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Formulation and in vitro evaluation of candesartan liquid solid compacts to enhance drug solubility

Sai raju.A*, Santhosh Kumar Kassula

Procadence Institute of Pharmaceutical Sciences, Pregnapur, Telangana, 502278

***Corresponding Author: Sai raju.A**

Email ID: sairaju42arshanapally@gmail.com

ABSTRACT

Liquisolid technique was chosen to enhance the dissolution properties of Candesartan. The Candesartan liquisolid compacts were prepared by using PEG 400, propylene glycol as the nonvolatile liquid vehicles. Avicel PH 102 and Aerosil were used as the carrier and coating material, respectively. From the results obtained from executed experiments, it can be concluded that the preformulation studies like melting point, flow properties of Candesartan were compiled with IP standards. The FTIR spectra revealed that, there was no interaction between polymer and drug. Polymers used were compatible with Candesartan. Among the PG in 1:3 ratio (F7) was showing best release. Stability studies showed that there were no significant changes in physical and chemical properties of tablet of formulation F7 after 3 months. This research work has produced encouraging results in terms of increasing the *in vitro* dissolution of poorly soluble drugs such as Candesartan using liquisolid technology. The technique being simple and effective can also be extended to other poorly soluble drugs. The *in vivo* performance of the liquisolid compacts has to be studied using animal models to claim a complete success in the development of these formulations.

Keywords: PEG 400, Propylene Glycol, Avicel PH 102 and Aerosil

INTRODUCTION

The new Liquisolid technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water insoluble solid drugs carried in non-volatile liquid vehicles) into powders suitable for tableting or encapsulation. Simple blending of such liquid medications with calculated quantities of a powder substrate consisting of certain excipient referred to as the carrier and coating powder materials can yield dry looking, non-adherent, free flowing, and readily compressible powders[8].

Type of Liquid, solid compacts based on the liquid medication:-

1. Powdered drug solutions
2. Powdered drug suspensions
3. Powdered drug emulsions
4. Powdered liquid drug

Concept

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e., the liquid initially absorbed in the interior of the particles is captured by its internal structure and, after the saturation of this process, absorption of the liquid on to the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics.[7]

In liquisolid systems the drug is already in solution in a liquid vehicle, while at the same time, it is carried by the powder particles (microcrystalline cellulose and silica). Thus, due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and consequently, improved

Oral bioavailability. Since the dissolution of a nonpolar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates. That is why soft gelatin elastic capsules containing solutions of such medications demonstrate higher bioavailability when compared to conventional oral solid dosage forms. A similar principle underlies the mechanism of drug delivery from liquisolid compacts and is chiefly responsible for the improved dissolution profiles exhibited by these preparations. The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Non volatile solvent present in the liquisolid system facilitates wetting of the drug particles by decreasing interfacial tension between dissolution medium and tablet surface.[9]

Mechanism of Liquisolid Compacts

Liquisolid system is a novel concept of drug delivery via the oral route. This technique is applied to water insoluble drugs and lipophilic drugs to sustain their release. Formulation and manufacture of the liquisolid tablet are quite simple method according to a new mathematical model described by Spire‟s et al[8]. The liquisolid tablet preparation method involves, first a mathematically calculated amount of pure drug Weighed and dissolved in the suitable amount of solvent into a molecularly dispersed state. For attaining good flow properties trial and error methods were used, i.e. changing the carrier: coating material ratio of 50:1 to 5:1 ratios according to new mathematical model expressions proposed by Liao.[11] this liquid medication is poured on the suitable amount of the carrier material. The liquid medication is absorbed into the carrier material internally and externally and then a suitable disintegrant was added to this material. Finally, coating material was added for dry looking, adhere to the carrier material for achieving good compression properties. As the drug is in the form of liquid medication, it is either solubilised or molecularly dispersed state. Due to increased wetting and surface area for dissolution, liquisolid tablet of water insoluble drugs shows improved dissolution properties and in turn increased bioavailability.

Liquid medication is incorporated into carrier medication which has a porous surface and closely matted fibers in its interior as cellulose.[12] Both absorption and adsorption take place, i.e. the liquid absorbed into the interior of the particles is captured by its internal structure and after saturation of this process, adsorption of the liquid on to the internal and external surface of the porous carrier particles occurs.[11] Excipients Possessing fine and highly adsorptive particles such as various types of amorphous silicon dioxide (silica) are most suitable for this step. Before compression or encapsulation, various ingredients such as lubricants, disintegrants or Polymers, and binders, may be mixed with the finished liquisolid systems to produce liquisolid compacts in the dosage form of tablets or capsules.[13, 14, 15]

AIM AND OBJECTIVE OF THE WORK

The aim and objective of the present study is to develop a pharmaceutically stable, cost effective and quality improved robust formulation of

Candesartan Immediate Release tablets using liquid solid technique.

To achieve this goal various prototype formulation trials will be taken and evaluated with respect to the various quality control parameters such as dissolution, assay. The formula will be finalized by dissolution profile. The objective includes providing a robust formulation for the production of the dosage form for which the influence of various factors like concentration and nature of non volatile solvents along with the type of disintegrants used on disintegration time and dissolution parameters are to be studied and also analyzed

METHODOLOGY

Preparation of Standard Curve for Candesartan

Determination of Standard Curve

a. Stock solution of 1000µg/ml of condensation was prepared by dissolving 25mg of drug in 25ml of pH 6.8 Phosphate buffer.

b. From this take 10ml and make up to 100ml using buffer to get a stock solution of 100 µg/ml.

c. From the above solution take 0.4, 0.8, 1.2, 1.6, 2.0ml and dilute to10 ml with buffer to get concentrations of 4µg/ml, 8µg/ml, 12µg/ml, 16µg/ml, and 20µg/ml.

d. The absorbance of the different diluted solutions was measured in a UV Spectrophotometer at 232nm.

A calibration curve was plotted by taking concentration of the solution in µg/ml on X-axis and absorbance on Y-axis and correlation co-efficient "r2" was calculated.

FORMULATION OF LIQUISOLID COMPACTS

- Model drug was initially dispersed in the non volatile solvent systems (Propylene glycol, PEG 400) termed as liquid vehicles with different drug: vehicle ratio.
- Then a mixture of carrier (Avicel pH 102) was added to the above liquid by Continuous mixes for a period of 10 to 20 minutes in a mortar.
- Then to the above mixture, coating material (silica gel powder) was added and mixed thoroughly. The amount of carrier and coating materials added were based On the R value.
- To the above binary mixture disintegrant like cross caramellose and other remaining additives such as Glidant (magnesium stearate) are added according to their application and mixed in a mortar. The final blend was compressed.

RESULTS AND DISCUSSION

Identification of authenticity of Candesartan pure drug

Melting point determination

The melting point of condensation was found to be158. 2°C, which complied with BP standards, thus indicating the purity of obtaining a drug sample.

Table no 1: Melting point determination

Drug	Observed melting point
Candesartan	158.2^0c

Standard calibration curve

Table No 2: Standard calibration curve

S.no	Concentration	Absorbance
1	0	0
2	4	0.112
3	8	0.223
4	12	0.339
5	16	0.451
6	20	0.569

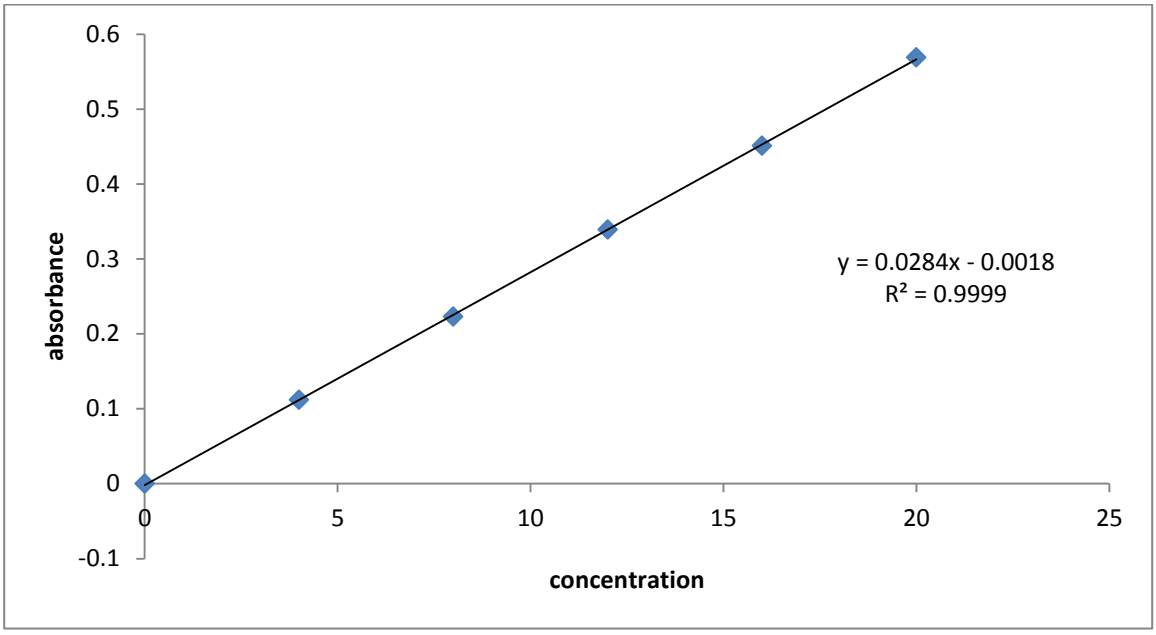

Figure 1: Calibration graph

Drug-Excipient Compatibility study

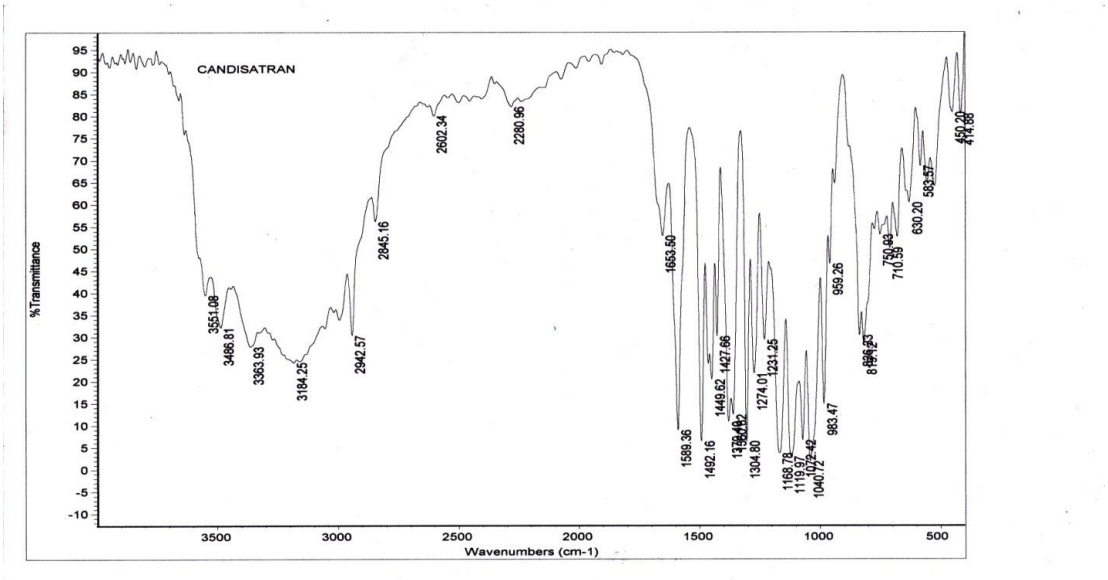

Fig No 2: FTIR Spectra of Candisartan

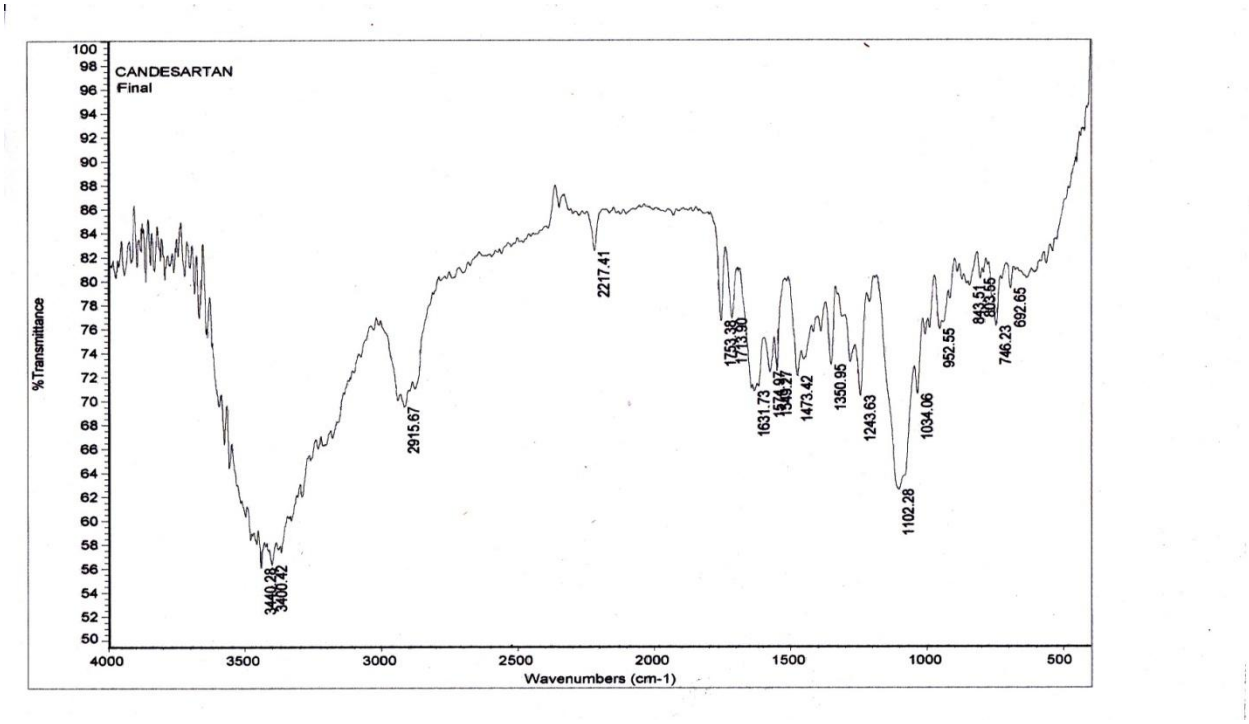

Fig No 3: FTIR Spectra of Candisartan final

BLEND PROPERTIES OF DIFFERENT FORMULATIONS

Preformulation evaluation parameters

Table No 4: Evaluation of Flowability and Compressibility of Liquisolid Powders

Formulation	Blend Property			
	B.D(gm/ml)	**T.D(gm/ml)**	**C.I (%)**	**H.R**
F1	0.380	0.500	23.91	1.310
F2	0.710	0.873	19.714	1.251
F3	0.371	0.483	23.188	1.299
F4	0.483	0.681	29.03	1.409
F5	0.461	0.608	24.177	1.32
F6	0.453	0.583	22.299	1.288
F7	0.710	0.873	19.714	1.251
F8	0.461	0.608	24.177	1.32
F9	0.541	0.691	21.62	1.276

Evaluation of tablets

Table No 5: Evaluation of Tablets

S.No	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
1	**Weight variation (%)**	1.65	1.57	1.42	1.54	1.18	1.35	1.44	1.23	1.48

2	**Hardness (kg/cm^2)**	5.8	5.6	5.3	4.5	5.52	5.25	5.31	4.42	5.51
3	**Thickness (mm)**	2.1	2.11	2.15	2.2	2.13	2.16	2.19	2.2	2.11
4	**Friability %**	0.45	0.52	0.21	0.18	0.38	0.57	0.46	0.48	0.55
5	**Disintegration**	1min	1min	2min	2min	1min	2min	1min	1min	2min
	Time	46sec	52sec	32sec	22sec	44sec	28sec	50sec	48sec	13sec

Table no 6: dissolution profiles

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	25	37	22	20	63	49	34	29	19
20	56	48	53	51	77	73	72	64	36
30	62	59	64	68	82	78	82	83	43
40	70	63	70	72	84	80	87	88	50
50	79	69	76	79	87	86	89	90	59
60	85	73	80	84	89	85	98	92	63

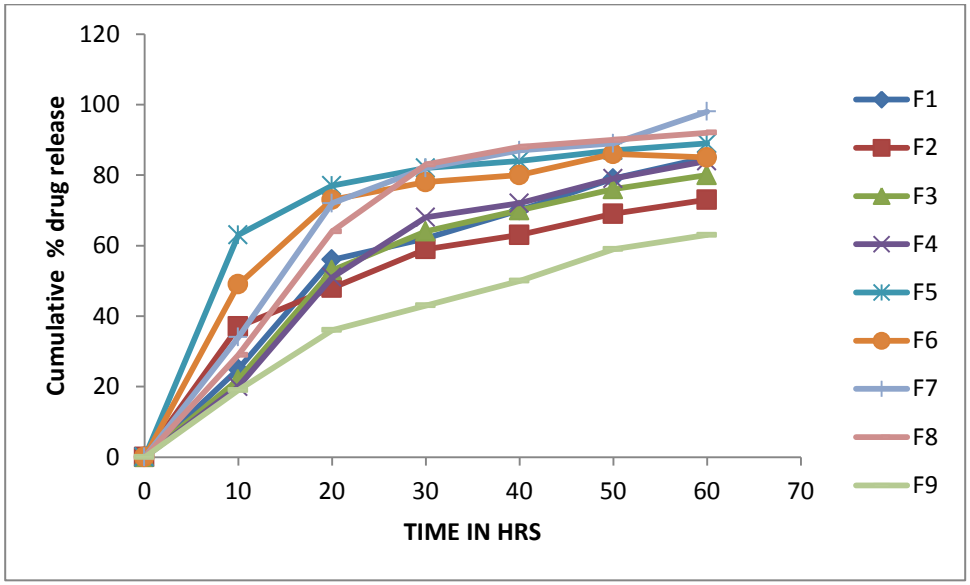

Fig No 4: Dissolution Graphs for F1-F9

Liquid, solid compacts displayed more distinct in-vitro release characteristics. Among all, F7 showed a higher release rate (98%) at the end of the 60th minute. It was confirmed that at 10th min F7 had the highest drug release 52.15% compared with other formulations. Since the liquisolid compacts contain a solution of the drug in non-volatile vehicles used for the preparation of the liquisolid compacts, the drug surface available for the dissolution is tremendously increased.

In essence, after disintegration, the liquisolid primary particles suspended in the dissolving medium contain the drug in a molecularly dispersed state, whereas the directly encapsulated compacts are merely exposed micronized drug particles. Therefore, in the case of liquisolid compacts, the surface area of drug available for dissolution is much greater than that of the directly encapsulated compacts.

According to the Noyes and whitey, the drug dissolution rate (DR) is directly proportional not only to the concentration gradient (Cs-C) of the drug in the stagnant diffusion layer, but also to its surface area (S) available for dissolution. Moreover, since all dissolution tests for both Candesartan preparations were carried out at a constant rotational speed (50RPM) and identical dissolving media, it is assumed that the thickness

(h) of the stagnant diffusion layer and the diffusion coefficient (D) of the drug molecules transported through it remain almost identical under each set of dissolution conditions. Therefore, the significantly increased surface area of the molecularly dispersed Candesartan in the liquisolid compacts may be principally responsible for their higher dissolution rates. The consistency and higher dissolution rate displayed by liquisolid compacts will improve the absorption of the drug from the GI tract.

Stability studies of candesartan complexes

The inclusion complexes of Candesartan (F7) were subjected to short-term stability test by storing the complexes at room temperature.

Table 7: Stability studies of Candesartan complex at room temperature

Time	Color	Percent drug content ± St.D. at Room Temperature	Cumulative % drug release ± St.D. at 60^0
First day	White	98	98
30 days	White	97.5	97.3
60 days	White	97.25	96.85
90 days	White	96.89	96.64

Results from stability studies indicate that the formulated microspheres are stable for a period of 3 months under room temperature, i.e., 30˚C temp and 65±5% RH. There were no remarkable changes were observed during the period of storage.

CONCLUSION

The aim of this study was to improve the dissolution profile thereby increase solubility. Solubility is the major criteria to achieve the desired concentration of the drug in the systemic circulation. About 80% of the drugs are poorly soluble in nature. So in order to overcome that problem, several techniques have been developed to enhance the solubility of those drugs. Among them liquisolid compacts are one of the most promising and new technique which promotes the dissolution rate of water insoluble drugs. Hence, in this study, liquisolid technique was chosen to enhance the dissolution properties of Candesartan. The Candesartan liquisolid compacts were prepared by using PEG 400, propylene glycol as the non volatile liquid vehicles. Avicel PH 102 and Aerosil were used as the carrier and coating material, respectively

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