INFLUENCE OF FORMULATION PARAMETERS ON DISSOLUTION RATE ENHANCEMENT OF ACYCLOVIR USING LIQUISOLID FORMULATION

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ABSTRACT

Objective: The objective of this research work is to explore the use of liquisolid technique in enhancement of acyclovir dissolution rate. This current study was planned to assess the impact of different formulation variables, such as non-volatile liquid type and concentrations of acyclovir on its dissolution rates profile.

Method: Acyclovir liquisolid tablets were prepared with Tween 60 (liquid vehicle), Microcrystalline cellulose PH 102 (acted as a carrier to turn liquid medication into free-flowing powder) and Syloid XDP (coating material). In vitro, drug dissolution rate of liquisolid formulations of acyclovir was performed and compared with pure acyclovir drug using USP dissolution apparatus (Type II) for 60 min at a paddle speed of 50 rpm and filled with 900 mL of distilled water.

Results: The dissolution study showed that 94.1% of the drug was released in 60 min of ratio 10 while only 66% of the pure drug acyclovir was released in 60 min. Hence, present work concluded that the acyclovir dissolution rate profile has been improved with the formation of liquisolid formulations.

Conclusion: From the present study, it may be ratified that the drug dissolution rate of acyclovir has been improved with the utilization of liquisolid formulations approach.

Keywords: Acyclovir, Dissolution, Non-volatile liquid, Liquisolid tablets.

INTRODUCTION

Nowadays, low solubility is the principle issue related with new drug moieties which should be overcome. The vast majority of the procedures that have prevailing with regard to conquering this issue are spray drying, micronization approach, β-cyclodextrins inclusion complexes, solid dispersions, and eutectic mixtures. However, among all, the feasible and financially savvy is liquisolid system. In liquisolid strategy, the drug is held in a solubilized state and molecularly dispersed in a liquid which helps to achieve the improved drug dissolution [1].

To overcome the bioavailability issue of poorly soluble drugs due to insufficient dissolution rate, numerous techniques are being utilized. Hydrophilic polymers as solubility enhancers are used in various approaches which perform through many ways in the development of various techniques such as cosolvency and inclusion complexes which provide numerous advantages toward formulation development. However, most of the time, during storage, these techniques show stability issues, and low industrial viability and are not commercially successful. Moreover, these techniques suffered with limitations such as hygroscopic and sticky mass which lead to poor flow of powders [2].

Liquisolid technology emerged as a new drug delivery system, differentiated due to its features and potential to deliver numerous drugs. These systems have drawn the attention of pharmaceutics scientists and scholars in the area of poorly soluble drugs for their solubility enhancement and controlled dissolution profile as per the formulation requisite [2]. This technology is patented by Spireas et al, in 1999, and is a simple process of physical mixing with selected excipients which turns it into a free-flowing, dry powder. The main formulation components of liquisolid systems are non-volatile liquid vehicle, a carrier, and a coating material. Moreover, as per the objectives and need of the study, sometimes other excipients such as disintegrants or superdisintegrants are used [3-5].

One of the anticipated mechanisms for the enhance the dissolution rate of the drug from the liquisolid compact mass is the wettability of the latter in the dissolution media. The component that helps in the wetting of drug particles in liquisolid system is the non-volatile solvent [6]. These solvent systems reduce the interfacial tension which was exist between the tablet surface and selected dissolution medium which results in increase effective surface area and wettability for dissolution [7]. Due to this fact, these liquisolid compacts show improved dissolution profile and enhanced bioavailability of poorly soluble drugs. The release of drug from these liquisolid compacts is mainly depends on few parameters, such as drug characteristics, type of carrier, and the type of liquid vehicle used in the formulation. Therefore, these should be optimized, and its effect on dissolution rate should be evaluated [8,9].

The main components of liquisolid systems are carrier material, coating material, non-volatile solvent, and disintegrant. Carrier material such as various grades of sorbitol, cellulose, lactose, and starch holds sufficient adsorption property [10]. Coating materials are highly adsorptive and usually in very fine particle size range. These are various grades of colloidal silica such as Syloid
The formula is \( Lf = \frac{W}{C} \) (1).

The batches containing Syloid XDP were calculated as per the formula of the coating materials amount in each formulation [12]. Therefore, the \( Lf \) of drug are useful parameter which helps in determination of carrier and of different ratios, namely 10, 20, and 30 were obtained. The \( Lf \) of the (800 mg) and drug (100 mg) was added until good flow of powders and in 0.8 mL of liquid medication, weighed quantity of coating agent drug (50 mg) was added until a good flow of powder was achieved 0.4 mL of liquid medication, weighed quantity of carrier (400 mg) and - MCC PH102 and one coating agent - Syloid XDP was used. Hence, in equation (1), \( W \) is the weight of the liquid medication in grams (g), and \( C \) is the weight of the carrier used.

**Drug content determination in liquisolid powder sample**

Acyclovir amount in the sample (dried) was estimated by dissolving liquisolid compact sample (e.g., containing acyclovir, Syloid XDP, and MCC PH 102) about 5 mg in distilled water (10 mL) and then sonicated for 30 min. Subsequently, the sample was filtered, and its absorbance reading (in triplicate) was noted using UV/visible Spectrophotometer at a wavelength of 255 nm [5].

**Flow properties - liquisolid powders**

**Angle of repose**

Angle of repose can be calculated with the help of a funnel placed on a tripod stand. This method is used to determine the frictional forces present in loose powder. The angle of repose is the maximum angle which is possible between the surface of a powder pile and the horizontal plane [4,13-15]. The formula for calculation of angle of repose is given below in equation (2).

\[
\tan \theta = \frac{h}{r} 
\]

(In equation 2, \( h \) is the height of powder conical pile, and \( r \) is the radius of the conical pile base).

**Bulk density**

Bulk density expressed in grams per milliliter (g/mL) is the weight of powder divided by its bulk volume [4,15]. The equation (3) for determining bulk density (\( \rho_b \)) is:

\[
\rho_b = \frac{M}{V_b} 
\]

(In equation 3, \( \rho_b \) is Bulk density, \( M \) is mass of a sample in grams, and \( V_b \) is Bulk volume in cm\(^3\)).

**Tapped density**

Tapped density can be defined as the mass of blend in the measuring cylinder divided by its tapped volume [4,15]. The equation (4) for determining tapped density (\( \rho_t \)) is:

\[
\rho_t = \frac{M}{V_t} 
\]

In equation 4, \( \rho_t \) is Tapped density, \( M \) is mass of blend (g), and \( V_t \) is Tapped volume (cm\(^3\)).

**Moisture content**

Moisture content is a test that is taken to ensure the removal of all the moisture present in the liquisolid powder. It is done by putting the powder in Petri plates and placing them in an autoclave then checking their moisture content by weighing at different time intervals, i.e., after every 15–30 min [4,15]. The formula of moisture content is shown in equation (5):

\[
\text{Moisture content (\%)} = \frac{w_1-w_3}{w_1-w_2} \times 100 
\]

In equation (5), \( w_1 \) is the weight of empty Petri plates, \( w_2 \) is the weight of Petri plate with sample, and \( w_3 \) is the weight of Petri plate with sample after drying.

**Product yield**

Product yield or percentage yield is the product amount which is calculated from limiting reactant. Limiting reactant is that reactant in a chemical reaction which is going to limits the amount of final formed product. The practical yield is the actual amount that is produced when a reaction is carried out [4]. The difference between the practical yield and theoretical yield (gram or mole) and actual yield (gram or mole) can be calculated from the formula given in equation (6):
Preparation of acyclovir liquisolid tablet

Acyclovir liquisolid compacts were prepared by dispersing in Tween 60 which was used as the liquid vehicle to prepare the liquid medication [4]. The latter was added into the mixture of carrier-coating materials with continuous stirring which was compressed into a liquisolid tablet using tablet machine manually. The acyclovir liquisolid tablets prepared and are compared with pure acyclovir tablets. Different formulation attributes affecting the liquisolid compact tablets such as carrier-type, different Lf were taken into account during preparation of liquisolid tablets [15,16].

Dissolution studies of acyclovir

In vitro, dissolution studies were performed on USP Dissolution Test Apparatus Type II (Lab India, DS-8000, Mumbai, India) for acyclovir liquisolid tablets and compared with pure acyclovir conventional tablet [17,18]. The amount of acyclovir release with time for 60 min was determined using distilled water (900 mL) as medium maintained at 37±0.5°C at a paddle speed of 50 rpm. 10 mL aliquots were withdrawn from the dissolution medium at predetermined time intervals of 5, 10, 15, 30, 45, and 60 min, respectively, and the medium was replaced with 10 mL of distilled water to maintain the sink condition. The aliquots were withdrawn, filtered through membrane filter (0.45 µm) and analyzed in triplicate using UV/visible spectrophotometer at 255 nm [4,15,19].

For each formulation, drug release (%) is calculated using the following formula in equation (7):

\[
\text{Drug release (\%)} = \frac{\text{Sample absorbance} \times \text{Standard dilution}}{\text{Standard absorbance} \times \text{Sample dilution}}
\]

\[
(7)
\]

RESULTS AND DISCUSSION

Standard plot of acyclovir was prepared using distilled water as a solvent. A range of 2–10 mcg/mL acyclovir dilutions were prepared, and absorbance was noted at the wavelength of 255 nm using a UV-visible spectrophotometer, as shown in Fig. 1.

Solubility studies demonstrate that the drug acyclovir has revealed highest solubility in Tween 60 (i.e., 31.65 %) as compared to PEG400 and Tween 80 (Table 1). Hence, Tween 60 was selected as the better solvent vehicle for preparation of liquid medication [4].

Previous literature suggested that additives improve the flow properties and compatibility of liquisolid formulations. Lf ([Table 2]) was calculated. From Table 2, it was concluded that the liquisolid sample of ratio 10 has the highest Lf.

The absorbance for pure drug and liquisolid powder of coating agent only was observed at 255 nm, and the results are shown in Table 3. From the absorbance reading, the acyclovir content in liquisolid tablet was found to be 77.44% [4].

The flow properties, i.e., angle of repose, bulk density, and tapped density are calculated and reported in Tables 4 and 5, respectively. In Table 5, the highest bulk density was seen in liquisolid powder of ratio 30 and the highest tapped density in the liquisolid sample with coating agent only [4].

Table 1: Solubility studies of acyclovir in non-volatile liquid vehicle

| S. No | Non-volatile liquid vehicle | Ppm | Solubility (%) |
|-------|-----------------------------|-----|----------------|
| 1     | PEG 400                     | 100 | 24.5           |
| 2     | Tween 60                    | 10  | 10.8           |
| 3     | Tween 80                    | 100 | 26.5           |

PEG: Polyethylene glycols

Table 2: Lf of different liquisolid ratios

| Liquisolid sample | Lf (W/C) |
|-------------------|----------|
| Liquisolid sample | In grams | In µL  |
| of coating agent  |          |       |
| only              | 0.4      | 400   |
| Liquisolid sample | 1.68     | 1680  |
| of ratio 10       | (coating+carrier) | |
| Liquisolid sample | 1.64     | 1640  |
| of ratio 20       | (coating+carrier) | |
| Liquisolid sample | 1.63     | 1630  |
| of ratio 30       | (coating+carrier) | |

Lf: Loading factor

Table 3: Determination of drug content in liquisolid powder sample

| Sample                        | Absorbance (nm) |
|-------------------------------|-----------------|
| Pure drug                     | 3.222           |
| Liquisolid powder             | 2.495           |
| Actual drug content (%) in liquisolid powder | 77.44 |

Table 4: Angle of repose of liquisolid powders (Data in triplicate)

| Liquisolid sample | Angle of repose (°) |
|-------------------|---------------------|
| With coating agent only | 7.9     |
| With ratio 10      | 13.5    |
| With ratio 20      | 13.41   |
| With ratio 30      | 17.11   |

Fig. 1: Standard curve of acyclovir in distilled water at 255 nm
Table 5: Powder flow properties of acyclovir liquisolid tablets

| Acyclovir liquisolid sample                  | Bulk density       | Tapped density after 100 tappings |
|---------------------------------------------|--------------------|-----------------------------------|
| Powder with coating agent only              | 0.75/1.6=0.47      | 0.75/1.2=0.63                     |
| Ratio 10 (carrier+coating agent)            | 2.07/4.5=0.46      | 2.07/3.4=0.61                     |
| Ratio 20 (carrier+coating agent)            | 2.08/4.6=0.45      | 2.08/3.5=0.59                     |
| Ratio 30 (carrier+coating agent)            | 1.91/4.0=0.48      | 1.91/3.1=0.62                     |

Table 6: Moisture content of liquisolid samples

| Liquisolid sample   | W1   | W2   | W3   | Quotient |
|---------------------|------|------|------|----------|
| Powder with coating | 37.30| 38.05| 35.50| 3.4      |
| only                |      |      |      |          |
| Ratio 10            | 26.89| 28.95| 24.96| 1.99     |
| Ratio 20            | 31.50| 33.58| 30.50| 1.48     |
| Ratio 30            | 33.70| 35.58| 32.60| 1.59     |

Table 7: Product yield

| Liquisolid sample | Practical yield | Theoretical yield | Product yield (%) |
|-------------------|-----------------|-------------------|-------------------|
| Powder with     | 0.71            | 0.85              | 83.52             |
| coating agent    |                 |                   |                   |
| only             |                 |                   |                   |
| Ratio 10         | 1.94            | 1.78              | 108.98            |
| Ratio 20         | 1.94            | 1.74              | 111.49            |
| Ratio 30         | 1.77            | 1.7266            | 102.51            |

Table 6 depicts that the liquisolid sample with the coating agent only had the highest amount of moisture content loss [15]. Among the various carrier to coating ratios used, the liquisolid powders having lowest carrier to coating ratio (i.e., R = 10) showed the lowest angle of repose value.

Table 7 shows that the highest product yield was seen in liquisolid powder of ratio 20.

The dissolution results of unprocessed acyclovir and its liquisolid formulations prepared by varying the carrier to coating ratio are shown in Fig. 2. The results clearly indicated that the dissolution profile of drug present in liquisolid formulations got significantly increased (p<0.05) as that unprocessed drug. It was observed that only 66% of drug got released from the unprocessed powder in 60 min, whereas, more than 80% drug got released within 5 min from all the liquisolid formulations. Such observations clearly revealed that acyclovir got completely dissolved in tween-80 and remain adsorbed in solution state in the matrix of carrier and coating material [19]. Once they were introduced in the dissolution medium, the homogeneous solution of tween-80 and drug got completely miscible with the medium. Among the various ratios, the liquisolid formulations having R equal to 10 showed the higher extent of drug release. This could be probable due to that fact that Syloid XDP is amorphous silica and has higher surface area as that of MCC PH 102. In lower ratio, the amount of Syloid XDP was more than that Syloid XDP is amorphous silica and has higher surface area as that of MCC PH 102 which would have enhanced the wettability of formulation in the medium [20,21].

CONCLUSION

This current study provides evidence that due to the liquisolid technique now it is possible to increase the dissolution of poorly soluble drug. The liquisolid tablets of acyclovir exhibit a remarkably improved dissolution rate in comparison with acyclovir plain tablet. Results of dissolution study showed greater dissolution rate of acyclovir from liquisolid compacts. The results are affected by changing the ratio of the carrier to coating material.

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