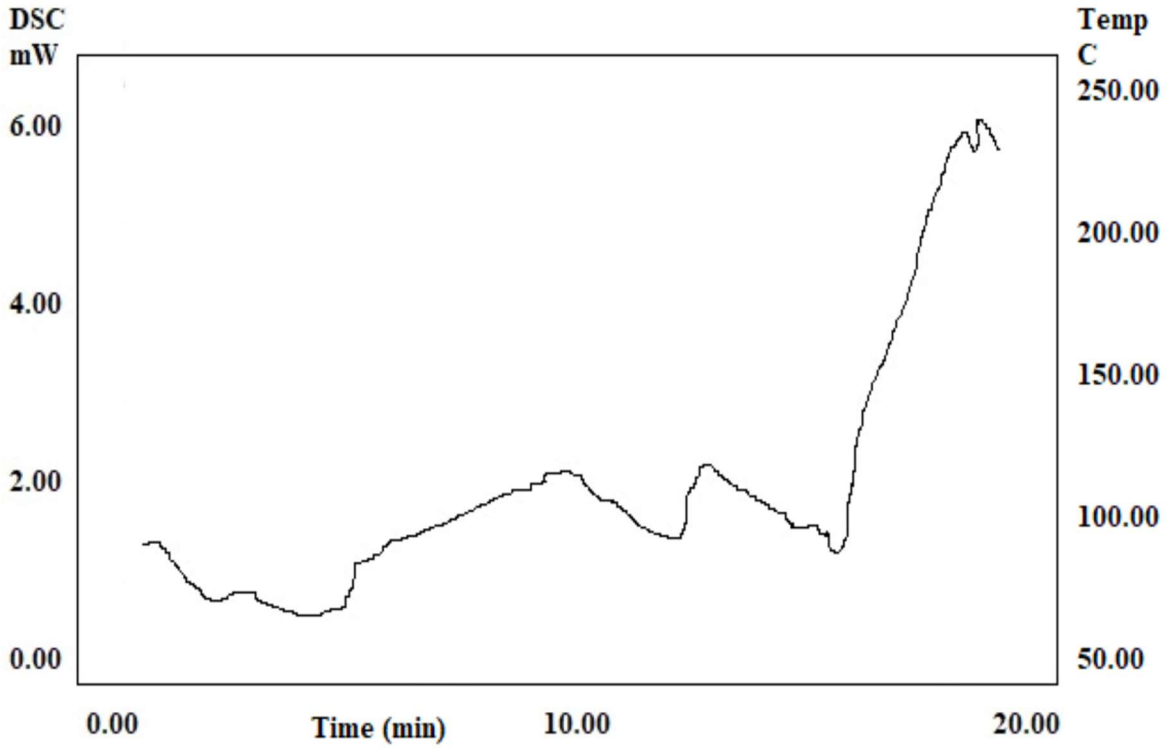


Figure 11: DSC of Hydrochlorothiazide and Telmisartan SD mixture B2 (1:2)

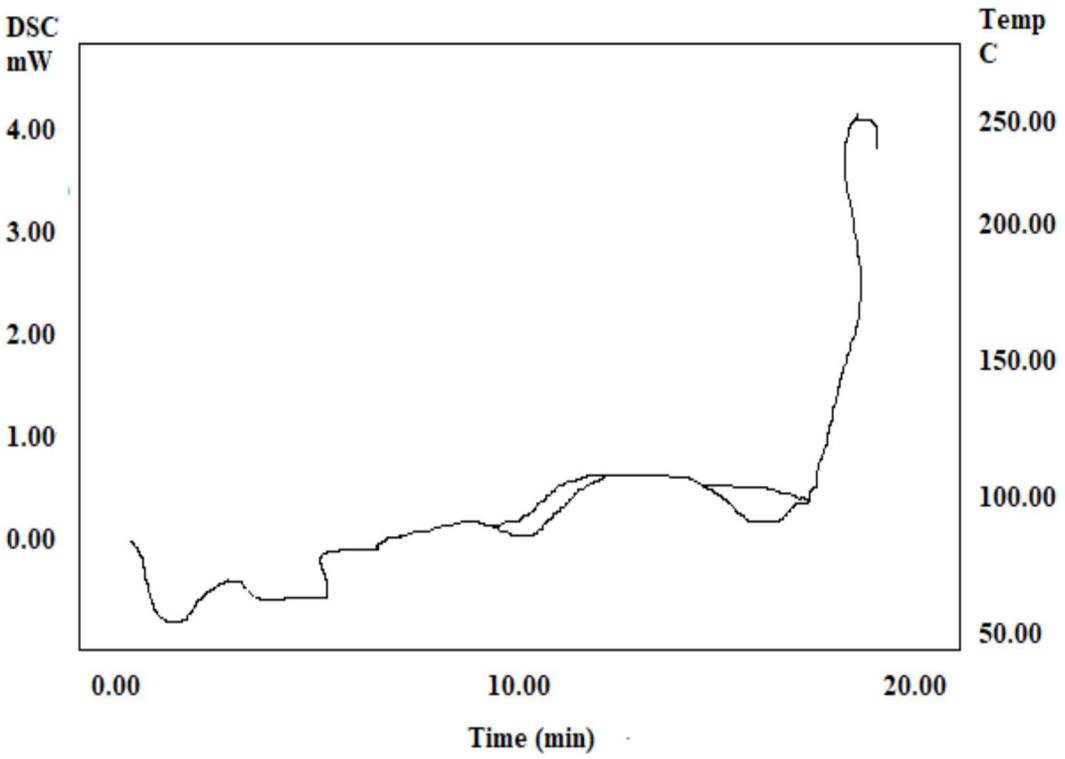


Figure 12: DSC of Hydrochlorothiazide and Telmisartan SD mixture B3 (1:4)

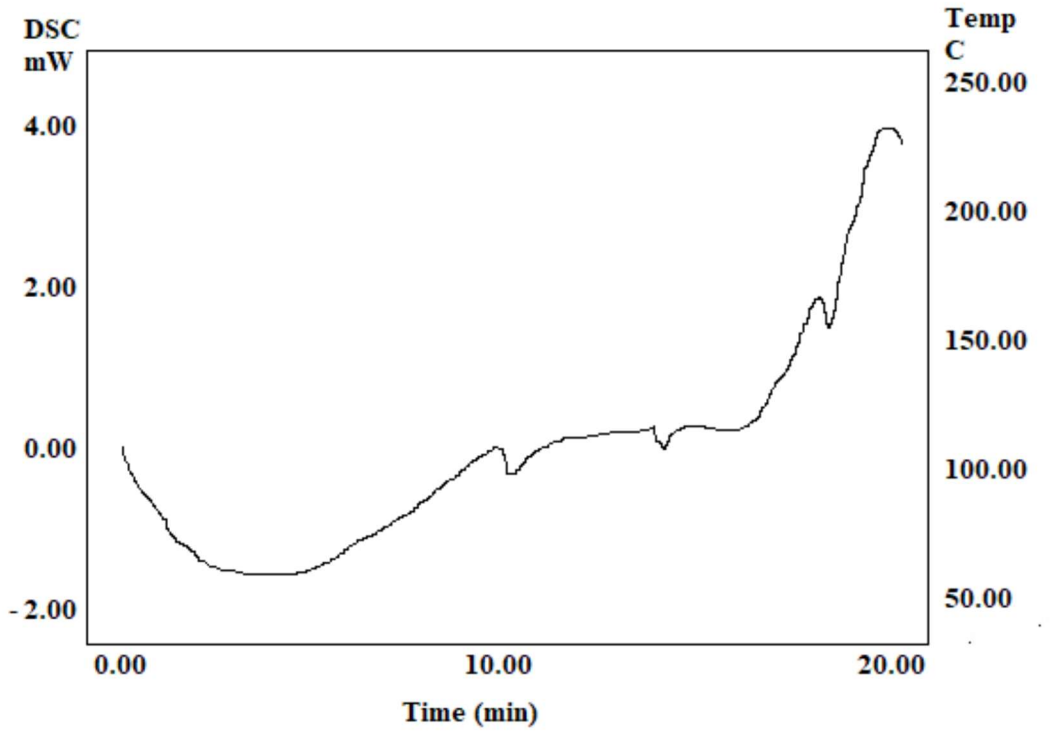


Figure 13: DSC of Hydrochlorothiazide and Telmisartan PM Mixture B3 (1:4)

3.4 DISSOLUTION STUDY

The dissolution profiles of pure Hydrochlorothiazide, physical mixtures, and solid dispersion were assessed following the procedure outlined by the USFDA. The vessel was filled with 900mL of the dissolving medium (0.1N HCL), which was kept at a temperature of 370.5ºC. The medium was added to the sample, and dissolution was carried out at 100 revolutions per minute. At 10, 20, 30, 40, etc., minutes, 10 ml samples were taken out, and an equal volume of dissolution medium was added to keep the sink condition. Filtered samples with a porosity of 0.45 m were used for spectrophotometric analysis at 270 nm for HCT and 240 nm for TLM. The trials were run in triplicate, and the means and standard deviations were noted. The *in vitro* release of solid dispersion has shown enhanced dissolution of Hydrochlorothiazide as compared to physical mixture.

Table 5: *In-Vitro* Dissolution Profile of Pure Hydrochlorothiazide in 0.1N HCL

Time(min)	Trial 1	Trial 2	Trial 3	Mean cumulative %drug release
0	0	0	0	0
10	3.17	3.21	4.50	3.62 ± 0.756
20	9.15	8.97	9.12	9.08 ± 0.096
30	16.42	17.51	17.14	17.11 ± 0.6025
40	19.25	19.27	19.25	19.31 ± 0.092
50	24.19	25.12	24.11	24.47 ± 0.5615
60	34.45	33.21	34.36	34.00 ± 0.6914
70	45.15	44.17	44.84	44.72 ± 0.5009
80	53.7	54.73	54.30	54.24 ± 0.5173
90	59.9	60.1	60.2	60.06 ± 0.1528
100	65.2	66.24	66.1	65.84 ± 0.5644
110	67.42	68.43	67.2	67.68 ±0.655
120	72.81	72.92	73.32	73.01 ± 0.268
130	76.32	75.92	77.1	76.44 ±0.6001
140	85.12	84.89	85.3	85.103± 0.2055
150	92.13	92.15	93.16	92.48 ± 0.5890
160	96.62	95.92	96.53	96.3566 ± 0.3808
170	98.13	98.14	98.23	98.16 ± 0.055
180	98.39	99.2	99.62	99.07 ± 0.6252

Table 6: Comparative dissolution of Hydrochlorothiazide and Telmisartan in 0.1N HCl of Physical mixtures

Time (mins)	PM1		PM2		PM3	
	HCT	TLM	HCT	TLM	HCT	TLM
0	0	0	0	0	0	0
10	32.01	80.01	22.13	80.03	26.57	80.95055
20	51.233	84.37	41.22	83.68	45.67	89.05647
30	62.133	85.65	61.94	87.84	67.1	92.38427
40	70.60	87.34	70.19	92.07	73.53	98.49296
50	78.901	85.91	76.8	93.29	79.97	97.43381
60	82.016	91.916	81.2	94.41	83.52	99.31992
70	87.99	93.19	89.71	95.48	89.04	97.9842
80	91.27	96.12	91.97	96.35	93.73	98.37075
90	95.476	96.6	94.54	99.02	97.68	98.86895

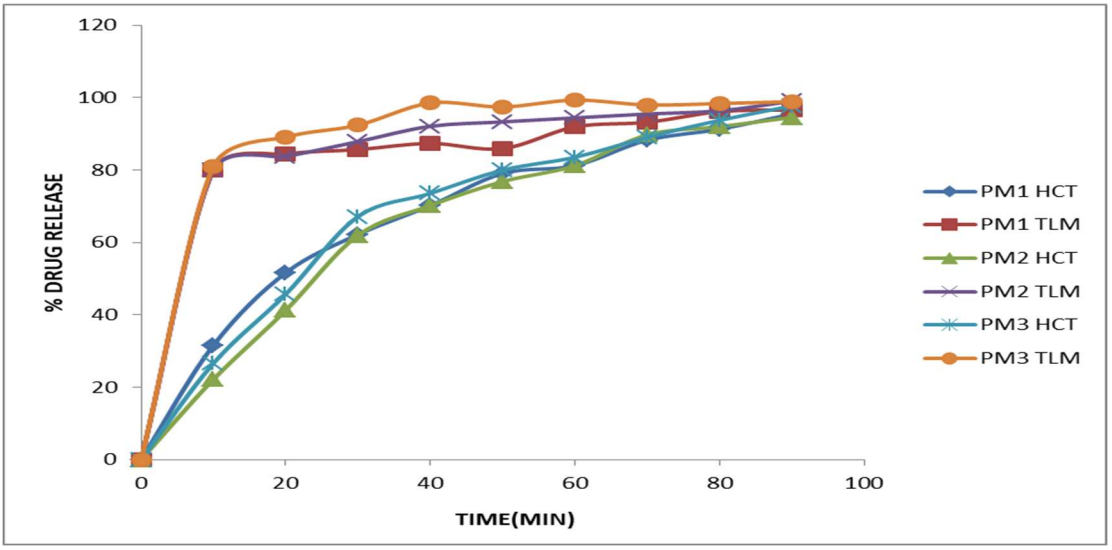


Figure 14: Comparitive drug release of Physical mixture

Table 7: Comparative dissolution of Hydrochlorothiazide and Telmisartan in 0.1N HCl of Solid dispersion

Time (mins)	SD1		SD2		SD3	
	HCT	TLM	HCT	TLM	HCT	TLM
0	0	0	0	0	0	0
10	17.92618	69.75968	25.39329	83.15735	34.97422	89.65235
20	38.39881	81.89524	44.62096	86.6357	59.8403	89.55629
30	74.60408	88.73518	64.17998	89.81148	73.18306	95.95883
40	80.96001	90.46971	76.61241	91.759	82.2804	96.03473
50	87.32291	94.43316	83.98315	93.86258	90.77125	97.62751
60	89.52669	94.35462	89.50617	96.73835	93.80371	97.9007
70	90.83872	95.4815	92.39234	97.15328	98.22965	99.33922
80	95.36725	96.40501	94.35257	97.56855	97.02034	98.77811

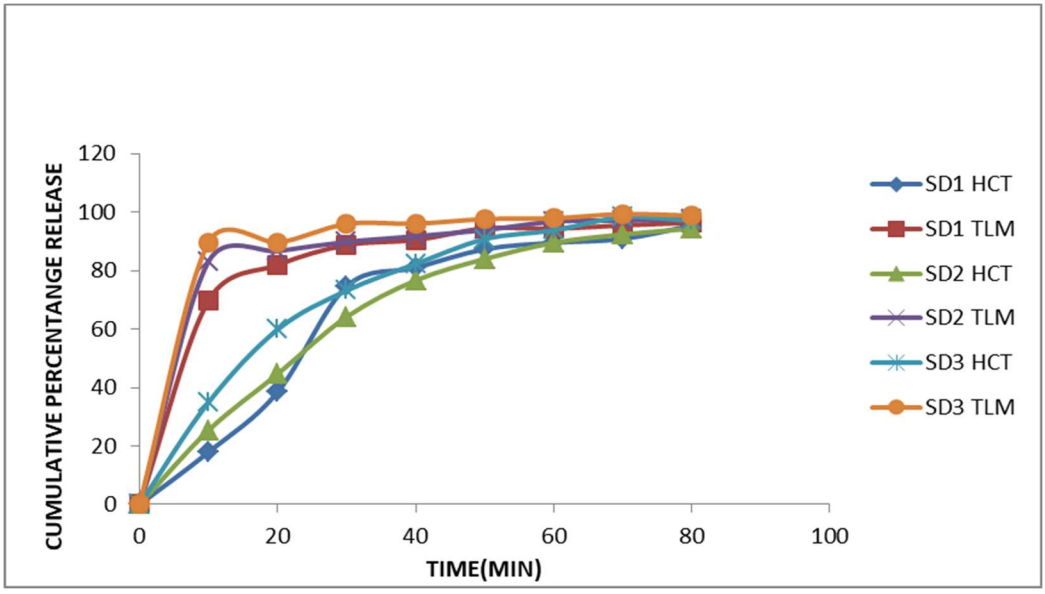
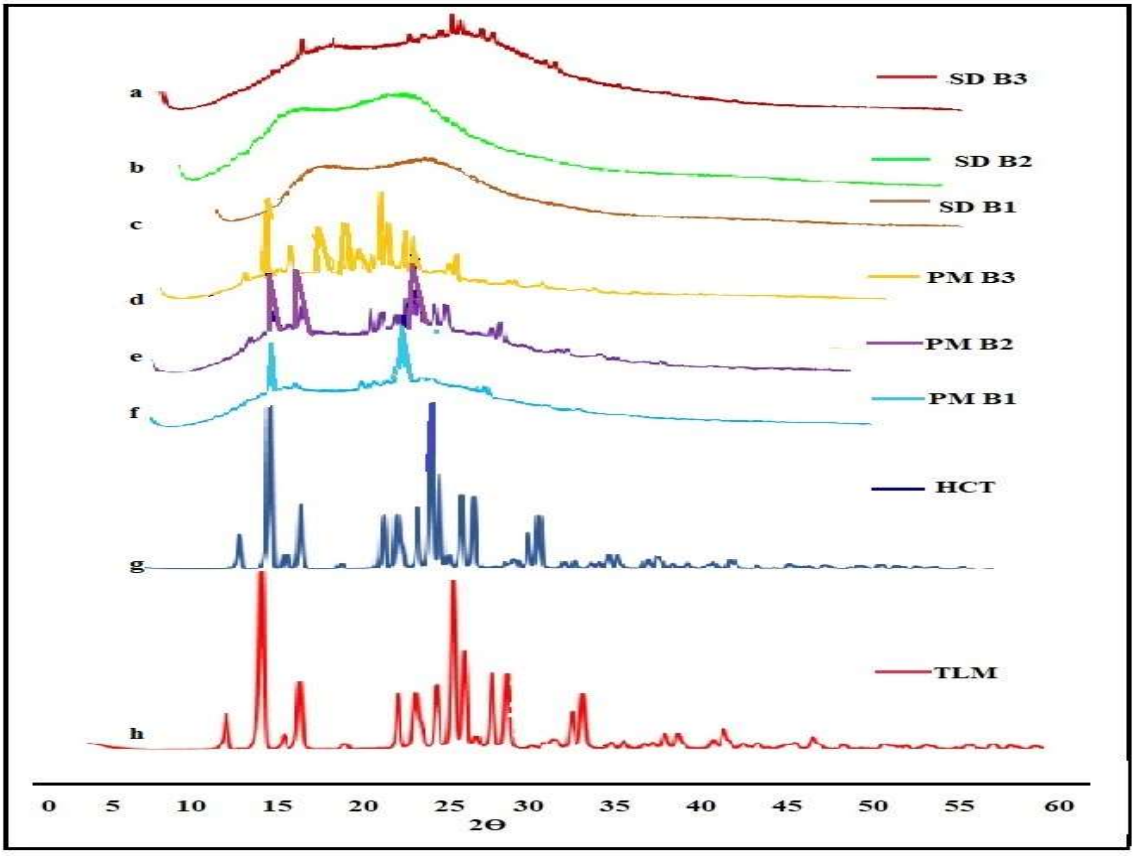


Figure 15: Comparative drug release of solid dispersion

3.5 X-ray Diffractometry study (XRD)

Telmisartan's powder X-ray diffractometry (PXRD) pattern revealed strong peaks that indicated the drug was crystalline. The amorphous nature of the developed formulations was shown by the diffractograms of solid.



3.6 Stability study

ICH guidelines (Q1A) were followed in conducting the stability investigations. The TLM, dry powder, and melt extrudates were packaged in bags made of aluminum. The sealed samples were subjected to temperatures of 100°C for three days, 25°C/60% RH, and 40°C/75% RH for 15 days. In sealed vials, the control samples were kept at 2 to 8°C. Using a developed and validated HPLC technology, the samples were examined for the content of drugs.

The formation of crystalline masses upon exposure of solid dispersion to 40°C/75 percent RH and 100°C was confirmed by DSC experiments. However, the endothermic peak at 25°C and 60% RH showed that the solid dispersion was stable at this temperature. PXRD experiments produced similar findings, demonstrating the stability

of solid dispersions. HPLC analyses of the TLM content of solid dispersions revealed 99.0 and 99.3 percent TLM content, respectively. showed a non-significant change (below 5%) as per ICH guidelines. Additionally, the impact of temperature and moisture on the prepared solid dispersions was evaluated. The formation of crystalline masses upon exposure of solid dispersion to 40°C/75 percent RH and 100°C was confirmed by DSC experiments. However, the endothermic peak at 25°C and 60% RH showed that the solid dispersion was stable at this temperature.

RESULT AND DISCUSSION

The data were compared with that of physical mixture of hydrochlorothiazide and Telmisartan and of pure hydrochlorothiazide. The results showed reduction in particle size, change from crystalline form to amorphous form and enhanced the dissolution rate of hydrochlorothiazide from solid dispersion as compared to physical mixture as well as pure hydrochlorothiazide. The findings of this study show that a unique technique to drug-drug solid dispersion can enhance the dissolving properties of the poorly soluble drug that was combined with the soluble drug in a fixed dosage formulation. In this study, the hypertension drug HCT-TLM was chosen as a paradigm for this innovative drug-drug solid dispersion technique and it's physicochemical; features of in vitro release were examined. Despite being quickly absorbed from the GIT after oral administration, HCT's weak solubility may limit absorption due to dissolution rate issues. When compared to a physical mixture the in vitro release of a solid dispersion has demonstrated improved HCT dissolution. The DSC thermogram shows that the HCT, which was present in crystalline form in the physical mixture, converted to an amorphous state in the solid dispersion. Since amorphous form of HCT is more soluble than its crystalline form, solid dispersion of HCT showed better HCT solubility. Additionally, the freely soluble TLM has made HCT more soluble due to its solvent action, as demonstrated by a phase solubility study.

CONCLUSION

The concept of formulating the solid dispersions of Hydrochlorothiazide and Telmisartan with water soluble carriers such as PEG-4000 offers a suitable and practical approach in serving desired objective of higher solubility, faster dissolution rate and improved bioavailability of drug. 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 hydrochlorothiazide and Telmisartan was significantly improved when formulated in solid dispersions as compare to pure drugs.

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REFERENCE:

[1] R.C.Doijad, A.B.Pathan, S.S. Gaikwad, S.S. Baraskar, N.B. Pawar, V.D.Maske, Liquisolid. A novel technique for dissolution enhancement of poorly soluble drugs current pharma research vol.3(1) 2012.

[2] M.Jeresamarin, M.Victoria margarit, E.Gloria. Scledo Charaterization and solubility study of solid dispersion of flunarizine and polyvinyl pyrrolidone.2002.

[3] Toshioohara, Satoshikitamura, Teruyukikitagawa, Katsuhideterada Dissolution mechanism of poorly water-soluble drug from extended release solid dispersion system with ethylcellose and hydroxypropyl methylcellose. International journal of pharmaceutics volume 302 (2) 2005.

[4] S.S.Mudgal,S.S.Pancholi Formulation of glibenclamide solid dispersion by solvent evaporation technique journal of chemical and pharmaceutical research vol4(1) 2012.

[5] Dingradipti, Bhandarianil R.B, Gupta ranjana, Guptasachin enhancement of dissolution rate of slightly soluble drug domiphene citrate by solid dispersion. International journal of pharm tech research vol2(3) 2010.

[6] Nehaper, Artibagda, Meghalpatel, Sandippatel formulation strategy for dissolution enhancement of simvastatin IJPSR vol 3(10) 2012.

[7] Shahviral, Pateldhiren, Sandeepmane, Upadhyay umesh Solubility and dissolution rate enhancement of licofelone by using modified guar gum. International journal of pharm tech research vol 2(3) 2010.

[8] Vyasjigar, Pateljayvadan, Jain D.A Preparation and characterization of solid dispersion of modafinil for improment of dissolution profile. International journal of pharmacy and pharmaceutical sciences vol 4(5)2012.

[9] Sheth, P., Sandhu, H., Singhal, D., Malick, W., Shah, N., Kislalioglu, M.S., 2012. Nanoparticles in the pharmaceutical industry and the use of supercritical fluid technologies for nanoparticle production. Curr. Drug Deliv. 9, 269–284.

[10] Newa, M., Bhandari, K.H., Li, D.X., Kwon, T.H., Kim, J.A., Yoo, B.K., Woo, J.S., Lyoo, W.S., Yong, C.S., Choi, H.G., 2007. Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188. Int. J. Pharm. 343, 228–237.

[11] Healy AM, Deirdre C, Owen C. Physicochemical and in vitro deposition properties of salbutamol sulphate/ipratropium bromide and salbutamol sulphate/excipients spray dried mixtures for use in dry powder inhalers, Int. J. Pharm., 322, 2006, 22-30.

[12] Kumon M, Kwok PC, Adi H, Heng D, Chan HK, Can low dose combination products for inhalation be formulated in single crystalline particles, Eur. J. Pharm. Sci. 40, 2010, 16-24.

[13] Learoyd TP, Burrows JL, Frenchc E, Seville PC, Sustained delivery by Leucine modified chitosan spraydried respirable powders, Int. J. Pharm., 372, 2009, 97- 104.