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SOLUBILITY ENHANCEMENT OF CANDESARTAN CILEXETIL BY USING DIFFERENT HYDROTROPIC AGENTS

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ABSTRACT

Conventional Candesartan Cilexetil is practically insoluble in water, have slow onset of action and poor bioavailability (15-20%), and therefore cannot be given in emergency clinical situations like hypertension or pulmonary edema. The purpose of research is to provide a fast dissolving oral dosage form of candesartan, which can provide quick onset of action by using the concept of mixed hydrotropy. Initially solubility of candesartan is determined individually in 4 hydrotropic agents namely urea, sodium acetate, sodium benzoate and sodium citrate at concentration of 10, 20, 30 and 40% w/v solutions using purified water as solvent. Highest solubility was obtained in 40% sodium benzoate solution. Different combinations of all hydrotropic agents in different ratios were used to determine solubility, so that total concentration of hydrotropic agents was always 40%. Highest solubility was obtained in solution which contains (sodium acetate,sodium benzoate,sodium citrate)at optimum ratio of 13.33. This optimized combination was utilized in preparing solid dispersions by common solvent evaporation technique using distilled water as solvent. Solid dispersions were evaluated for flow properties like bulk density, tapped density, angle of repose, compressibility index, hausner ratio and SEM. Dissolution studies of solid dispersion were done using USP Type II apparatus. It was concluded that the concept of mixed hydrotropic solid dispersion is novel, safe and cost-effective technique for enhancing the bioavailability of poorly water-soluble drugs by dissolving drug in non ionized form. The magical enhancement in solubility of Candesartan Cilexetil is clear indication of its potential to be used in future for other poorly water-soluble drugs in which low bioavailability is major concern.

KEYWORDS: Bioavailability, Candesartan Cilexetil, Mixed Hydrotropy, Solid Dispersion.

INTRODUCTION

The formulation of poorly water-soluble drugs have always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programs are poorly water-soluble.[1,2]

The bioavailability of many poorly water-soluble drugs is limited by their dissolution rates, which are in turn controlled by surface area that they present for dissolution.

There are consecutive two processes can be identified to describe the oral absorption of drugs from solid dosage forms.[1,2]

• Dissolution of the drug in *vivo* to produce a solution and
• Transport of the dissolved drug across the gastrointestinal membrane.

Each process can be characterized by a rate constant. If the rate of dissolution of the drug is significantly slower than the rate of absorption, the dissolution of the drug becomes the rate-limiting step in the absorption process. Consequently, numerous attempts have been made to modify the solubility and dissolution characteristics of certain drugs in an effort to attain more rapid and more complete absorption. And the particle size of the drug is of great importance in the transport from the gastrointestinal (GI) tract to the site of action by increasing the dissolution rate in the GI tract.[3]

Solubility is defined in quantitative terms as concentration of solute in concentrated solution at a certain temperature, and in qualitative way it can be defined as a spontaneous interaction of two or more substances to form a homogenous molecular dispersion.[4,5]

Hydrotropy[6]

The term hydrotropic agent was first introduced by Neuberg (1916) to designate anionic organic salts which, at high concentrations, considerably increase the aqueous solubility of poorly soluble solutes. Hydrotropy is a solubilisation phenomenon whereby addition of large amount of second solute results in an increase in the aqueous solubility of another solute. The chemical structure of the conventional Neuberg's hydrotropic salts (proto-type, sodium benzoate) consists generally of two parts, an anionic group and a hydrophobic aromatic ring

or ring system. The anionic group is obviously involved in bringing about high aqueous solubility, which is a prerequisite for a hydrotropic substance.

The type of anion or metal ion appeared to have a minor effect on the phenomenon. On the other hand, planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilisation. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism". Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute.[7]

Mechanism of Hydrotrope Action[8]

A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solutions. Typically, hydrotropes consist of a hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self-aggregation. Hydrotropes do not have a critical concentration above which self aggregation' suddenly' starts to occur. Instead, some hydrotropes aggregate in a step-wise self-aggregation process, gradually increasing aggregation size. However, many hydrotropes do not seem to self aggregateat all, unless a solubilisation has been added.

Advantages of Hydrotropic Solubilization Technique[9]

1. Hydrotropy is suggested to be superior to other solubilisation method, such as miscibility, Micellar solubilisation, co solvency and salting in, because the solvent character is Independent of pH, has high selectivity and does not require emulsification.
2. It only requires mixing the drug with the hydrotrope in water.
3. It does not require chemical modification of hydrophobic drugs, use of organic solvents, orPreparation of emulsion system.

Mixed Hydrotropy[9]

Mixed hydrotropic Solubilization technique is the phenomenon to increase the solubility of poorly water-soluble drugs in the blends of hydrotropic agents, which may give miraculous synergistic enhancement effect on solubility of poorly water soluble drugs, utilization of it in

the formulation of dosage forms of water insoluble drugs and to reduce concentration of individual hydrotropic agent to minimize the side effects (in place of using a large concentration of one hydrotrope a blend of, say, hydrotropes can be employed in 1/5th concentrations reducing their individual toxicities.

Advantages of Mixed Hydrotropic Solubilization[10]

1. It may reduce the large total concentration of hydrotropic agents necessary to produce modest increase in solubility by employing combination of agents in lower concentration.
2. It is new, simple, cost-effective, safe, accurate, precise and environmental friendly method for the analysis (titrimetric and spectrophotometric) of poorly water-soluble drugs titrimetric and spectrophotometric precluding the use of organic solvents.
3. It precludes the use of organic solvents and thus avoids the problem of residual toxicity,error due to volatility, pollution, cost etc.

Hypertension[11]

Hypertension (high BP) is a disease of vascular regulation in which the mechanisms that control arterial pressure within the normal range are altered. Predominant mechanisms of control are the central nervous system (CNS), the renal pressor system (renin-angiotensin-aldosterone system), and extracellular fluid volume

Types of Hypertension

- primary hypertension
- secondary hypertension
- accelerated hypertension

MATERIALS

Candesartan cilexetil was obtained as a gift sample from Pharma tech lab,Hyderabad. Urea, sodium benzoate, sodium citrate and sodium acetate were provided by Signet chemical Hyderabad.

METHOD

Fourier Transform Infra-Red (FTIR) Spectroscopy[12,13]

FTIR study was carried out to check compatibility of drug with polymers. Fourier transform infrared spectrophotometer was determined by using Kbr dispersion method. The base line

correction was done using dried potassium bromide. Then the spectrum of dried mixture of Candesartan and potassium bromide was run followed by Candesartan with various polymers by using FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

Procedure to Determine the Solubility of Drug in Different Hydrotropic Agents

Initially solubility of Candesartan was determined individually in solutions of 4 hydrotropic agents (Ha) namely urea (U), sodium acetate (A), sodium benzoate (B), sodium citrate (C) at concentration of 10%, 20%, 30% and 40% solutions using purified water as solvent.

1. For determining solubility, accurately measured 10ml of a particular blend of hydrotropic agent was taken in a 10 ml volumetric flask and excess amount of drug was added and mechanically shaken until saturated solution was formed.
2. The volumetric flask was shaken on mechanical shaker for 12 h so that equilibrium solubility can be achieved and solution was allowed to equilibrate for 24 h.
3. Then solution was centrifuged at 2000 rpm for 5 min in ultra-centrifuge and then solution was filtered through Whatman grade 41 filter.
4. Aliquot was suitably diluted with purified water and analyzed using UV spectrophotometer at 245 nm.
5. However, highest solubility was obtained in 40% sodium benzoate solution. Then, different combinations of above-mentioned 4 hydrotropic agents in different ratios were tried to determine enhancement in solubility, so that total concentration of hydrotropic agents was always 40% w/v The blend A+B+C in the ratio of 13.33 gave the highest solubility enhancement, and therefore, this optimized combination of hydrotropes was selected for the preparation of solid dispersions.

SER = Absorbance of drug in hydrotrope/Absorbance of drug in distilled water.

SER- solubility enhancement ratio.

Preparation of Hydrotropic Solid Dispersions by Solvent Evaporation Method

Hydrotropic solid dispersion containing drug and hydrotropic blend (sodium acetate, sodium benzoate and sodium citrate) were prepared. Minimum (possible) quantity of distilled water at 80-85^{o}C contained in a 250 ml beaker was used to dissolve the sodium benzoate, sodium

acetate and sodium citrate. Then, drug was added to this solution (at 30-40^{o}C) and stirred using magnetic stirrer, maintaining the temperature 30-40^{o}C. Stirring was continued until a semisolid mass was obtained. Then semisolid mass was dried on watch glasses as thin layers at 40^{o}C after almost complete drying, the powder of solid dispersion passed through sieve and stored in air-tight glass bottles.

Evaluation Parameters

Pre-Compression Parameters

Angle of Repose

Angle of repose will be determined using funnel method. The blend will be poured through funnel that can be raised vertically until a maximum cone height (h) will be obtained. Radius of the heap (r) will be measured and angle of repose will be calculated using the formula.

$\theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose, h is height of pile, r is radius of the base of pile.

Bulk density

Apparent bulk density (ρb) will be determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of powder (M) will be determined. The bulk density will be calculated using the formula.

$\rho b = M/ Vb$

Tapped Density

The measuring cylinder containing known mass of blend will be tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight (M) of the blend will be measured. The tapped density (ρb) will be calculated using the following formula.

$\rho b = M/ Vt$

Carr's or Compressibility Index

The simplest way of measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility. The compressibility index of the granules will be determined by Carr's compressibility index (I), which is calculated by using the following formula.

$I = (Vb – Vt) \times 100/ Vb$

Hausner's Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following Formula.

Hausner's ratio = ρt/ ρb

Where ρt is tapped density and ρb is bulk density. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

***In vitro* Drug Release Studies[14,15,16]**

Solid dispersion equivalent to 20mg of Candesartan were tested in dissolution rate studies using USP XXIII (type II) dissolution test apparatus with paddle to rotate at 50 rpm, 900 ml of water was taken as dissolution media with temperature of 37^0C. At definite time interval 10ml of the sample were withdrawn and were analysed for drug content and also replaced with fresh dissolution medium. Calculations for the amount of drug were done using regression equations. The solid dispersion equivalent to 20mg was taken in a muslin cloth for performing the test.

Scanning Electron Microscopy (SEM)

SEM was used to investigate solid state physical structure of the prepared solid dispersions. SEM photographs of Candesartan and its solid dispersions were obtained using a scanning electron microscope model JEOL JSM 5600 with accelerating voltage from 0.5 to 30 KV

RESULTS AND DISCUSSION

Compatibility Study by FTIR

The FTIR spectrum of Candesartan was shown below and the interpretations of IR frequencies were represented below.

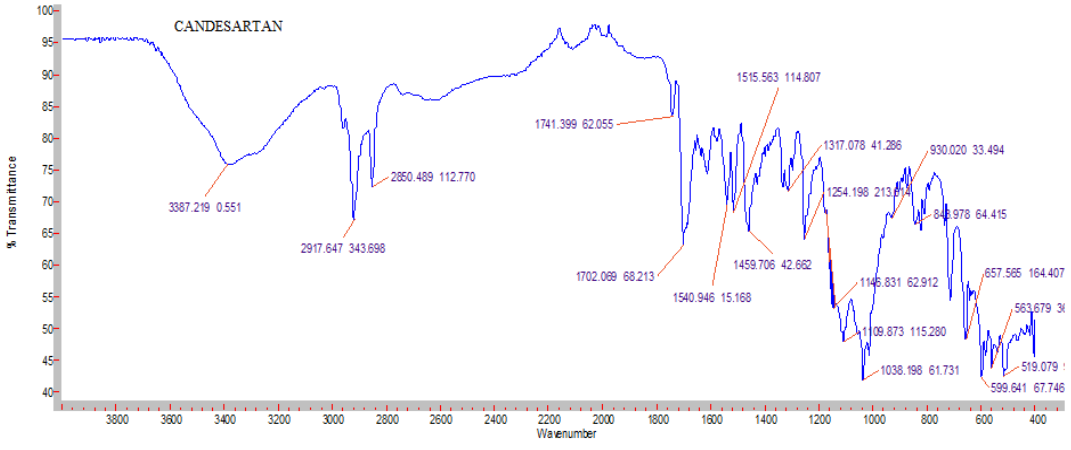

Figure 1: FTIR Spectra of Candesartan Cilexetil.

Major functional groups present in Candesartan showed characteristic peaks in FTIR Spectrum.

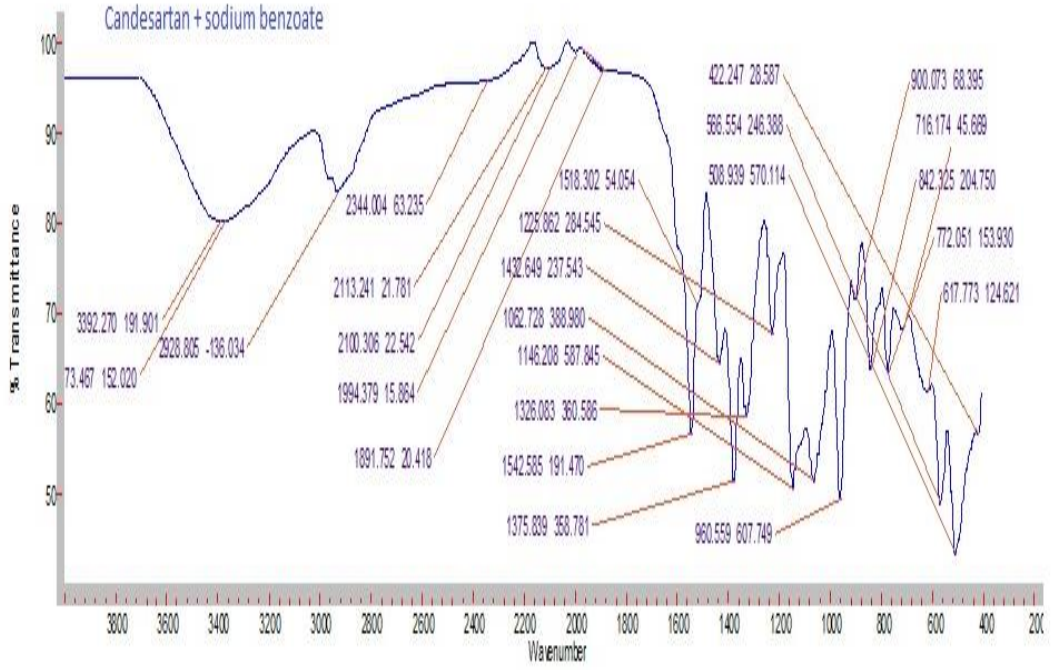

Figure 2: FTIR Spectra of Candesartan +sod.benzoate.

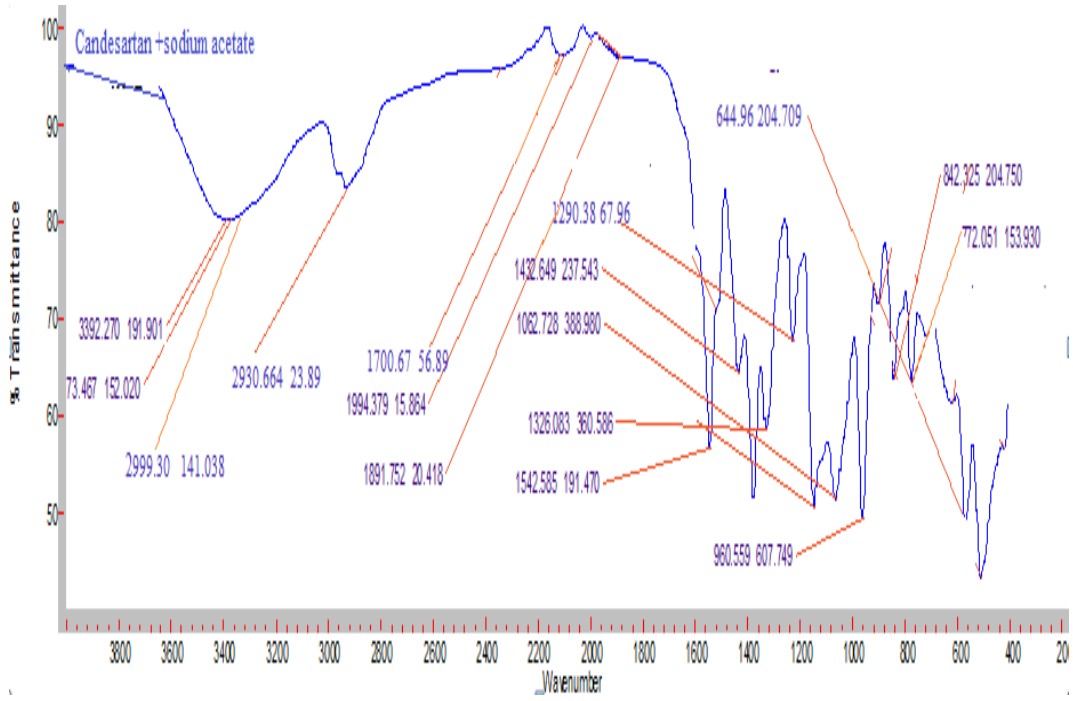

Figure 3: FTIR Spectra of Candesartan +sod.acetate.

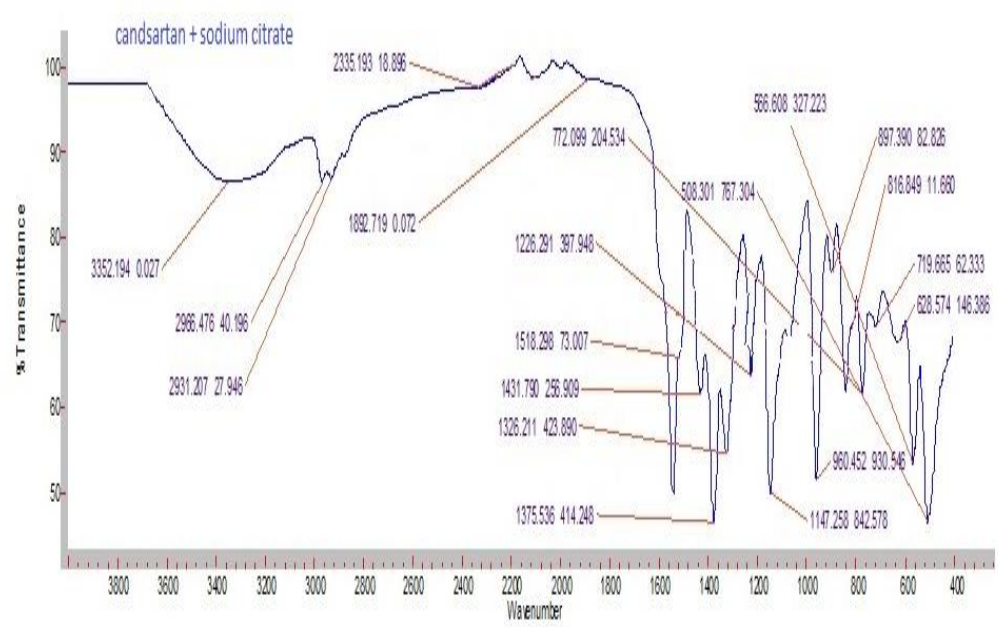

Figure 4: FTIR Spectra of Candesartan +sod.citrate.

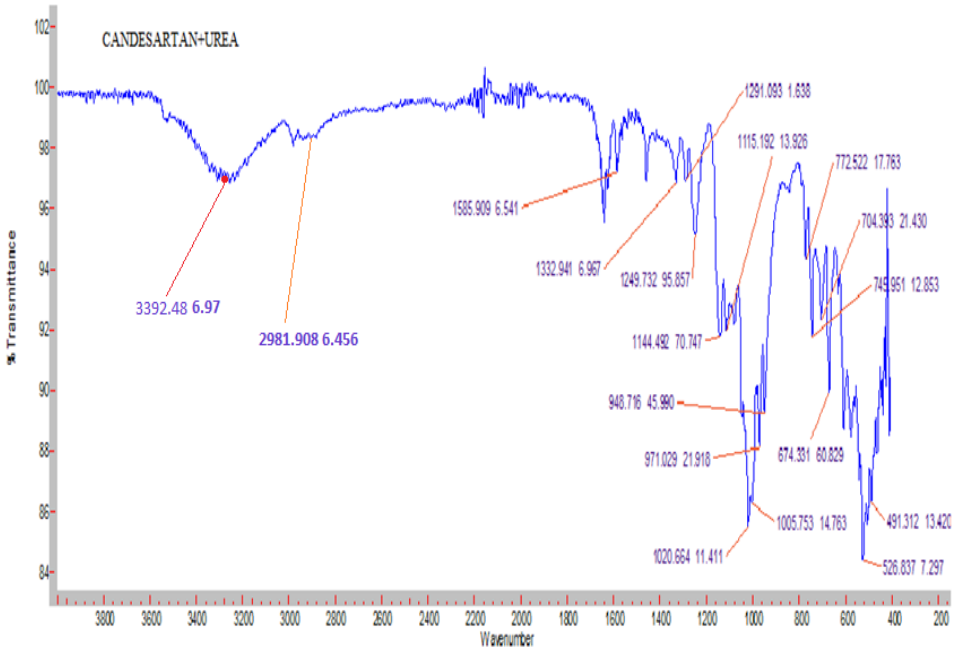

Figure 5: FTIR Spectra of Candesartan +urea.

Table 1: Interpretation of FTIR of Candesartan formulations.

Functional groups	FTIR region	Pure drug	Candesartan+ sodium benzoate	Candesartan+ sodium acetate	Candesatan+ sodium citrate	Candesartan+urea
C=0	1670-1820	1702	1805	1770	1850	1800
O-H	2800-3380	3379	3396	2999	3350	3392
0-substituent	600-750	657	617	644	628	674
C-0	1210-1350	1317	1225	1290	1328	1332
ARO C-H	2850-2950	2850	2928	2930	2931	2981

The peak values of functional groups of FTIR of pure drug and combination of pure drug and hydrotropic agents were showing no shift so it has been found that no incompatibility between the drug and polymer used.

Table 2: Solubility of Candesartan in different hydrotropic agents.

SL No	Hydrotropic Agent Used	Concentration of Hydrotropic Agent Used							
		10%	SER	20%	SER	30%	SER	40%	SER
1	Urea (U)	0.013	51.04	0.041	187.5	0.061	259	0.095	367
2	Sodium Acetate(A)	0.014	89.5	0.051	240	0.099	390	0.11	483
3	Sodium Benzoate(B)	0.25	1026	0.35	1472	0.4	1698	0.55	2232
4	Sodium Citrate(C)	0.09	389.5	0.16	672.9	0.22	959	0.33	1353

Table 3: Solubility of Candesartan in mixture of different hydrotropic.

Sl No	Combination	Total Conc (% w/v)	Individual Conc (% w/v)	Solubility (% w/v)	SER
1	U+A	40	20	0.502	21.6
2	U+B	40	20	2.772	115.3
3	U+C	40	20	0.206	8.83
4	A+B	40	20	3.184	132
5	A+C	40	20	0.92	38.6
6	B+C	40	20	3.166	131.92
7	U+A+B	40	13.33	3.615	150
8	U+A+C	40	13.33	3.238	134
9	A+B+C	40	13.33	3.822	159

U-Urea, A-Sodium Acetate, B-Sodium Benzoate, C- Sodium Citrate *In vitro* dissolution profile of pure drug, physical mixture and solid dispersion of Candesartan.

Table 4: Cumulative % drug release of various solid dispersion, physical mixture and pure drug.

	Cumulative % drug release								
	Solid Dispersion				Physical Mixture				
Time(min)	(B+C)	(U+A+B)	(U+A+C)	(A+B+C)	(B+C)	(U+A+B)	(U+A+C)	(A+B+C)	Pure Drug
5	42.22	45.86	49.4	52.89	13.58	19.692	21.88	25.96	13.37
10	50.16	53.23	59.41	65.9	27.46	31.793	33.101	36.9	17.03
15	62.11	68.21	70.07	72.6	47.62	51.805	55.77	58	29.49
20	73.94	75.71	78.46	80.9	56.37	60.111	64.65	69	33.72
25	81.74	84.61	81.49	88.9	60.3	61.361	66.57	75	37.08
30	85.34	88.4	94.39	98.8	61.78	63.888	68.2	80	40.34

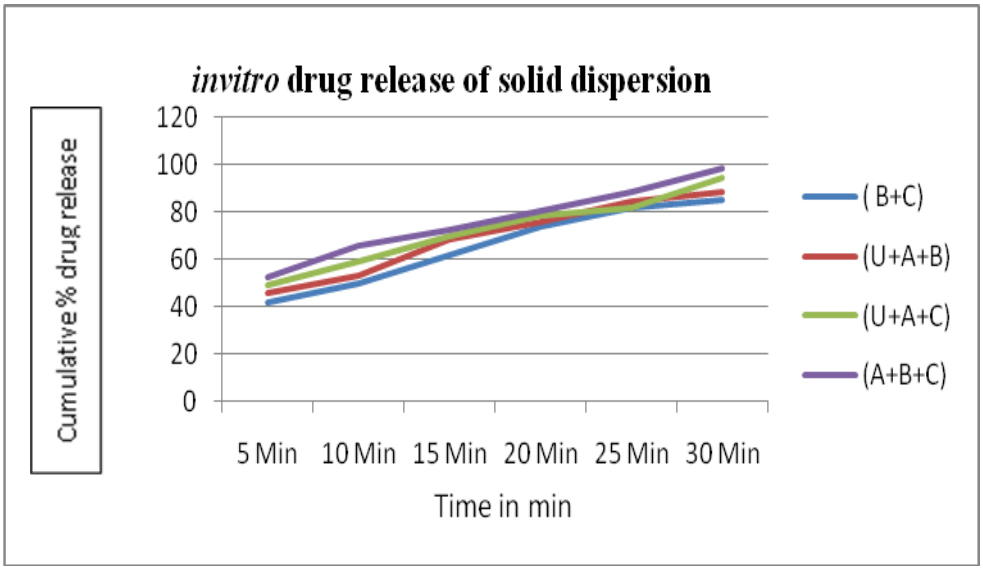

Figure 6: *In vitro* drug release for solid dispersion.

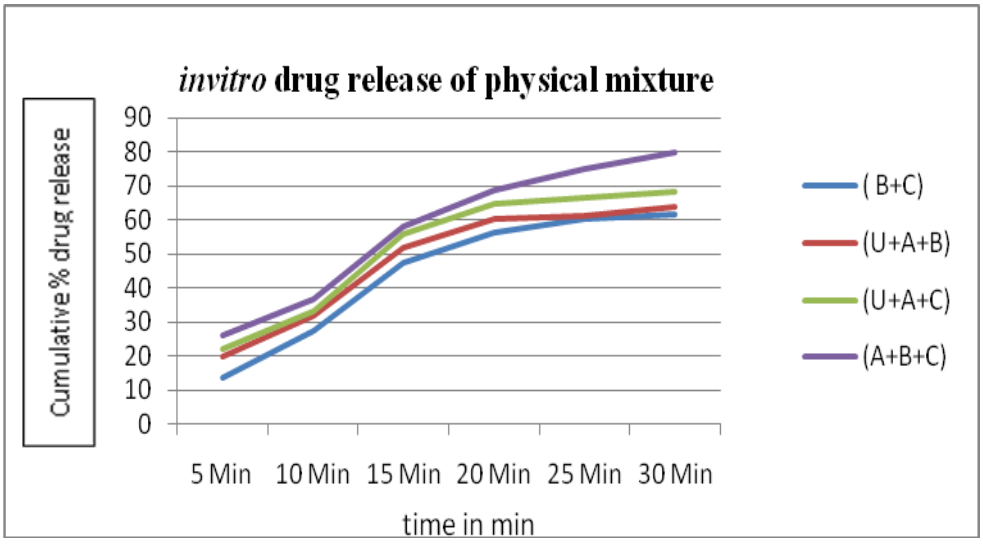

Figure 7: *In vitro* drug release for physical mixture.

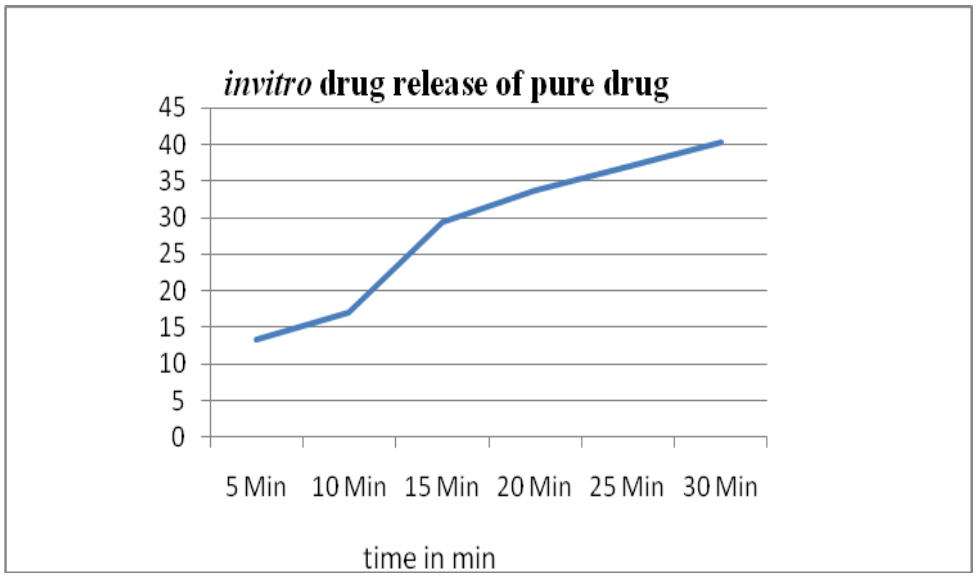

Figure 8: *In vitro* drug released for pure drug.

Among all the formulations, 9th(A+B+C) formulation which is showing maximum solubility enhancement ratio (159) have shown the good release till 30 min and the percentage cumulative drug release of the optimized formulation 9th(A+B+C) of Candesartan solid dispersion is 98%.On comparing the optimized formulation 9th of Candesartan solid dispersion with the physical mixture (drug+ hydrotropic agent) and the pure drug the percentage cumulative drug release of solid dispersion of Candesartan show the good results. From the data we can find that the hydrotropic agent which are used in the formulation sodium citrate, sodium benzoate, sodium acetate for increasing the solubility shown good results.

Table 5: Pre compresssion parameters of solid dispersion.

Formulation	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner ratio
B+C	$31^0$1.7'	0.386±0.0019	0.434±0.0049	11.06±0.02	1.12±0.005
U+A+B	$34^0$0.9'	0.423±0.0086	0.489±0.0051	13.49±0.24	1.15±0.058
U+A+C	$35^0$0.5'	0.424±0.0084	0.498±0.0068	13.85±0.44	1.17±0.006
A+B+C	$30^0$0.7'	0.507±0.0109	0.68±0.0096	14.6±0.42	1.10±0.004

Table 6: Pre compression parameters of physical mixture.

Formulation	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner ratio
B+C	$30^0$0.16'	0.346±0.084	0.444±0.0075	11±0.0.9574	1.10±0.0049
U+A+B	$33^0$0.84'	0.412±0.091	0.499±0.0088	12.90±0.4573	1.12±0.0054
U+A+C	$33.5^0$0.8'	0.420±0.096	0.480±0.0093	13.95±0.98	1.16±0.0054
A+B+C	$34.4^0$0.9'	0.423±0.098	0.570±0.0096	14.85±0.48	1.18±0.0079

Scanning Electron Microscopy (SEM)

SEM was used to investigate solid state physical structure of the prepared solid dispersions. SEM photographs of Candesartan, its physical mixture with hydrotropic agents and its solid dispersions were obtained using a scanning electron microscope model JEOL JSM 5600 with accelerating voltage from 0.5 to 30 KV.

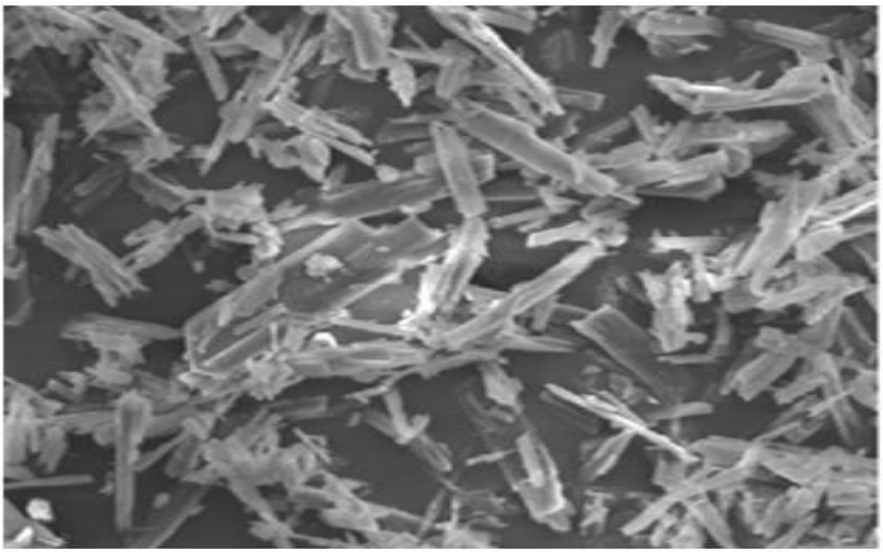

Figure 30(a) Scanning electron microscope of Candesartan pure drug.

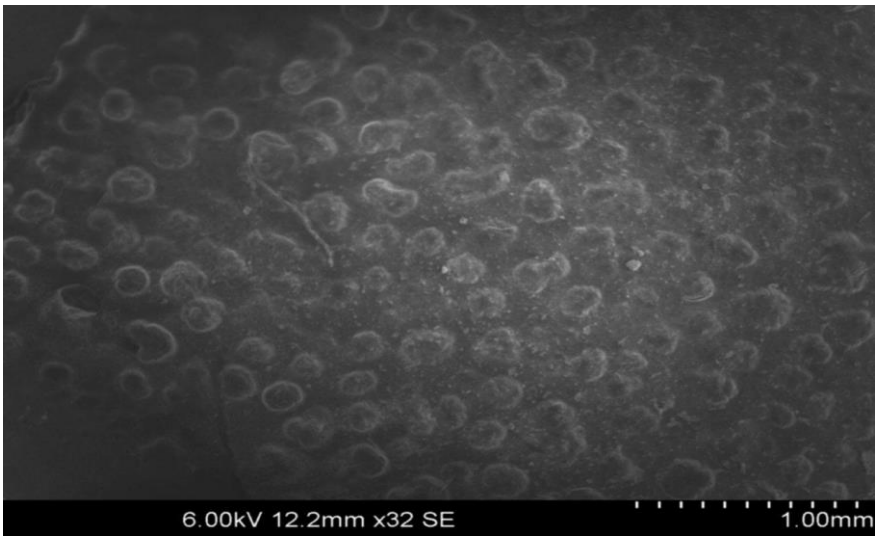

Figure 30 (b) SEM image of Candesartan solid dispersion.

SEM of pure drug and solid dispersion is done and the results were found that pure drug is crystalline in nature and solid dispersion is amorphous in nature so we can say that solubility is increased because the drug changes from crystalline to amorphous.

CONCLUSION

Different solubilisation techniques were used for the poorly soluble Candesartan using various hydrotropic agents; results from studies were found satisfactory. It was concluded that aqueous solubility of Candesartan greatly enhance by synergistic effect of different hydrotropic agents together. Thus the research work overcome the problem of poorly water soluble drugs and present methodology is a viable and cost effective means to increase the solubility of poorly water soluble drugs. Solubility enhancement of such magnitude is a clear indication of its potential to be used in future for other poorly water soluble drugs. From the FTIR results we can say that no incompatibility is there between the drug and hydrotropic agents.

It is evident from dissolution rate studies that solid dispersion was dissolved in 30 min. The values of bulk density and tapped density indicated the free flowing property of solid dispersions. The values of compressibility index, Hausner ratio and angle of repose indicates that flow character of solid dispersion is fair and no aid is needed to increase the flow properties.

By comparing the SEM images of pure drug and solid dispersion we can say that drug is crystalline in nature and it is converting into amorphous by solid dispersion and increasing the solubility of the Candesartan.

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