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ENHANCED DISSOLUTION RATE OF CANDESARTAN CILEXETIL BY LIQUISOLID TECHNIQUE

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ABSTRACT

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation. Therapeutic effectiveness of a drug depends upon bioavailability, ultimately upon the solubility of drug molecules. Candesartan cilexetil is a BCS class II drug which has low solubility and high permeability. By increasing the solubility of the drug, the dose is reduced and bioavailability is increased. This is the main reason to increase solubility of Candesartan by liquisolid technique in which hydrophilicity is imparted to Candesartan by tween. Starch and hydroxy propyl methyl cellulose (HPMC) are used as carrier materials and Aerosil is used as coating material. The solubility is enhanced by 26% using liquisolid technique when compared to pure drug in the dissolution medium.

KEYWORDS: Carrier material, coating material, solubility, bioavailability.

INTRODUCTION

Solubility is one of the key physicochemical parameters of a new molecule that needs to be assessed in drug discovery and drug candidate selection process.[1-3] To achieve pharmacological activity, the molecules must exhibit certain solubility in physiological fluids. Drug substances for which solubility enhancement can improve oral bioavailability are the substances those are classified under BCS class II (low soluble and high permeable).

Solubility is improved by physical and chemical modification techniques[4,5],

1. Physical modifications

Particle size reduction, modification of the crystal habit, drug dispersion in carriers, complexation and liquisolid technique.

2. Chemical modifications

Altering pH of drug by salt formation, use of co-solvents, formulating as liposomes and micro emulsions.

Solubility enhancement by liquisolid technique[6-9]

Liquisolid technique is a promising alternative for formulation of water insoluble solid drugs and liquid lipophilic drugs. The water insoluble drug should be initially dissolved or suspended in a suitable non-volatile solvent system to produce a drug solution or drug suspension of desired concentration. The non-volatile solvent may be hydrophilic or lipophilic in nature based on selection of type of formulation like immediate or control release.[10] Some of hydrophilic solvents are polyethylene glycol (PEG), polypropylene glycol (PPG) and tween 80, some of lipophilic solvents are liquid paraffin, cremophore L etc., next, a certain amount of the prepared drug solution or suspension, or the liquid drug itself, is incorporated into specific quantity of carrier material which should be preferably of porous nature and possessing sufficient absorption properties. If hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carriers in liquisolid systems, sustained release formulations can be obtained. Presence of non-volatile solvent reduces glass transition temperature (Tg) of polymers and imparts flexibility there by prolong the release. For immediate release formulations hydrophilic carriers like methyl cellulose, ethyl cellulose, starch powder and granular grades of microcrystalline cellulose (MCC) are preferred. The resulting wet mixture is then converted into a dry looking, non-adherent, free-flowing and readily compressible powder by the simple addition and mixing of a calculated amount of coating material. 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 excipients such as lubricants and disintegrants (immediate) or binders (sustained-release) may be mixed with the finished liquisolid system to produce liquisolid compacts i.e. tablets or capsules.

MATERIALS AND METHODS

Candesartan cilexetil (obtained from Jubliant Organosis, Noida), excipients like tween 80 (SD fine chem. Limited, Mumbai), microcrystalline cellulose, hydroxy propyl methyl cellulose, starch and Aerosil are obtained from Loba chemic Pvt. Ltd.

Standard curve of Candesartan Cilexetil in 0.5% tween-80 in phosphate buffer pH 6.4

Candesartan cilexetil standard solution was prepared by adding 5 ml of methanol to accurately weighed 10 mg of Candesartan cilexetil in 10 ml volumetric flask. It was sonicated for 10 min, then volume was made up with methanol, and 1ml of this solution was further diluted to 100 ml with 0.5% tween 80 in phosphate buffer of pH 6.4. From this final concentrations of 2, 4, 6, 8 and 10 µg/ml solutions were prepared and absorbance values were measured (table 1). Standard curve was shown in fig 1.

Preparation of powder mixtures[11,12]

Non-volatile solvent tween 80 was accurately weighed in 20 ml glass beaker and heated up to 60-70^{0}c then calculated quantities of drug was added and mixed thoroughly. The resulting hot medication was incorporated into required quantities of starch and HPMC as carrier material and colloidal silicon dioxide as coating material. Mixing process was carried out in three steps, in the first stage the system was blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder. In the second stage the powder mixture was evenly spread as a uniform layer on the surface of a mortar and left standing for approximately 5 min to allow drug solution to be absorbed in the interior of powder particles. In the third stage, the powder is scraped off the mortar surface by means of spatula and then blended with microcrystalline cellulose for another 30 sec in a similar way to the first stage. This gives final liquisolid formulation which was free-flowing and readily compressible. Like this five different compositions of physical mixtures were prepared by changing concentrations of tween 80 with respect to Candesartan(table 2). The prepared mixtures were stored in a desiccator in glass vial till further use.

RESULTS AND DISCUSSION

Calculation of yield and drug content

The yield was calculated from the formula

Percentage yield = (total weight of the mixture obtained / sum of individual weights of components)*100

The drug content in a mixture was determined to assess the degree of homogeneity in the mixture so that an equivalent of 16mg could be taken for dissolution studies.

Method

For the purpose of content uniformity determinations exactly weighed amount of mixture was dissolved in little amount of methanol and then diluted with 0.5% tween 80 in phosphate buffer of pH 6.4. The contents were determined at 260 nm spectrophotometrically (table 3 and table 4).

Powder flow characteristics[13]

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to reduce high dose variations Flow characteristics of prepared powder mixtures were analysed by angle of repose. Fixed height glass funnel method was used here.

The height and diameter of the powder cone was measured and angle of repose was calculated.

$\tan \theta = h/r$

Where, θ is the angle of repose, h is the height in cm, r is the radius in cm.

All formulations had shown angle of repose values of 28 to 30 which indicates good flow characteristics.

***In vitro* dissolution study[14-16]**

A comparative study of both pure drug and prepared liquisolid mixtures were evaluated for drug dissolution studies. Amount of mixture which was equivalent to 16 mg of Candesartan cilexetil was weighed and added to 900 ml of 0.5% tween 80 in phosphate buffer of pH 6.4. USP type II dissolution apparatus (paddle type) was set at 50 rpm and the temperature of dissolution medium was kept at 37 ± 0.5^0c. The samples were withdrawn (each 5ml) at 5, 10, 20, 30, 45, 60 min from the beginning of dissolution study. The contents of the drug was analysed by UV spectrophotometer at 260 nm. In the same way pure drug of 16 mg was also subjected to *in vitro* dissolution studies at the same conditions of liquisolid formulations (table 5).

Table 1: Standard curve data of Candesartan cilexetil in 0.5% tween 80 in phosphate buffer of pH 6.4.

S.NO	Concentration (µg/ml)	Absorbance
0	0	0
1	2	0.069
2	4	0.114
3	6	0.184
4	8	0.23
5	10	0.288

Table 2: Compositions of formulations F_1 to F_5.

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5
Tween 80	10	20	30	40	50
Candesartan cilexetil	100	100	100	100	100
Starch	300	300	300	300	300
HPMC	20	20	20	20	20
MCC	5	5	5	5	5
Aerosil	5	5	5	5	5

Table 3: Percent yield data of formulations F_1 to F_5.

Formulations	F_1	F_2	F_3	F_4	F_5
Theoritical weight	440	450	460	470	480
Practical weight	387	400	396	381	307
% yield	88	89	86	81	64

Table 4: Drug content data of prepared liquisolid formulations.

S.No	Composition	absorbance	Amount of Candesartan cilexetil (mg)
1	F_1	0.28	93.10
2	F_2	0.26	95.50
3	F_3	0.28	96.33
4	F_4	0.28	89.20
5	F_5	0.26	69.90

Table 5: Dissolution data of pure drug and liquisolid formulations (F_1 - F_5) in 0.5% tween 80 in phosphate buffer of pH 6.4.

Time (min)	% cumulative drug release					
	Pure drug	F_1	F_2	F_3	F_4	F_5
0	0	0	0	0	0	0
5	32.16±1.2	47.41±1.45	55.74±1.49	60.26±1.43	52.13±1.67	50.32±1.66
10	33.31±0.23	50.22±1.23	56.85±1.70	61.37±1.23	52.23±1.87	52.23±1.76
20	36.34±1.60	50.82±1.98	59.36±1.56	63.18±1.45	52.53±1.65	55.44±1.09
30	36.49±1.45	51.12±1.75	59.76±1.54	63.48±1.98	53.73±1.54	55.84±1.50
45	37.5±1.50	52.13±1.45	60.87±1.38	63.68±1.56	54.54±1.32	56.95±1.23
60	38.79±1.67	52.73±1.95	61.47±1.72	64.48±1.43	56.75±1.12	57.05±1.17

Graphs

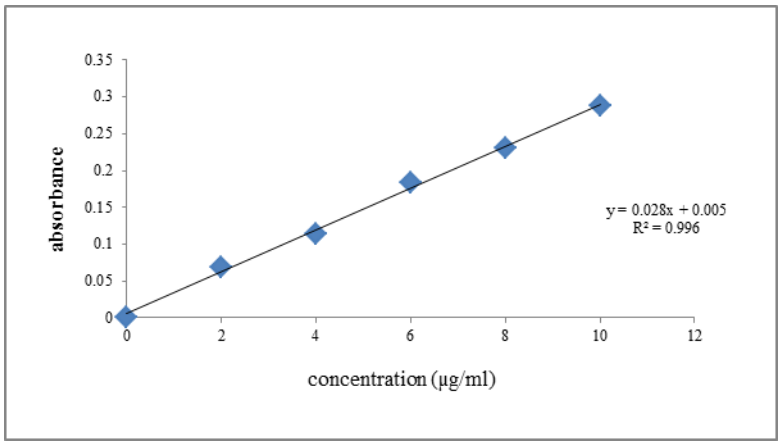

Fig. 1: Standard curve of Candesartan cilexetil in 0.5% tween 80 in phosphate buffer of pH 6.4.

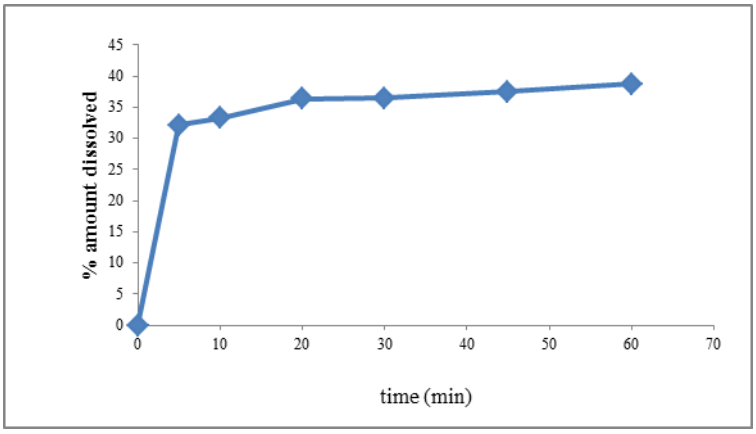

Fig. 2: Dissolution profile of pure drug Candesartan cilexetil in 0.5% tween 80 in phosphate buffer of pH 6.4.

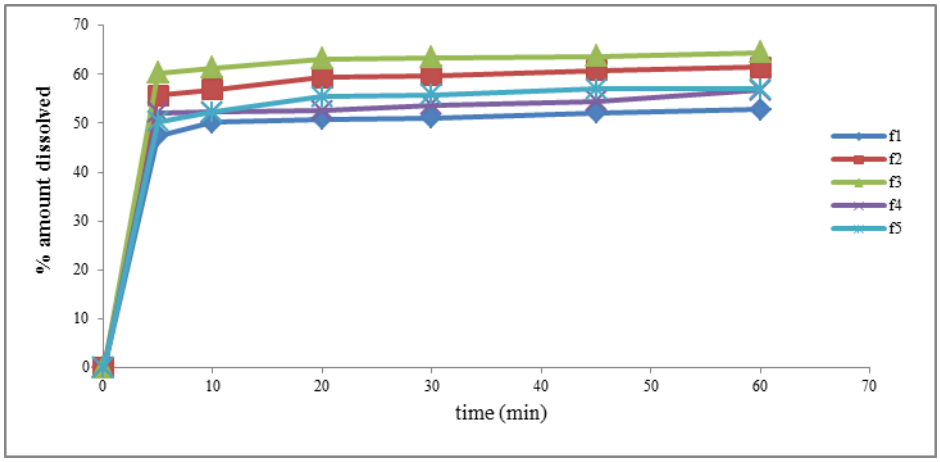

Fig. 3: Comparative dissolution profiles of prepared liquisolid formulations in 0.5% tween 80 in phosphate buffer of pH 6.4.

The wettability of the prepared powders by the dissolution medium is one of the proposed mechanisms to explain the enhanced dissolution rate of Candesartan cilexetil from liquisolid mixtures. The liquisolid technique proved to be as suitable method for solubility enhancement of poorly soluble drugs. Non-volatile liquid tween 80 was used to enhance the dissolution rate of drug by decreasing interfacial tension between drug and dissolution medium and increases wetting properties of drug. Carrier materials like starch and HPMC imparts hydrophilicity to drug there by increasing the dissolution rate and bioavailability of poorly soluble drug Cadesartan cilexetil. The coating material, Aerosil is necessary to convert wet mixture into a non-adherent, dry looking and imparts desirable flow characteristics to the powder. Microcrystalline cellulose acts as disintegrating agent in liquisolid compacts (tablets and capsules).

CONCLUSION

Liquisolid powder mixture which contains 30% tween 80 had shown high dissolution rate when compared to other formulations i.e., almost 65% in 1hr. Liquisolid technique increases solubility of Candesartan cilexetil by almost 26% when compared to pure drug which has only solubility of 39% (shown in table 4) in 1hr in dissolution medium (0.5% tween 80 in phosphate buffer of pH 6.4), after that increasing the concentration of tween decreases solubility of drug.

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