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Solubility enhancement studies of hydrochlorothiazide by preparing solid dispersions using losartan potassium and urea by different methods

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ABSTRACT

Drugs having poor aqueous solubility present one of the major challenges for good bioavailability of such drugs. Many approaches have been used for solubility enhancement such as salt formation, complexation, solid dispersion etc. Hydrochlorothiazide (HCT) is one of the BCS class II drug having poor water solubility. Thus to increase its water solubility by solid dispersion technique many inert carriers are employed. HCT is used in combination of losartan potassium for management of hypertension. In present investigation we have used novel method by employing losartan potassium as a carrier for solid dispersion of HCT (SD_L) as well as both losartan potassium and inert carrier urea in combination for solid dispersion of HCT (SD_{LU}). Both the solid dispersions were prepared by physical mixture, paste method, solvent evaporation method and fusion method. Out of this SD_L and SD_{LU} prepared by solvent evaporation method exhibited maximum solubility. The FTIR study confirmed absence of any physical interaction between drugs and excipients. The XRD studies show the conversion of crystalline form of drug into amorphous form and hence, increase in the solubility. Tablets of SDT_L and SDT_{LU} were prepared by employing direct compression method and their release profiles were compared with marketed tablet containing HCT and losartan potassium. Drug release studies showed that at 90 mins release of HCT by SDT_{LU} was found to be maximum i.e. 88.24±0.04 as compared to SDT_L (74.45±0.17) and marketed tablet (62.46±0.20). Thus the studies carried out exhibited good scope of using losartan potassium and urea together for enhancing the aqueous solubility of HCT up to the mark especially when HCT is to be used in combination with Losartan potassium.

Keywords: Hydrochlorothiazide, Losartan potassium, Urea, Solid dispersion, Solvent evaporation.

INTRODUCTION

The oral route of drug administration is the most common route of delivery due to convenience and ease of ingestion. Oral route of administration of drugs thus confers patient compliance which makes it more effective when compared with other routes of administration for example,

parenteral. The drugs with poor aqueous solubility typically exhibit dissolution rate limited absorption and hence, show poor bioavailability. Such drugs seem to be problematic and less effective mode of delivery via oral route. Therefore the present work was undertaken to improve the bioavailability of poorly water soluble drug i.e. hydrochlorothiazide, by enhancing its solubility in GIT. Various techniques like complexation (1); solid dispersion (2, 3) etc. can be used to enhance the solubility. In present study we have used solid dispersion (SD) techniques for enhancing the solubility of hydrochlorothiazide.

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly in amorphous particles (clusters) or in crystalline particles. The solid dispersion enhances the drug solubility by the various mechanisms: by reducing the particle size; by improving bioavailability; by increasing porosity; by converting the crystalline forms of drug into amorphous form.

The various water soluble carriers such as PVP (4), PEG (5), Urea (6), Mannitol (7), etc. were used for increasing the solubility of drugs. Recently, Padma PS (8) *et al.* found that the salt form of the drug captopril i.e. captopril hydrochloride has ability to enhance the solubility of poorly water soluble Hydrochlorothiazide.

The hydrochlorothiazide (6-chloro-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide) is poorly water soluble drug (0.7 mg/mL) (9) which is diuretic and used in the management of hypertension. The losartan potassium (LP) is form of losartan which is freely water soluble is an angiotensin II receptor blocker used for treating the hypertension. Hydrochlorothiazide and losartan potassium are used in combination for management of hypertension (10), but hydrochlorothiazide show bioavailability only up to 65% due to its low solubility in GIT.

In this study we have tried to improve the solubility of poorly aqueous soluble drug hydrochlorothiazide by solid dispersion technique using losartan potassium alone as drug carrier and also by using losartan potassium along with inert carrier urea.

MATERIALS AND METHODS

Hydrochlorothiazide (HCT) was the drug selected for enhancement of solubility and Losartan potassium (LP) which was selected as a hydrophilic carrier for preparing solid dispersion were supplied by Vama Pharmaceuticals Ltd. (Wadi, Nagpur, India). Other reagents and solvents used were of analytical reagent grade.

Phase Solubility Study

Excessive amount of pure hydrochlorothiazide was added to 100 ml of deaerated water containing varying concentrations of losartan potassium i.e. 1-6% in a stoppered flask. The solution was equilibrated by continuous stirring for 24 hrs maintained at 37^0C filtered through whatman filter paper and analyzed by spectrophotometer (Shimadzu 160A UV/VIS spectrophotometer, Shimadzu Corp, Tokyo, Japan). The solubility was then calculated to determine the optimize ratio of HCT and LP which have maximum solubility.

For further study, fixed ratio of HCT and LP (1:4) was added to various concentration of urea (0.5-3%) and solubility was determined for comparisons.

Preparation of Solid Dispersions

The solid dispersions of hydrochlorothiazide were prepared by using-
1. drug as a hydrophilic carrier i.e. Losartan potassium (SD_L).
2. losartan potassium and inert carrier Urea (SD_{LU}) in combination.

Various methods used to prepare solid dispersions of HCT includes: physical mixture; fusion method; paste method and solvent evaporation method.

Drug Content

Solid dispersions SD_L and SD_{LU} equivalent to 12.5 mg of hydrochlorothiazide and 50 mg of losartan potassium were accurately weighed and dissolved in 100 mL methanol, from that 1 mL of solution was diluted and assayed for drug content by spectrophotometeric method at λ max 254 nm and 272 nm.

Interaction Study

Fourier-transform infrared spectroscopy

To determine possible solid state interactions between the drug and excipients, the IR spectra of pure HCT, pure LP, pure urea and the solid dispersion of SD_L (1:4) and of SD_{LU} (1:4:1.5) were carried out using FTIR spectrophotometer (Shimadzu 8400S). The pellets of samples and KBr (1:1000) were prepared by using hydraulic press under a pressure (9 Ton/nm^2) and scanned between 400 and 4000 cm^{-1}.

Powder X- ray diffraction (XRD)

The powder samples of pure HCT, pure LP, pure urea and the solid dispersion of SD_L (1:4) and of SD_{LU} (1:4:1.5) prepared by solvent evaporation were packed in the x-ray holder from the top before analysis. X-ray powder diffraction patterns were recorded on Rigaku diffractometer using nil filterd, Cu α K radiation, voltage of kV and a 300 mA current. These samples were continuously spun and scanned at a rate of 0.02^0s^{-1} over 2θ range of $3\text{-}50^0$.

Micromeritics properties of solid dispersion

Various parameters were studied for determining micromeritics properties of solid dispersion prepared by solvent evaporation method which includes bulk density, tapped density, Carr's Compressibility index, Hausner's ratio and angle of repose.

Tablet Preparation and Characterization

The solid dispersions of optimize batch of SD_L (1:4) and SD_{LU} (1:4:1.5) both equivalent to 12.5 mg of HCT and 50 mg of LP were accurately weighed and mixed well with starch, avicel, magnesium stearate and talc. The mixture was passed through a sieve no. 30. The sample was compressed into tablet using a Cadmach single punch tablet press using circular flat 6mm punch. The formulation of tablet of solid dispersion of hydrochlorothiazide with losartan potassium in ratio of 1:4 and with losartan potassium and urea in ratio of 1:4:1.5 given in table 1.

***In Vitro* Dissolution Study**

In vitro dissolution studies of SDT_L, SDT_{LU} and marketed tablet were performed using 900 mL of 0.1N HCL at 37 ± 0.5^0C, as a dissolution medium at 100 rpm using 6-station USP XXII apparatus- II (TDT-50, Electrolab, Mumbai, India) .Samples were withdrawn at fixed intervals, filtered (pore size 0.22 μm), diluted suitably with dissolution medium and analysed for hydrochlorothiazide content spectrophotometrically at 272 nm.

Table 1: Formulation of tablets of SD_L and SD_{LU}

Sr. No.	Ingredients	Quantity (mg) For 1 tablet	
		SDT_L (1:4)	**SDT_{LU} (1:4:1.5)**
1	Solid Dispersion (Eqivalent to 2.5 mg of hydrochlorothiazide and 50 mg of losartan potassium)	64.12	71.05
2	Starch	25.0	25.00
3	Avicel	50.89	43.95
4	Magnesium stearate	5.0	5.0
5	Talc	5.0	5.0

SDT_L: Tablets of solid dispersion of HCT: Losartan Potassium
SDT_{LU}: Tablets of solid dispersion of HCT: Losartan Potassium: Urea

RESULTS AND DISCUSSION

Solubility study of hydrochlorothiazide for the determination of optimized ratio

1. With Losartan potassium

Table 2: Solubility of Hydrochlorothiazide in varying concentration of Losartan potassium

Sr. No.	1	2	3	4	5	6
Ratio of HCT: LP	1:1	1:2	1:3	**1:4**	1:5	1:6
Solubility (µg/mL)	6.88 ± 0.019	8.45 ± 0.116	9.61 ± 0.245	**11.52 ± 0.159**	11.26 ± 0.312	11.00 ± 0.039

2. With varying conc. of urea by taking optimized ratio of HCT: LP (1:4)

Table 3: Solubility of Hydrochlorothiazide in varying concentration of Urea in optimized ratio of HCT: LP (1:4)

Sr. No.	1	2	3	4	5	6
Ratio of HCT: LP: Urea	1:4:0.5	1:4:1	**1:4:1.5**	1:4:2	1:4:2.5	1:4:3
Solubility (µg/mL)	8.02 ± 0.175	11.00 ± 0.098	**14.71 ± 0.242**	14.52 ± 0.026	14.09 ± 0.143	14.59 ± 0.187

Solubility studies revealed that the maximum solubility of HCT i.e. 11.52±0.159 **µg/mL** was obtained when HCT and LP were present in ratio of 1:4 which is the general dose ratio in which drugs are administered in combination. Further study also exhibited that the solubility of HCT was increased to another extent i.e. 14.71±0.242 µg/mL when HCT, LP and urea were present in ratio of 1:4:1.5. Thus these ratios exhibiting maximum solubility were chosen for preparation of solid dispersions.

Comparison of solubility of solid dispersion by various methods

Table 4: Comparison of solubility of solid dispersion of HCT: LP (1:4) by various methods (SD_L)

Sr. No.	Methods	Solubility (µg/mL)
1	Physical Mixture	6.23 ± 0.032
2	Paste method	4.85 ± 0.162
3	Fusion method	11.47 ± 0.037
4	Solvent Evaporation method	13.02 ± 0.076

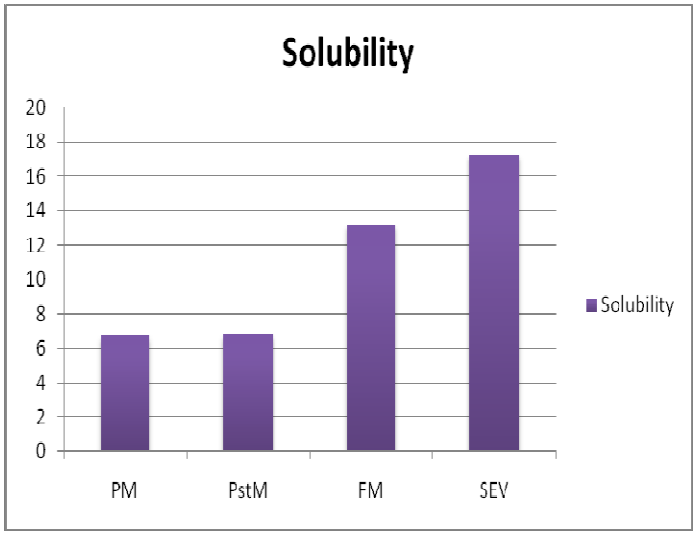


Fig 1: Comparison of solubility of solid dispersion of Hydrochlorothiazide: Losartan Potassium (1:4) by various methods (SD_L)

Table 5: Comparison of solubility of solid dispersion of HCT: LP: Urea (1:4:1.5) by various methods (SD_{LU})

Sr. No.	Methods	Solubility (µg/mL)
1	Physical Mixture	6.76 ± 0.145
2	Paste method	6.83± 0.210
3	Fusion method	13.16± 0.154
4	Solvent Evaporation method	17.26± 0.034

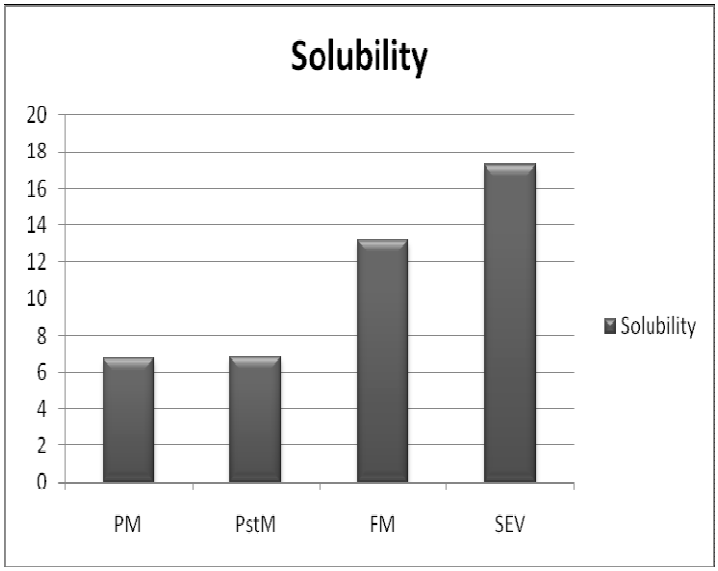


Fig 2: Comparative solubility chart of solid dispersion of Hydrochlorothiazide: Losartan Potassium: Urea (1:4:1.5) by different methods (S_{LU})

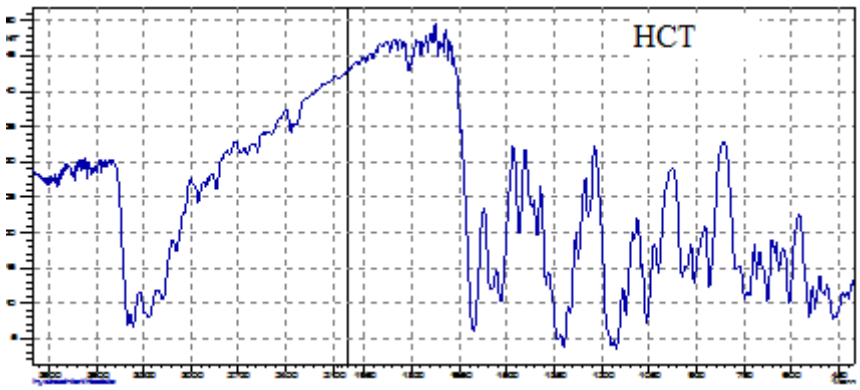
When solid dispersion of HCT with LP was prepared by various methods, the solid dispersion prepared by solvent evaporation method exhibited maximum enhancement of solubility as compared to other methods as shown in table 4 (figure 1) and table 5 (figure 2).

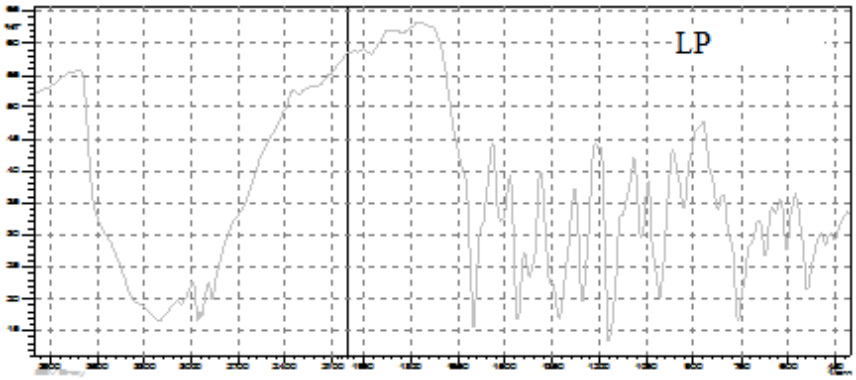
Drug Content

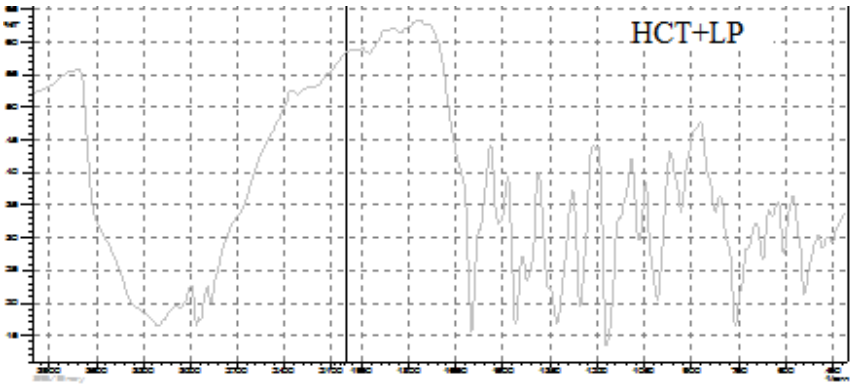
Drug content for all the solid dispersion was found to be in the range of 97.46% for SD_L and 98.52% for SD_{LU} which is acceptable as per USP (11).

Interaction Study

Fourier-transform infrared spectroscopy







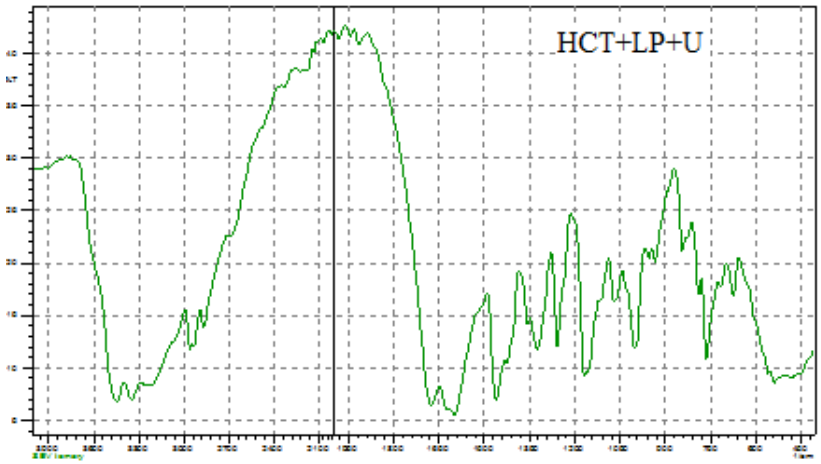


Fig 3: FTIR Spectrum of HCT: Pure Hydrochlorthiazide, LP: Pure Losartan potassium, U: Pure Urea and HCT+LP+U: Hydrochlorthiazide+Losartan potassium+Urea (1:4:1.5)

The FTIR spectrum of pure HCT exhibited presence of characteristic peaks which included peaks at 3380,3280,3150 for NH- stretching, peaks at 3080,3020 for CH-stretching, peaks at 2960, 2900 for CH_2 stretching and at 1600,1525 for C=C stretching. The FTIR study did not show any additional peak, but most of the peaks of drug were present. This confirms the absence of any physical interaction between drugs and excipients.

Powder X- ray diffraction (XRD)

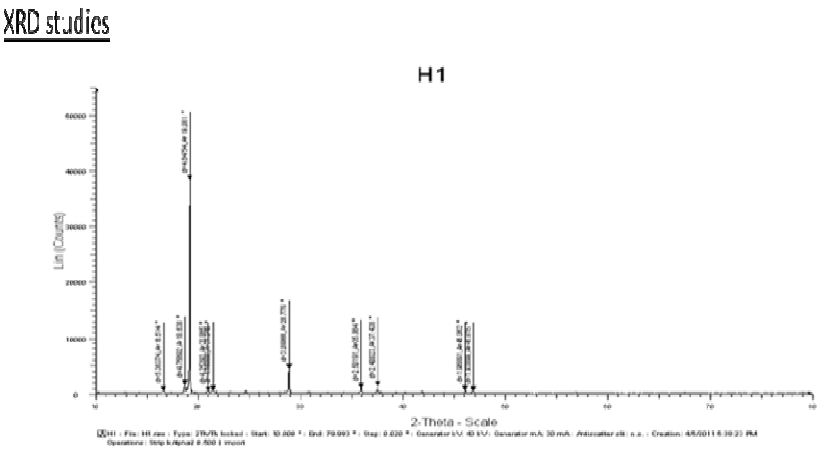


Fig 4: Diffractogram of Hydrochlorthiaizde

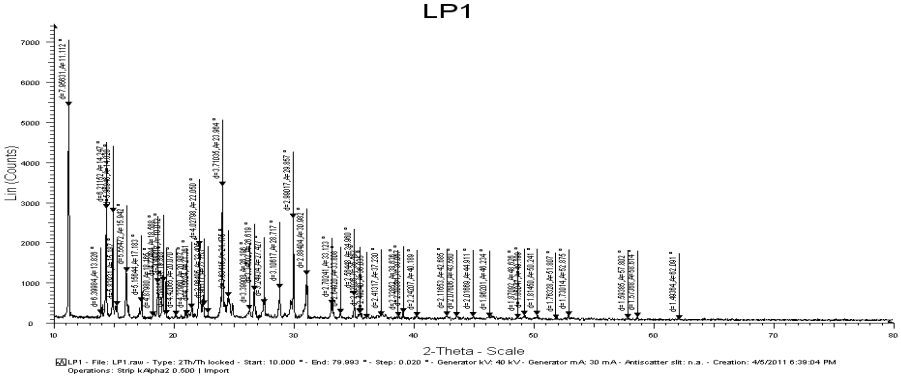


Fig 5: Diffractogram of Losartan potassium

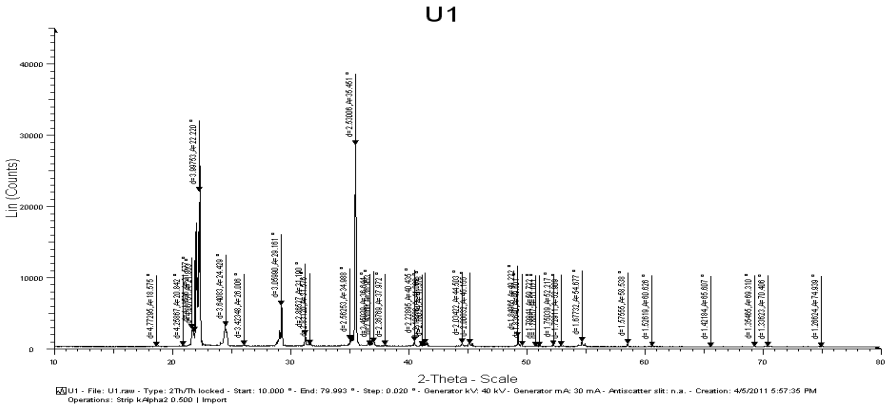


Fig 6: Diffractogram of Urea

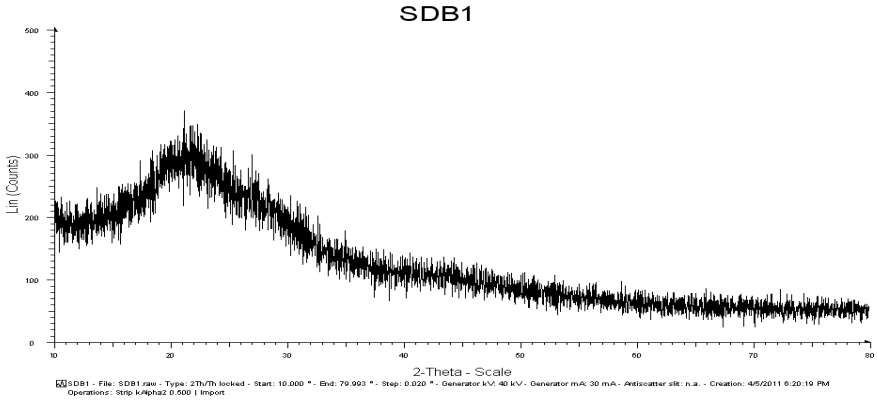


Fig 7: Diffractogram of Hydrochlorothiazide + Losartan potassium (1:4)

From the figure 7, it was found that the diffraction of SD_L was very closer as compared to pure HCT and LP. The XRD studies show the conversion of crystalline form of drug into amorphous form and hence, increases the solubility.

Micromeritics Properties

Table 6: Physico-chemical characterization of prepared solid dispersion with excipients (Micromeritics Properties)

Formulations	Parameters (Mean ± SD, n=3)				
	Bulk Density	Tapped Density	Hausner's Ratio	Carr's Index	Angle of Repose
T_M	0.610 ± 0.039	0.669 ± 0.029	1.098 ± 0.027	8.89 ± 2.38	27.29 ± 1.4
SDT_L	0.601 ± 0.045	0.653 ± 0.044	1.087 ± 0.025	7.57 ± 1.33	28.30 ± 1.1
SDT_{LU}	0.592 ± 0.028	0.632 ± 0.035	1.069 ± 0.011	6.47 ± 0.96	29.19 ± 0.9

T_M: Marketed preparation of Hydrochlorothiazide and Losartan potassium
SDT_L: Tabletting material containing solid dispersion of HCT: LP and excipients.
SDT_{LU}: Tabletting material containing solid dispersion of HCT: LP: Urea and excipients.

From the table 6 findings, it was observed that the powder containing solid dispersion of SD_L and SD_{LU} showed good flow properties.

In-Vitro Dissolution Studies

Table 7: Cumulative % Release of HCT from solid dispersions STD_L and STD_{LU} and marketed tablet

Sr. No.	Time (min)	Cumulative Percentage Release (%)		
		(SDT_L)	(SDT_{LU})	T_M (Marketed)
1	0	0	0	0
2	15	18.52 ± 0.40	21.95 ± 0.20	15.34 ± 0.31
3	30	24.78 ± 0.32	37.46 ± 0.142	18.26 ± 0.19
4	45	47.81 ± 0.12	56.71 ± 0.06	28.62 ± 0.06
5	60	58.17 ± 0.02	62.82 ± 0.21	38.04 ± .04
6	75	67.38 ± 0.12	73.96 ± 0.13	51.37 ± 0.13
7	90	74.45 ± 0.17	88.63 ± 0.04	62.46 ± 0.20
8	105	73.87 ± 0.07	88.24 ± 0.07	62.29 ± 0.119
9	120	73.92 ± 0.25	88.54 ± 0.106	61.17 ± 0.092

T_M: Marketed Tablets of Hydrochlorothiazide and Losartan potassium
SDT_L: Tablets containing solid dispersion of HCT: LP
SDT_{LU}: Tablets containing solid dispersion of HCT: LP: Urea

When compared with the marketed tablet containing hydrochlorothiazide and losartan potassium in fixed dose combination the tablet formulation containing solid dispersion in same concentration showed more *in vitro* drug release.

Also it was found that solid dispersion prepared by using urea and losartan potassium, solubility was enhanced even more as compared to solid dispersion prepared by using losartan potassium alone (Table 7 and figure 8).

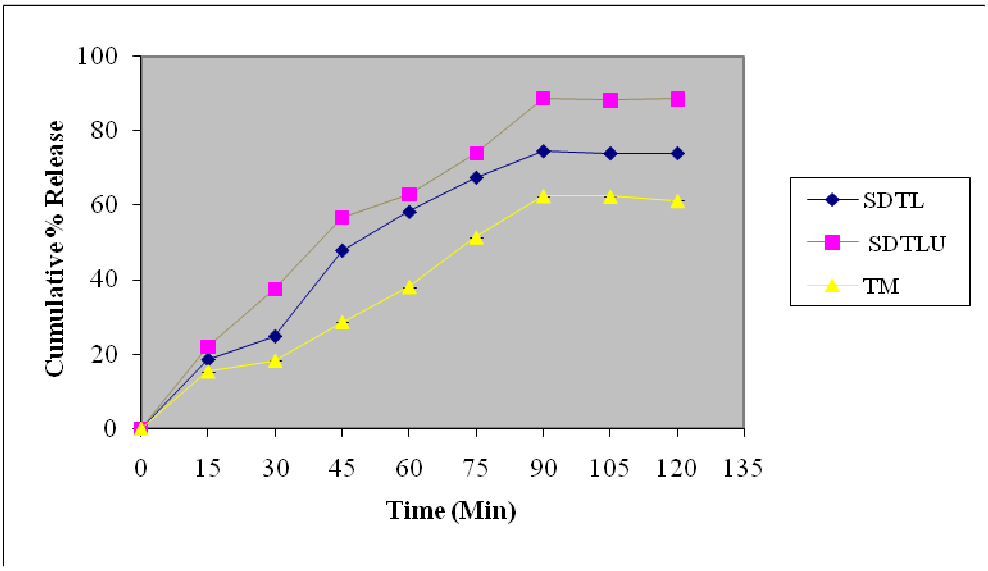


Figure 8: Hydrochlorothiazide release profile from solid dispersions prepared by the solvent evaporation method

CONCLUSION

The study done reveals that the water solubility and hence bioavailability of hydrochlorothiazide can be enhanced in even more better rate by using losartan potassium and urea in combination as carrier for preparing solid dispersion. Studies also exhibited that solvent evaporation method can give solid dispersion having maximum solubility as compared to physical mixture, paste method

and fusion method. Thus it can be concluded that when hydrochlorothiazide is used in combination with losartan potassium going for solid dispersion technique using losartan potassium alone as a carrier or in combination with urea can be a better approach to achieve maximum solubility.

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