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Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2011, 3(4):150-158

ISSN No: 0975-7384
CODEN(USA): JCPRC5

Effect of losartan potassium on the solubility of hydrochlorothiazide by solid dispersion technique

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ABSTRACT

The present study was carried out to study the feasibility of a novel drug-drug solid dispersion for improving the dissolution of poorly soluble drugs. Hydrochlorothiazide - losartan potassium, which is a fixed dose combination and used for treatment of hypertension was selected as a model for the study. Hydrochlorothiazide is poorly soluble and its absorption is dissolution rate limited. Losartan potassium is freely soluble and used to effect solid dispersion of hydrochlorothiazide. Solid dispersion of hydrochlorothiazide-losartan potassium (1:4) was prepared by solvent evaporation method 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 losartan potassium 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, Losartan potassium, Poorly Soluble Drugs, Dissolution Enhancement, Solid Dispersion.

INTRODUCTION

Orally administered drugs should undergo dissolution in the gastro-intestinal fluids before absorption can commence. Insoluble or poorly soluble drugs are generally poorly absorbed from the gastro-intestinal tract after oral administration. The absorption behaviour of such drugs can be best studied by in-vitro dissolution characteristics. In other words, in-vitro dissolution is considered the index of in-vivo absorption of poorly soluble drugs[1]. The process of drug dissolution involves the transfers of individual molecule from a solid state into an aqueous environment. The underlying principles involved in the solubility process are diffusion, chemical

reactivity and hydrodynamic behavior[2] . The rate of dissolution of drug particles is explained by Noyes-whitney equation.

Solid dispersion is a unique approach to present a poorly soluble drug in an extremely fine state of subdivision to the gastro intestinal fluids. It can be prepared by fusion, co-precipitation and kneading methods.

Solid dispersion can form either a eutectic mixture or solid solution or glass solution or amorphous precipitation in a crystalline carrier or compound or complex formation.

The following factors[3] may contribute to improved dissolution rate and bioavailability exhibited by a drug present in the form of solid dispersion system.

1. An increase in aqueous solubility of the drug because of its extremely small particle size.
2. A possible solubilization effect [4]on the drug by the carrier in the diffusion layer surrounding each dissolved drug particle in the gastrointestinal fluids.
3. A possible formation of metastable polymorphic forms.
4. A reduction or absence of aggregation and agglomeration of drug particles.
5. Excellent wettability and dispersibility of the exposed drug particles in the gastrointestinal fluids.

The fixed dose combination of drugs is effective in the treatment of essential hypertension and of systolic hypertension in the elderly patient[5] .Hydrochlorothiazide and losartan potassium is one of the fixed dose combinations that have been effectively employed in the management of hypertension[6]. Losartan potassium is an angiotensin receptor blocker (ARB), and controls hypertension through this mechanism. Hydrochlorothiazide is a thiazide diuretic and it indicated along with the suitable antihypertensive drugs in the management of hypertension. Hydrochlorothiazide inhibits Na^+ and Cl^- reabsorption in the early distal tubule and collecting system[7] .

Considering the above factors a novel solid dispersion approach was proposed in the present study wherein the poorly soluble drug can be solid dispersed in the water soluble drug (both type of drugs available in a fixed dose combination) that improves dissolution of the poorly soluble drug and hence its absorption.

Hydrochlorothiazide is poorly soluble whereas losartan potassium is freely soluble in water. Owing to its poor solubility hydrochlorothiazide poses dissolution rate limited absorption problem. An increase in dissolution rate of Hydrochlorothiazide will certainly prove beneficial with improved absorption characteristics[8]. Further, hydrochlorothiazide coexists with losartan potassium in the fixed dose combination and hence the viability of solid dispersion of hydrochlorothiazide in losartan potassium, a novel solid dispersion approach, was examined in the present study.

EXPERIMENTAL SECTION

Materials:

Hydrochlorothiazide (USP) was obtained from Mecleods Pharmaceuticals Ltd, Mumbai. Losartan potassium (USP) was obtained from Candila Pharmaceuticals Ltd, Gujarat. Methanol, Lactose, Starch, Magnesium Stearate, Avicel and Talc were obtained from Loba Chemie pvt. Ltd, Mumbai.

Preformulation (compatibility) studies:
Compatibility study of drug with the carrier was determined by using Perkin Elmer spectrum RX1 FT-IR spectrometer model. The pellets were prepared at high compaction pressure by using potassium bromide and the ratio of sample to potassium bromide is 1:100.

Estimation of Pure drugs, Physical mixtures and Solid dispersions:
Method 1 (Mixed standards method):
Pure sample of Losartan and potassium were analyzed by Spectrophotometer method as described by M.Gandhimathi et.al.[9]

100mg of Losartan potassium 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 Losartan potassium 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 Losartan potassium were accurately weighed at the ratio of 1:4, pulverized, and then 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 losartan potassium at the ratio 1:4 was prepared by solvent method. Hydrochlorothiazide and losartan potassium were dissolved in methanol and mixed with magnetic stirrer. Solvent was evaporated under reduced pressure at 40^{o}C in a rotary evaporation apparatus. Subsequently solid dispersion was stored in vacuum over silica gel for 12hrs at room temperature. After 12hrs dried solid dispersion was passed through a 250µm sieve. Sample was stored in a desiccator and used.

Characterization studies:
Determination of equilibrium solubility of Hydrochlorothiazide/Losartan potassium in deaerated water:
Excessive amount of pure hydrochlorothiazide (250mg) was added to 100mL of Deaerated Water containing varying concentration of losartan potassium (.0025%, 0.005%, 0.01%w/v) in stoppered flasks. These suspensions were equilibrated by intermittent shaking for 72hrs maintained at 37±2^{o}C. These suspensions were filtered trough a whatman filters. The concentration of hydrochlorothiazide was determined by mixed standards method.

Preparation of tablets:
Solid dispersion or physical mixture of Hydrochlorothiazide and Losartan potassium (1:4) were accurately weighed and mixed well with Starch, Avicel, Magnesium Stearate and Talc. The

mixture was passed through a (280) µm sieve. The sample was compressed in to tablet using a cadmach single punch tablet press using circular flat punch. The composition of the tablets was described in table 1.

Table 1: Composition of Physical Mixture and Solid Dispersion

Ingredients	Quantity in mg/tablet (PM)	Quantity in mg/tablet (SD)
HCT-LSP	60	60
Starch	80	80
Avicel	56	56
Magnesium stearate	1	1
Talc	3	3

HCT-Hydrochlorothiazide, LSP-Losartan potassium, PM-Physical Mixture, SD-Solid Dispersion

Equilibrium solubility study:

The equilibrium solubility study showed that the solubility of hydrochlorothiazide increased with increase in concentration from 0.246mg/ml to .654mg/ml of losartan potassium, thus indicating the solvent effect of losartan potassium on hydrochlorothiazide.

Table 2: Effect of losartan potassium on the solubility of hydrochlorothiazide

Concentration of Losartan potassium(%w/v)	Solubility of HCT* in Losartan potassium solution(mg/ml)
0	0.246
0.0025	0.3267
0.005	0.5391
0.01	0.6535

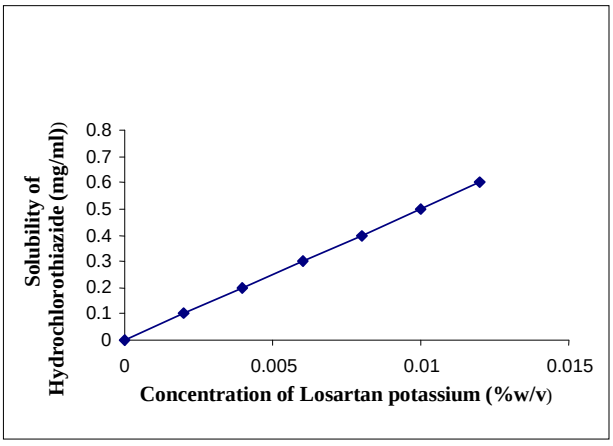

Fig 1: Effect of Losartan potassium on the solubility of Hydrochlorothiazide.

Evaluation of tablets:

1. Disintegration time:

The disintegration time of the solid dispersion and physical mixture, and commercial tablets were determined as per IP-1996 method.

2. Hardness:

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Monsanto hardness tester.

3. Friability:

The procedure was followed as per USP. 5 tablets were weighed and transferred to friabilator. It was then rotated for 4 min at 25 rpm. The tablets were removed and weighed again. Friability was calculated from the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight- Final weight}}{\text{Initial weight}} \times 100$$

4. Drug content:

All formulated tablets and commercial tablets were assayed for drug content as per mixed standards method.

Table 3: Physico-chemical characteristics of Hydrochlorothiazide-Losartan potassium solid dispersion tablets, physical mixture tablets and Commercial tablets

Tablets	Colour	Hardness (Kg/cm^2)	Disintegration (mins)	Friability (%)	Drug content – HCT%	Drug content – LSP%
Solid dispersion tablets	Pale white	4.5±0.05	3±0.1	0.54%	97.15±0.1	99.32±0.5
Physical mixture tablets	Pale white	4±0.11	3.6±0.05	0.52%	97.02±1.1	99.75±0.3
Commercial tablets	Pink	4±0.11	3±0.1	0.50%	86.55±1.2	99.90±1.7

**All values are expressed as mean ±S.D,n =2.*

5. Dissolution test for tablets:

Dissolution profile of pure hydrochlorothiazide, physical mixture and solid dispersion were evaluated according to the method described in USFDA[10].900mL of the dissolution medium (deaerated water) was placed in the vessel and temperature of medium was maintained at 37±0.5°C.the sample was placed in the medium and the dissolution was performed at 100rpm. 10 ml of samples were withdrawn at 10, 20, 30, 40……. .90 min and equivalent amount of dissolution medium were added to maintain the sink condition. Samples were filtered (0.45 µm pore size) and analyzed by spectrophotometry. The experiments were carried out in duplicate and mean values and SD were recorded.

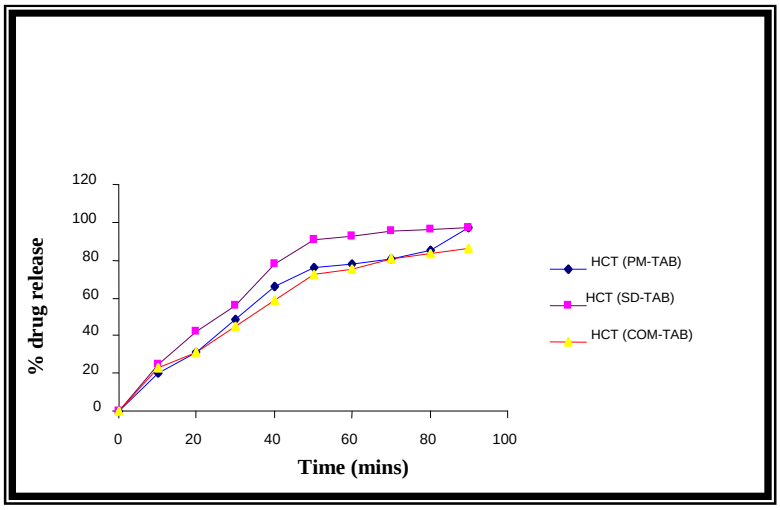

Fig 2: Comparative Dissolution Profile of Physical Mixture tablets, Solid dispersion tablets and commercial tablets of Hydrochlorothiazide

Table 4: Comparison of $t_{50\%}$ and $t_{90\%}$ of drugs released from Solid dispersion tablets, Physical mixture tablets and Commercial tablets

Tablets	Hydrochlorothiazide		Losartan potassium	
	$t_{50\%}$ (mins)	$t_{90\%}$ (mins)	$t_{50\%}$ (mins)	$t_{90\%}$ (mins)
Solid dispersion tablets	23	52	5	21
Physical mixture tablets	42	78	6	26
Commercial tablets	35	>90	6	35

6. Kinetic release data:

Table 5:- Kinetic release data of Hydrochlorothiazide from solid dispersion and physical mixtures of Hydrochlorothiazide-Losartan potassium (1:4)

Time (min)	% of Hydrochlorothiazide dissolved		% of Hydrochlorothiazide undissolved		Log % of Hydrochlorothiazide undissolved	
	Solid dispersion	Physical mixture	Solid dispersion	Physical mixture	Solid dispersion	Physical mixture
0	0	0	100	100	2	2
10	25.14	18.37	74.86	81.36	1.8742	1.9118
20	52.79	25.39	47.21	74.61	1.6740	1.8727
30	69.76	31.53	30.24	68.47	1.4805	1.8355
40	80.22	45.67	19.78	54.33	1.2962	1.7350
50	88.91	63.37	11.09	36.63	1.0449	1.5638
60	93.00	76.77	7.0	23.23	0.8450	1.3660
70	94.21	84.25	5.79	15.75	0.7626	1.1972
80	95.88	91.70	4.12	8.3	0.6148	0.0190
90	97.01	97.02	2.99	2.98	0.4756	0.4742

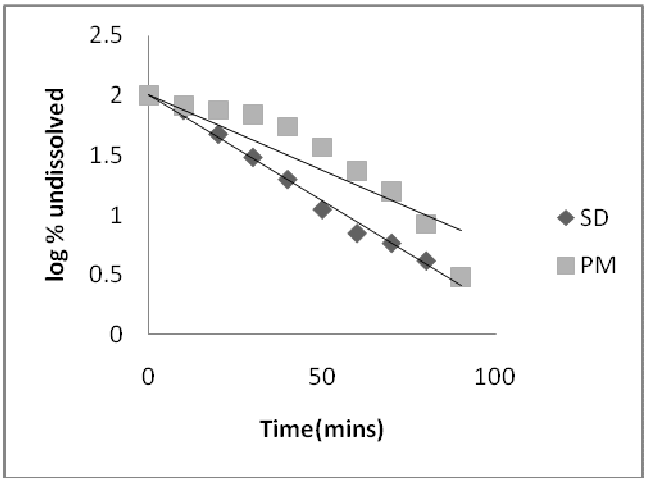

Fig 4: Release of Hydrochlorothiazide from Hydrochlorothiazide-Losartan potassium Solid dispersion and Physical mixture tablets follows first order.

7. Stability Studies:

Tablets were taken in a well closed container and stored at $40^{o}\pm2^{o}$C/75% RH. Samples were withdrawn at 0, 8, 16 and 30 days and analysis for drug content. Samples were also subjected to in vitro dissolution studies as per USFDA[11] method described earlier. The percentage of drug released was determined at 10, 20, 30, 40……90 min and results were recorded.

Table 6:- Stability study of Solid dispersion tablets, Physical mixture tablets and Commercial tablets stored at $40^0C \pm 2^0C/75\% \pm 5\%$ RH

% of drug dissolved at	Solid dispersion tablets (% of drug dissolved)		Physical mixture tablets (% of drug dissolved)		Commercial tablets (% of drug dissolved)	
	HCT	LSP	HCT	LSP	HCT	LSP
0 days	97.02±1.80	99.31±0.62	97.02±3.16	99.75±0.20	86.55±3.61	99.90±0.83
8thday	96.79±0.036	99.31±0.20	97.02±0.036	99.73±0.41	86.39±1.80	99.86±1.03
16thday	96.77±0.36	99.15±0.62	96.98±0.54	99.72±0.41	86.34±3.61	99.80±0.41
30thday	97.02±3.61	99.15±0.20	97.02±0.72	99.70±0.20	86.09±0.54	99.52±0.62

** All values are expressed as mean ±S.D, n =2*

RESULTS AND DISCUSSION

Compatibility study:

The FTIR spectra exhibited presence of characteristic peaks of drugs in physical mixture and in solid dispersion indicating that there was no chemical interaction between the drugs. The FTIR spectra were given in figures 3 and 4.

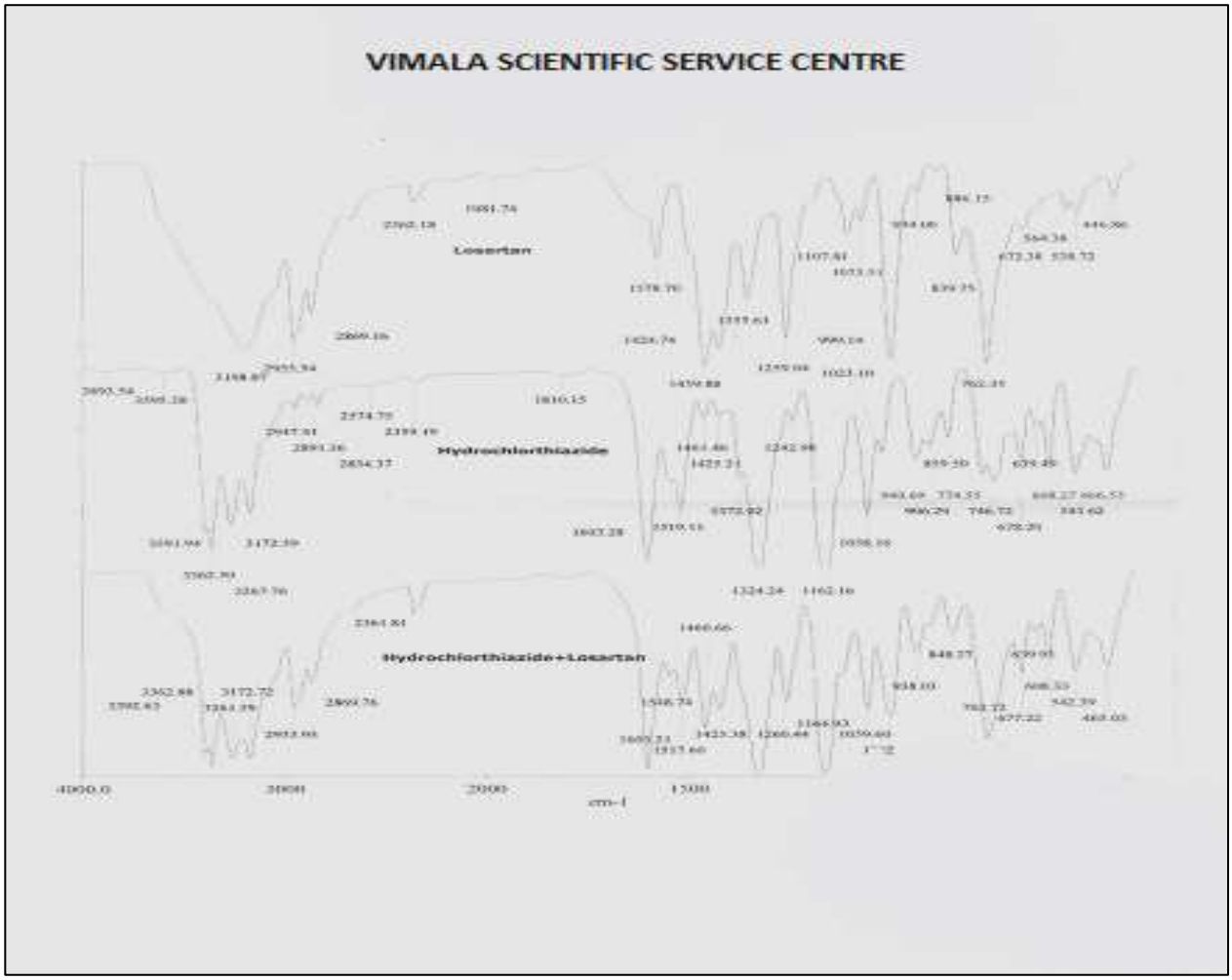

Fig.3. FTIR spectra of pure drug, Physical mixture of Hydrochlorothiazide-Losartan potassium

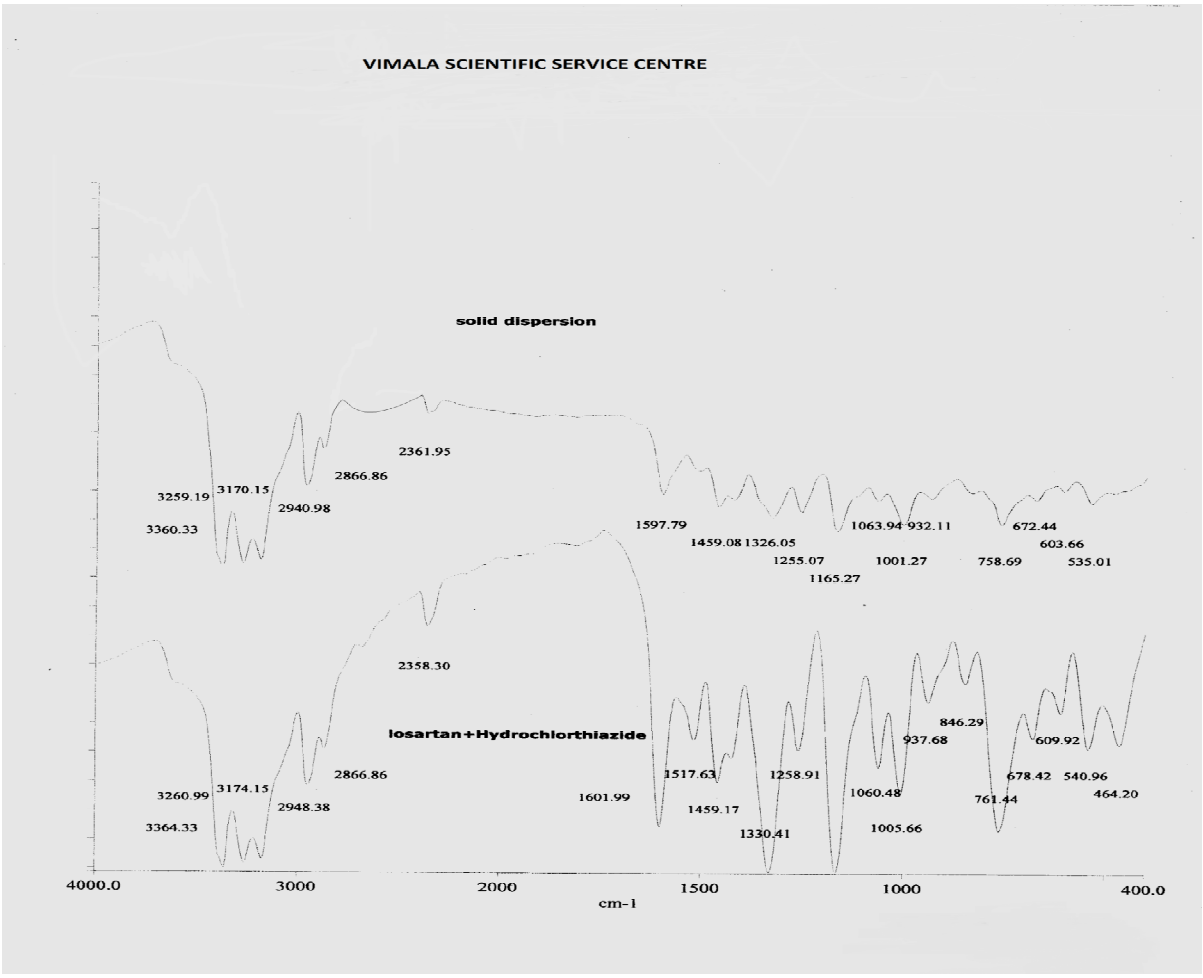

Fig.4. FTIR spectra of Physical mixture and Solid dispersion of Hydrochlorothiazide-Losartan potassium

Infrared spectra of pure drug, Physical mixtures and Solid dispersion of Hydrochlorothiazide and losartan potassium showed similar characteristic peaks in all cases hence no interaction occurred.

The characteristic peaks were observed with hydrochlorothiazide, physical mixture and solid dispersion containing hydrochlorothiazide in the following wave number region. NH (Stretching) - 3362.88 cm^{-1}, 3360.33 cm^{-1} ;NH (Bending) - 1603.21 cm^{-1}, 1597.79 cm^{-1};S=O (Stretching) - 1461.46 cm^{-1}, 1459.17 cm^{-1}, 1459.08 cm^{-1};Aromatic (CH-Stretching) -2947.41 cm^{-1}, 2948.38 cm^{-1}, 2929.09 cm^{-1};Aromatic (CH-Bending) - 846.29 cm^{-1}, 758.69 cm^{-1};C-Cl (Stretching) - 678.42 cm^{-1}, 672.44 cm^{-1}.

The characteristic peaks were observed with losartan potassium, physical mixture and solid dispersion containing losartan potassium in the following wave number region. NH (Stretching) - 3198.59 cm^{1}, 3174.15 cm^{-1}, 3170.15 cm^{-1};CH3-group CH (bending) -1424.74 cm^{-1}, 1459.17 cm^{-1}, 1459.08 cm^{-1};C-Cl (Stretching) - 762.35 cm^{-1},761.44 cm^{-1},758.69 cm^{-1};C-N (Stretching) - 1259.04 cm^{-1}, 1258.91 cm^{-1}, 1255.07 cm^{-1};C-C multiple bond (Stretching) - 1578.7 cm^{-1}, 1517.63 cm^{-1}, 1597.79 cm^{-1};Aromatic hydrocarbon chromophore, CH (stretching) - 2955.54 cm^{-1}, 2948.38 cm^{-1}, 2929.09 cm^{-1};Aromatic ring<two adjutants H atom - 839.75 cm^{-1}, 846.24 cm^{-1}, 758.69 cm^{-1} .

The quality control tests were adopted for the tablets. The hardness of the floating tablets ranged between 4 Kg/Cm^2 to 4.5 Kg/Cm^2. The percent friability of the prepared tablets was well with in

acceptable limit. There was no significant weight variation observed between average weight and individual weight. The drug content in all the formulations was with in the range of 86.55.mg to 97.15mg, ensuring uniformity of drug content in the formulations. The effect of losartan potassium on the solubility of hydrochlorothiazide was studied.

The drug release followed first order kinetics and the graph was drawn in between the log % undissolved verses time were found to be linear. The stability studies of Solid dispersion tablets, Physical mixture tablets and Commercial tablets are done and stored at $40^0C \pm 2^0C/75\% \pm 5\%$ RH.

CONCLUSION

The novel drug – drug solid dispersion approach clearly indicates that such an approach can be extended to all fixed dose combination of insoluble/poorly soluble and water soluble drugs for improving dissolution and bioavailability of poorly soluble drugs. A detailed assay on the therapeutic integrity of the drugs is essential for viability of this novel approach for development of formulations with improved bioavailability.

Acknowledgements
The authors are thankful to Bactolac Formulations, Hyderabad for providing the adequate laboratories facilities in the execution of this work.

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