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Original Article

Design and development of liquisolid compact of candesartan cilexetil to enhance dissolution

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ABSTRACT

Background: Candesartan cilexetil is an angiotensin-II receptor antagonist used for the treatment of hypertension. It is hydrophobic drug which belongs to BCS class II and its half life is 5.1 h with 15–40% bioavailability. Attempt had made to investigate the use of liquisolid technique in improving the dissolution of candesartan cilexetil in a solid dosage form.

Methods: The liquisolid tablets were formulated by using Tween 80, as liquid vehicle, microcrystalline cellulose as a carrier material, silica as a coating material and sodium starch glycolate used as a superdisintegrant. The new mathematical model and 3^2 full factorial design was utilized to formulate various liquisolid powder systems.

Result and discussion: All prepared liquisolid batches were subjected to, weight variation, drug content uniformity, hardness, friability test, disintegration test and dissolution tests. Liquisolid system is also tested for DSC, XRD and IR .All the tested liquisolid tablet formulations showed higher drug dissolution than the conventional, directly compressed tablet.

Conclusion: DSC and XRD study suggested loss of candesartan cilexetil crystallinity upon liquisolid formulation which was further confirmed by SEM, it indicates that drug is held within the powder substrate in a solubilized, almost molecularly dispersed state, which lead to the enhanced drug dissolution properties.

1. Introduction

The low solubility of many active pharmaceutical ingredients is one of the technical challenges in formulating as suitable dosage form for its best use. Recently more than 40% of new chemical entities developed in pharmaceutical industry are practically insoluble in water.[1] When combined with the in vitro dissolution characteristics of the drug product, the Biopharmaceutical Classification System (BCS) takes into account three major factors: solubility, intestinal permeability, and dissolution rate, all of which govern the rate and extent of oral drug absorption from immediate release solid oral-dosage forms.[2] For BCS class II drugs, the dissolution process is the rate-controlling step, which determines the rate and degree of its absorption.[3] "Liquisolid compact technique" is successful tool to improve the solubility and dissolution of poorly water soluble drugs and consequently bioavailability.[4]

Liquisolid system refers to the formulations formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents, into dry, non-adherent, free-flowing

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and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials.[5] In this study, candesartan cilexetil was selected as a model drug, since it is a sparingly soluble in water thus, it is an ideal candidate for testing the potential of rapid-release liquisolid compacts. Candesartan cilexetil is an angiotensin-II receptor antagonist used mainly for the treatment of hypertension. It is a hydrophobic drug which belongs to BCS class II and its half life is 5.1 h with 15–40% bioavailability.[6] The aim of this study was to investigate the use of liquisolid technique in improving solubility and dissolution profile of candesartan cilexetil in the form of a liquisolid compact. New mathematical model is applied to calculate the required amounts of powder excipients (carrier and coating materials) for the formulation of liquisolid systems.[7,8] 3^2 full factorial design is applied to study the effect of drug: excipient ratio (X_1) and drug concentration in liquid medication (X_2) on angle of repose, disintegration and dissolution of liquisolid compact of candesartan cilexetil.

2. Material and methods

2.1. Material

Candesartan cilexetil was kindly gifted by Indoco Remedies Ltd., Mumbai. Avicel PH 102, Aerosil 200, Tween 80, sodium starch glycolate, polyethylene glycol, Span 80, Tween 20, was purchased from Loba Chemie Ltd. Mumbai.

2.2. Methods

2.2.1. Saturation solubility study

Saturation solubility studies were carried out in four different non-volatile solvents, i.e. polyethylene glycol 400, glycerin, Tween 80 and Span 80.

2.2.2. Preparation of liquisolid tablets

The desired quantity of the previously weighed solid candesartan cilexetil was dissolved in liquid vehicle (Tween 80). The solution was then sonicated for 15 min until a homogeneous drug solution was obtained. Next, the calculated weights (W) of the resulting liquid medications (equivalent to 8 mg drug) were incorporated into the calculated quantities of the carrier Avicel PH 102 and mixed thoroughly. The resulting wet mixture was then blended with the calculated amount of the coating material Aerosil 200 using a standard mixing process to form simple admixture. Two factors were varied, concentration of the drug in liquid vehicle (Tween 80) and carrier: coating ratios. Different liquid load factors (L_f) ranging from 0.2262 to 0.2703 were employed. Finally 5% w/w of sodium starch glycolate was mixed with the above mixture for 10 min. The final blend of liquisolid powder system was compressed into tablets of desired weight of 8 mg strength each by using 9 station tablet compression machine (Rimek Mini Press II-DL Karnavati), flat faced punch and die size of 12 mm were used. Directly compressed conventional tablets (CND) which is used for comparisons with liquisolid compacts is prepared by directly compressing powder mixture of candesartan cilexetil with Avicel PH 102, Aerosil 200,and sodium starch glycolate.

2.2.3. Application of the 3^2 factorial designs for designing of candesartan cilexetil liquisolid system

Full factorial design was employed for the preparation of the liquisolid compacts. Two independent factors are studied, each at three levels, and experimental trials are performed on all 9 possible combinations. Excipients ratio (carrier: coating material, R) and percent drug concentration in liquid medication (cd %) were selected as independent variables. The angle of repose, disintegration time, percentage cumulative drug release at 30 min was selected as dependent variables.

The coded and the actual values of the experimental design are given in Table 1. The data analysis of values obtained from various batches for the angle of repose, disintegration time, percentage cumulative drug release at 30 min were subjected to multiple regression analysis using PCP Disso software. The response surfaces of the obtained results were also plotted. The equation fitted was

$$Y = ß_0 + ß_1X_1 + ß_2X_2 + ß_{11}X_1^2 + ß_{22}X_2^2 + ß_{12}X_1X_2$$

Where, Y is the measured response; X is the levels of factors; β is the coefficient computed from the responses of the formulations.

2.2.4. Application of the mathematical model for designing of candesartan cilexetil liquisolid system

To calculate the required ingredient quantities, the flowable liquid-retention potentials (Φ-values) of powder excipients were used.[7,8] Flowable liquid-retention potential for Avicel PH 102 and Aerosil 200 was 0.16 and 3.33 respectively.[9] The liquid load factor was computed from the flowable liquid-retention potential in accordance with equation (1) using an R value (excipient ratio).

$$L_f = \Phi + \Phi\,(1/R) \quad (1)$$

Where, L_f–liquid load factor

Φ – Flowable liquid retential potential of carrier

Φ – Flowable liquid retential potential of coating material

Table 1 – Coded levels and actual values of the variables of 3^2 factorial design.

Batch code	Variable levels in coded form		Translation of coded levels to actual values	
	X_1	X_2	X_1	X_2
LS 1	−1	−1	30	10
LS 2	−1	0	30	20
LS 3	−1	+1	30	30
LS 4	0	−1	40	10
LS 5	0	0	40	20
LS 6	0	+1	40	30
LS 7	+1	−1	50	10
LS 8	+1	0	50	20
LS 9	+1	+1	50	30

Where independent variables are: X_1 = Excipients ratio (carrier: coating material R), X_2 = % drug concentration in liquid medication (cd %).