Review Article

Review on Development of Liquisolid Compact Using Experimental Design

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ABSTRACT

Liquisolid technique is a novel process, where a liquid may be convert into a free flowing, readily compressible and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in non-volatile liquid vehicles, is included into the porous carrier material. This technique of liquisolid compacts has been successfully employed to improve the in-vitro release of poorly water soluble drugs. This technique is a promising alternative for formulation of water-insoluble solid drugs and liquid drugs.

Keywords: Liquisolid technique, flowability, dissolution, liquid load factor.

INTRODUCTION

The liquisolid technique as described by Spireas is a novel process, where a liquid may be convert into a free flowing, readily compressible and apparently dry powder by simple blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in non-volatile liquid vehicles, is included into the porous carrier material. Inert, preferably water-soluble organic solvent as liquid polyethylene glycols, propylene glycol, or glycerin are most used as a liquid vehicle [1].

As the carrier is saturated with liquid, a liquid layer is formed on the particle surface adsorbed by the fine coating particles. The liquisolid compacts are flowing and compressible powdered forms of liquid medications. The term '*liquid medication*' refers to liquid lipophilic drugs or water-insoluble drugs dissolved in suitable water-miscible non-volatile solvent systems termed as the liquid vehicle. Liquid medication may be converted into a dry-looking, non-adherent, free flowing and readily compressible powders by a simple mixing with selected powder excipients referred to as the "carrier and coating materials" [2]. In the liquisolid tablets, even though the drug might be in a solid dosage form, it is held within the powder substance in solution or in a solubilized, molecularly dispersed state[3].

Coating material is used to cover the surface and so maintain the powder flowability. The appropriate amounts of carrier and coating materials to produce good flowing and compactable powders are calculated using Eqs. (1)– (3), based on the physical properties of powders called "flowable liquid-retention potential" (Φ-value). The ratio (R) of the amount of carrier (Q) and coating (q) materials is related to the amount of liquid medication (W) [4]. The maximum amount of liquid loads on the carrier material, called "Liquid load factor" (Lf). The excipient ratio (R) is important for determining the "optimum flowable load factor" (Lf) which gives good flowing powders and is characterized by the ratio between (W) and(Q), as shown in Eqs. 1 and 2

$$L_f=\Phi_{CA}+\phi_{CQ}(1/R) \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where Φ_{CA} is the flowable liquid-retention potential of the carrier and is the ϕ_{CQ} flowable liquid-retention potential of the coating material [5].

$$L_f=W/Q \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

From Eq. (2), the amount of carrier material can be calculated and applied to the Eq. (3) to calculate the required amount of the coating (q) material. The amounts of Q and q used to prepare liquisolid formulations. It had been proposed that R value of 20 produces powder admixture with good flow and compactable properties this ratio will be used in this

$$R=Q/q \quad \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

The liquisolid tablets that containing water-insoluble drug are used to enhance drug dissolution because of increased wetting properties of the drug particles and the large surface area available for dissolution [6]. Liquisolid tablets are suitable to formulate low dose water-insoluble drugs. This proved that liquisolid technology can be developed either to improve or to reduce drug dissolution rates depending on the excipients added [7].

This technique of liquisolid compacts has been successfully employed to improve the in-vitro release of poorly water soluble drugs as hydrocortisone, methylclothiazide, hydrochlorothiazide, prednisolone and the liquid drug clofibrate [8]. Also several water insoluble drugs, namely, nifidipine, gemfibrosil, and ibuprofen, have exhibited higher bioavailability in rats as compared to their commercial counterparts. The in-vivo evaluation of hydrochlorothiazide liquisolid tablets in beagle dogs showed that the absolute bioavailability of the drug from

liquisolid tablets was 15% higher than from commercial tablets [9].

Selection of Non-volatile solvent

Selection of solvent was performed on the basis of solubility study. Solubility study of drug was performed in different solvents Like(propylene glycol, polyethylene glycol 200, polyethylene glycol 400, Glycerol, Tween 20, Tween 80, polyethylene glycol 600, Liquid paraffin, Cremophore® EL, Span 80, Span 20,Fixed oil, Castor oil, water, methanol, Phosphate buffer 6.8) to select suitable non-volatile solvent. Excess amount of drug was added to each of vial containing 2 ml of solvents [10-13].

The system was subjected to vortex mixing on Vortexer followed by shaking on rotary shaker for 72 hrs. at 37°c. After calibration for additional 72 hrs the solution was centrifuged on centrifuge, the supernants were diluted by methanol and analyzed by UV-spectrophotometer for the presence of drug[14].

Angle of slide measurement

The study involves an in-house lab model. The model consists of two wooden blocks jointed at one end. At the distal end of joint the upper wooden block was fixed with a polished metal surface [15-16].

Approximately 10 gms of each of material was weighed accurately until the plate containing block creates an angle with another wooden block at which the powder started to slide. The angle (ø) represented the angle of slide. It was used as a measure for the flow characters of powders. An angle of slide corresponding to 33^0 considered as ideal for optimal flow properties [17].

Figure 1: In- house lab-model for measurement of angle of slide

Flowable liquid retention potential determination

To the 10 gm of each of material, increasing amount of optimized solvent was added and mixed well. The corresponding Phi-value was calculated from the following equation after each addition of the non-volatile liquid [18].

$$\text{Phi} - \text{value} = \frac{\text{Weight of liquid(g)}}{\text{Weight of solid(g)}}$$

The Phi-values were plotted graphically against the corresponding angle of slide (Φ).The Phi-value corresponding to an angle of slide of 33^0 was recorded as the flowable liquid retention potential of coating and carrier material. The Phi-values for carrier and coating material has been abbreviated as Φ_{CA} and ϕ_{CO} respectively. The carrier and coating material with maximum liquid retention potential have been selected as optimum [19].

Calculation for the amount of carrier and coating material

On the basis of Phi-value of optimized carrier and coating material the liquid load factor (L_f) and quantities of carrier and coating materials were calculated by using following formula. [20-21]

$$L_f = \Phi_{CA} + \phi_{CQ}(1/R)$$

L_f= W/Q

R=Q/q

Where,

L_f=Liquid load factor

Φ_{CA}= Flowable retention potential for carrier material

ϕ_{CQ}= Flowable retention potential for coating material

R=Excipient ratio (Q/q)

W=Weight of liquid

Q=Weight of carrier material

q= Weight of coating material

Preparation of Liquisolid Compacts

Drug and solvent were accurately weighed in a beaker and heated to 40^0-50^0C, with constant stirring. Selected hot liquid medications were incorporated into carrier contained in a mortar [22]. Carrier material was blended with liquid medication in order to evenly distribute the liquid medication into the powder. Calculated quantities of coating material were added to the mortar. The powder blended with a calculated quantity of disintegrant (10%) for another 30 sec producing the final liquisolid formulation. The blend was compressed into tablets[23].

Experimental design

In an experiment, we deliberately change one or more process variables (or factors) in order to observe the effect the changes have on one or more response variables. The (statistical) design of experiments (DOE) is an efficient procedure for planning experiments so that the data obtained can be analyzed to yield valid and objective conclusions[24].

DOE begins with determining the objectives of an experiment and selecting the process factors for the study. An Experimental Design is the laying out of a detailed experimental plan in advance of doing the experiment[25]. Well chosen experimental designs maximize the amount of "information" that can be obtained for a given amount of experimental effort. The

statistical theory underlying DOE generally begins with the concept of process models.Design of experiment use in preparation and development of liquisolid compact preparation.Different design in experimental design[26].

Though design of experiments is not a substitute for experience, expertise, or intelligence, it is a valuable tool for choosing experiments efficiently and systematically to give reliable and coherent information [27]. Design of experiments is defined as "a structured, organized method for determining the relationship between factors affecting a process and the output of that process." Design of experiments can be used for comparative experiments, screening experiments, response surface modeling, and regression modeling [28].

Comparative experiments

These are used for choosing a better one between two alternatives. The selection is based on the comparison of average results generated from a sample of data from each alternative. For example, choosing a vendor for API from two or more vendors can be a comparative experiment. Comparative designs with narrow scope are suitable for an initial comparison, whereas with broad scope are suitable for a confirmatory comparison [29].

Screening experiments

Screening experiments involves the selection of key factors affecting a response. In these, we select relatively small number of factors which have critical effects on the desired response. These are an efficient way to determine the important factors using minimum number of runs. These experiments can be used as preliminary tools for developing response surface models[30].

Response surface modeling

This method is used after identifying the critical factors affecting a response. Response surface modeling can be used for hitting a target, maximizing or minimizing a response, reducing variation, making a process robust, and seeking multiple goals.

Hitting a target: This is used to find out the adjustments required to hit a target by fitting a model estimated from a small experiment such as adjustment of a compression machine tool.

Maximizing or minimizing a response: Response surface modeling can be used to increase desired response and decrease undesired responses. Here, we have to carry out experiments with multiple inputs to achieve a better response.

1. Mixture design
   Simplex lattice
   Simplex centroid
   Screening
   D-optional
   Distance-based
   User-defined
   Historical data
2. Response surface design
   Center composite
   Box-Benhken
   One factor
   Miscellaneous
   D-optional
3. Factorial design
   2- Layer factorial
   Min run Res V
   Plackett-burman
   Taguchi QA
4. Combine
   D-Optional
   Different statistical design used to optimize different formulation of pharma product.

Formulation and In Vitro Evaluation of Liquisolid Compacts of Cefuroxime Axetil for Dissolution Rate Improvement consisted of microcrystalline cellulose (Avicel pH 102) as carrier material, Aerosil 200 as coating material, and propylene glycol as nonvolatile solvent. Solubility studies of cefuroxime axetil in propylene glycol, Tween 80, polyethylene glycol 400 and glycerin were carried out and propylene glycol (11.12± 1.06 mg/ml) was selected as a non volatile solvent in which drug is having the highest solubility and optimize using a Box-Behnken Design. Independent Variables are Amount of non volatile liquid (%w/w)[X1], Carrier coating ratio (%w/w)[X2] and Liquid load factor[X3] and Dependent Variables Hardness (Kg/cm2)[Y1] Angle of repose (degree)[Y2] % Cumulative drug release [Y3][31]

Plackett-burman screening of olmesartan medoxomil liquisolid tablets: quality by design approach the aim of the present study was to develop Olmesartan medoxomil liquisolid tablets using Quality by Design (QbD) approach to screen the effect of four formulation and process factors on the formulation. OLM liquisolid tablets were prepared by Liquisolid technique. Independent variable Concentration of PEG 400, Neusilin US2, Aerosil and primo gel. Excipients like Neusilin US2, Aerosil 200, PEG 400 and Primojel showed an influential effect on the selected responses angle of repose, thickness and hardness[32].

Formulation and in-vitro evaluation of Efavirenz liquisolid compacts using a 2^3 Factorial design About 16 different formulations were developed using factorial design with carriers (Neusilin and Fujicalin), binder (PVP K-30) and vehicle (polyethylene glycol 300) as independent variables and Aerosil 200 is used as coating material. Independent variable Concentration of drug in the liquid vehicle (% w/w), Concentration of PVP-K30 in the formulation (% w/w) and Concentration of super disintegrant in the formulation (% w/w)[33]

Formulation and evaluation of liquisolid tablet of felodipine using a Surface Response plot which show effect of PEG 400 and Avicel 102 on drug release. Liquisolid tablet of drug Felodipine were prepared by using PEG-400, as non volatile liquid vehicle and Avicel PH

102, Aerosil 200 as carrier and coating materials, Sodium starch glycolate as Superdisintegrant respectively. Felodipine is BCS class II drugs which are having poor water solubility and Bioavaibility (15%) [34].

Design, development and optimization of olmesartan medoxomil liquisolid tablets using central composite design dissolution properties and solubility of olmesartan medoxomil (OLM) in a solid dosage form. This study was designed to optimize and evaluate the effects of different formulation variables: ratio of carrier to coating material (X_1) and drug concentration (X_2) on angle of repose (Y_1), hardness(Y_2), saturation solubility study (Y_3) and cumulative percentage release at 10 min (CPR)(Y_4) of formulation using five level two factor central composite design[35].

Formulation and characterization of ketoprofen liquisolid compacts by Box Behnken design Optimization was carried out using Box Behnken design by selecting liquid load factor, amount of coating material, and amount of magnesium oxide as independent variables; Cumulative percentage drug release and angle of repose were considered as dependent variables. The objective of the present work was to enhance the dissolution rate of ketoprofen using microcrystalline cellulose as carrier, Aerosil 200 as coating material, and polyethylene glycol as non volatile water miscible liquid vehicle[36].

Formulation and development of embelin liquisolid systems using quality by design approach optimized by utilizing design of experiments (DoE) and principal component analysis (PCA) with carrier-coating ratio (X1) and drug concentration in liquid (X2) as factors. Angle of repose and percentage drug release in 30 min were selected as dependent variables. The liquisolid systems were prepared using Solutol® HS-15 in combination of Synperonic® PE/L61 in ratio of 1:1 as non-volatile liquid, Neusilin US2 as carrier and Aerosil 200 as coating material[37].

Formulation Development and evaluation of fast disintegrating tablets of Lamotrigine using liquisolid technique prepared super disintegrating such as Crospovidone, SSG. The relative efficiency of these super disintegrating to improve the disintegrating and dissolution rates of tablets was in order to SSG> Crospovidone. The rate of drug release followed first order kinetics, and the data was fit into the Hixon Crowel cube root law indicating the mechanism of drug release[38].

Formulation, optimization and evaluation of liquisolid tablets containing tadalafil effect of powder substrate composition on the flow ability and compressibility of liquisolid compacts were evaluated. Specifically, several liquisolid formulations, containing 10mg Tadalafil, which containing different carrier to coating ratios in their powder substrates and a fixed liquid medication, were prepared[39].

Liquisolid Tablet Formulation as a Tool to Improve the Dissolution of Olmesartan Medoxomil using mathematical model was used to formulate many liquisolid powder systems using propylene glycol as a non-volatile water miscible liquid vehicle. The liquid loading factors of the vehicle were used to calculate the optimum quantities of carrier (Avicel PH 102) and coating materials (aerosil 200) needed to prepare acceptably flowing and compactible powder mixtures. Different excipient (R) ratios were used (20, 30, 40 and 50)[40].

Risperidone liquisolid compacts–Formulation and evaluation Different formulations were developed using carriers (Neusilin and Fujicalin), coating (Aerosil 200) and vehicle (propylene glycol). The empirical method as introduced by Spireas and Bolton was applied to calculate the amounts of carrier and coating materials. Using this method, improved flow characteristics and hardness of the formulation has been achieved by changing the proportion of carrier and coating materials. Further, a 2^3 factorial design is used and developed LSC using Neusilin (LSC-N1 to LSC-N8) and Fujicalin (LSC-F1 to LSC-F8)[41].

Design and Development of Liquisolid Compact of Carvedilol In the present study, carvedilol was dispersed in polyethylene glycol 400 as the liquid vehicle. Then a binary mixture of carrier–coating materials ((Avicel PH-102) as the carrier and silica200 as the coating material) was added to the liquid medication under continuous mixing in a mortar. The purpose of using 3^2 full factorial designs was to conduct comprehensive study of effect of process parameters like carrier: PEG 400 concentration (X 1) and coating material ratio i.e. R value (X2) and their interactions using a suitable statistical tool (Design expert software version 7.1.5) by applying one way ANNOVA at 0.05 levels. Mathematical modeling was carried out. Polynomial equation was obtained depending on significant influences among 2 factors on their experimental design[42].

CONCLUSION

This technique is a promising alternative for formulation of water-insoluble solid drugs and liquid drugs. Nowadays, new chemical entities often possess a high molecular weight and a high lipophilicity. Especially poorly soluble and highly permeable active pharmaceutical ingredients represent a technological challenge, as their poor bioavailability is solely caused by poor water solubility, which may result in low drug absorption. Numerous methods have been described to optimize the liquisolid compact. Different formulation factor (dependent variable) such as Liquid load factor, excipient ratio, Amount of carrier material, amount of coating material, Amount of Non-volatile liquid, amount of drug concentration on response such as Hardness, Angle of slide, Dissolution at different time interval.

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