



RESEARCH ARTICLE

FABRICATION AND CHARACTERIZATION OF EZETIMIBE SOLID DISPERSION FOR SOLUBILITY ENHANCEMENT

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Abstract

Objective: The objective of the present study was to formulate solid dispersions (SD) of Ezetimibe to improve the solubility and dissolution rate to facilitate faster onset of action. Ezetimibe is poorly water soluble BCS class II drug and used as a hypolipidemic agent. It has poor bioavailability (35-65%) due to its low dissolution profile in gastro intestinal tract.

Methods: In the present study, eight solid dispersion formulations of Ezetimibe with polymers PEG-4000 and PEG-6000 were prepared by solvent evaporation and fusion methods. Solid dispersion formulations were characterized by content uniformity, flow properties and *in vitro* dissolution studies.

Results: The solubility of Ezetimibe powder in distilled water at 37±0.5°C was 2.37±0.14 µg/ml, whereas solubility of the solid dispersion formulations was in the range of 322.43-37.48 µg/ml. Percent yield of eight solid dispersion formulations of Ezetimibe lies in range of 98.20 to 99.42% w/w.

Conclusion: Present study concluded that the Ezetimibe solid dispersion formulations are a suitable approach to improve the solubility and dissolution rate of ezetimibe than pure form of drug.

Keywords: Ezetimibe, PEG-4000, PEG-6000, solid dispersion.

INTRODUCTION

Solubility is an important aspect for oral dosage forms, to deliver required drug concentration in systemic circulation to produce desired pharmacological response¹. On an average more than 90% of available drugs have poor solubility, poor permeability, or both¹. For this reason there is always a need to use high doses of poor soluble drugs to achieve minimum effective concentration of drug in systemic circulation². There are so many approaches to enhance the solubility of such poorly water-soluble drugs like particle-size reduction, salt formation, solubilization, and complexation with β cyclodextrins. All these methods suffer from one or the other drawbacks³. Among various approaches, the solid-dispersion technique is the most successful in improving the dissolution and bioavailability of poorly soluble, active pharmaceutical ingredients because it is simple, economical and advantageous⁴. A solid dispersion can be defined as "dispersion of one or more active ingredients in an inert carrier matrix in solid-state". Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic

matrix and a hydrophobic drug⁵. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles by various methods. It enhances solubility by reducing particle aggregation, eliminating crystallinity, increasing wettability, dispersibility and altering the surface properties of drug particles⁶. When solid-dispersion is exposed to aqueous media the carrier dissolves and drug releases as fine colloidal particles, the resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs⁷. Ezetimibe is a BCS class II drug. Ezetimibe is poorly water soluble drug and act as a hypolipidemic agent⁸. Ezetimibe decreases plasma cholesterol levels by inhibiting the cholesterol absorption in the intestine. It has 35-65% of bioavailability due to its low dissolution profile in gastro intestinal tract⁹. Ezetimibe binds to a carrier of cholesterol absorption, the Niemann Pick C1-Like 1 (NPC1L1) protein on the gastrointestinal tract epithelial cells and in hepatocytes thus decreasing the LDL in the body and prevent various life threatening diseases. In the present investigation an attempt has been made to increase the dissolution profile of Ezetimibe by solid dispersion¹⁰. The aim of the present

study was to prepare solid dispersions in order to achieve increased dissolution rates. Therefore, in the present study, solid dispersions of Ezetimibe were prepared by solvent evaporation technique and fusion method. Acetone was selected as a solvent as drug has highest solubility in this solvent. Acetone is categorized under class II solvents, less toxic than other chlorinated solvents can be easily evaporated and recovered because of its low boiling point.

MATERIALS AND METHODS

Ezetimibe was gift sample from Afrab-chem Ltd, Nigeria. PEG 4000 and PEG 6000 were obtained from Dana Drugs Ltd, Lagos, Nigeria and all other reagents used were of analytical grade.

Preparation of solid dispersions

1. Solvent Evaporation method

Required amount of Ezetimibe was dissolved in 10 ml of acetone. Accurately weighed carriers PEG 4000, PEG 6000 corresponding to different drug: carrier ratio by weight was dispersed in drug solution. The solvent was allowed to evaporate on water bath under occasional stirring at temperature of 40-42°C in a protected environmental condition containing an exhaust system. The dried mass was pulverized and was passed through a mesh sieve of number of 100. The powder was subsequently dried at 40°C for 3 hours in a tray drier¹¹.

2. Fusion method

In fusion method the binary solid dispersions were made using PEG-4000, PEG-6000 as carriers with varying drug: carrier ratios by the fusion method. Solid dispersion of Ezetimibe and carriers were obtained by melting carrier in a porcelain dish at 80–85°C and to this Ezetimibe added with thorough mixing for 1-2 minutes followed by quick cooling. The dried mass was then crushed and passes through sieve no.40 to get uniform sized particles¹¹.

Solubility studies

The solubility studies of different Ezetimibe and solid dispersion formulations of Ezetimibe were conducted in distilled water and phosphate buffer of 1.2, 6.8 and 7.4 pH. An excess amount of Ezetimibe solid dispersion was weighed and transferred into conical flasks which contain 10 ml of media. The content in conical flask were sonicated for 2 hrs at room temperature, there after the samples were placed on a shaker, agitated at room temperature for 48 hrs. After it, the suspensions were filtered through a Whatman filter paper. The filtrate was suitably diluted and analyzed spectrophotometrically at a wavelength of 232 nm using a double beam UV-Visible spectrophotometer⁰.

Characterization of formulations

Percent yield

Percent yield was determined by following formula

$$\text{Yield} = \frac{a}{b + c} \times 100$$

where, a is the weight of solid dispersion sifted through a 60 number mesh sieve, b is the weight of Ezetimibe taken for solid dispersion preparation, and c is the

weight of polymer taken for solid dispersion preparation¹⁴.

Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles¹⁴. This is the maximum angle possible between surface of pile of powder or granules and angle of repose.

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted¹⁵. It is expressed in gm/ ml and is given by

Tapped density

Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed¹⁶.

Carr's Index

It indicates the ease with which a material can be induced to flow and powder compressibility¹⁶. It is expressed in percentage and is given by

$$\text{Carr, s Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner ratio (Hr) is an indirect index of ease of powder flow⁰. It is calculated by the following formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Drug content

Solid dispersions (100 mg) were accurately weighed and dissolved separately in 100 ml of 20 %v/v acetic acid. The solution was suitably diluted and the absorbance was measured at 232 nm. Drug content was calculated using the regression equation¹¹.

In vitro dissolution studies

Ezetimibe a pure drug and solid dispersions were subjected to dissolution test using *in-vitro* dissolution rate apparatus-I of USP XXIV (Basket method). This test was performed using 1000 ml of dissolution medium (0.1N HCL) at 37±2°C. Accurately weighed samples (plain drug and surface solid dispersions) of drug were filled in '00' size hard gelatin capsule by hand filling method and placed in basket of dissolution apparatus which was rotated at 50 rpm. A 5 ml aliquot of dissolution medium was withdrawn and replaced with equal volume of fresh dissolution medium at appropriate time intervals and analyzed spectrophotometrically by measuring absorbance at 232 nm.

RESULTS AND DISCUSSION

The equilibrium solubility data are presented in Table 2. The solubility of Ezetimibe powder in distilled water at 37±0.5°C was 2.37±0.14 µg/ml, whereas solubility of the solid dispersion formulations was in the range of 322.43-37.48 µg/ml. In other aqueous media i.e. in phosphate buffer of pH 1.2, 6.8 and 7.4, there was

increased solubility of solid dispersion formulations in comparison to pure drug. It was found that as the pH of the media increased, there was increase in solubility drug and solid dispersion formulations. These findings suggest that solid dispersions had much more enhanced

equilibrium solubility as compared with pure drug powder and physical mixtures. Calculated percent yield of eight solid dispersion formulations of Ezetimibe lies in range of 98.20 to 99.42% w/w.

Table 1: Composition of solid dispersion formulations of Ezetimibe.

Formulation code	Carrier	Drug: Carrier	Method	Acetone
SD1	PEG 4000	1:1	Fusion method	q.s.
SD2	PEG 4000	1:3	Fusion method	q.s.
SD3	PEG 6000	1:1	Fusion method	q.s.
SD4	PEG 6000	1:3	Fusion method	q.s.
SD5	PEG 4000	1:1	Solvent evaporation method	q.s.
SD6	PEG 4000	1:2	Solvent evaporation method	q.s.
SD7	PEG 6000	1:1	Solvent evaporation method	q.s.
SD8	PEG 6000	1:2	Solvent evaporation method	q.s.

Table 2: Solubility study of Ezetimibe and solid dispersion formulations of Ezetimibe.

Sample	Solubility (µg/ml)			
	Distilled Water	1.2 pH buffer	6.8 pH buffer	7.4 pH buffer
Pure drug	2.37±0.14	3.37±0.14	4.42±0.09	5.31±0.06
SD1	22.43±0.25	23.48±0.13	24.57±0.26	25.95±0.14
SD2	24.59±0.09	26.81±0.26	29.44±0.07	31.59±0.26
SD3	23.47±0.07	26.64±0.07	28.58±0.42	29.74±0.25
SD4	33.56±0.11	37.83±0.04	36.46±0.18	39.85±0.16
SD5	26.87±0.26	28.55±0.08	32.74±0.33	29.73±0.09
SD6	37.48±0.31	39.51±0.15	40.57±0.41	41.66±0.07
SD7	29.41±0.16	33.74±0.32	35.83±0.09	36.85±0.14
SD8	30.46±0.08	36.78±0.42	37.58±0.25	38.72±0.25

Out of all the formulation of batch SD6 have shown highest yield (99.42%) whereas formulation of batch SD2 have shown minimum yield 98.20%. Solid dispersion formulations of Ezetimibe were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio (Table 3). Angle of repose was less than 35° and Carr's index values were less than 21 and Hausner's ratio was less than 1.25 for all the batches indicating good flow properties. The drug content in all Ezetimibe solid dispersion formulations containing PEG 4000 as well as PEG 6000 is above than 98.15% as shown in Table 3.

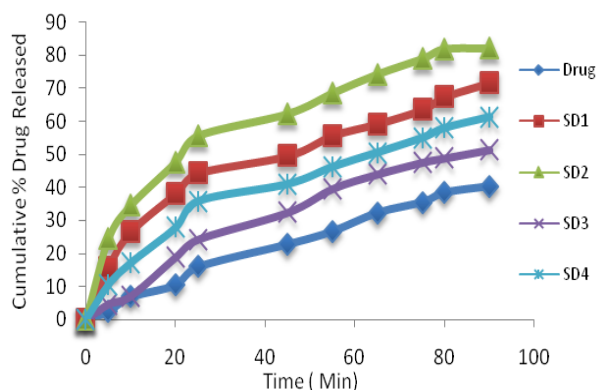


Figure 1: Dissolution profile of Ezetimibe solid dispersion formulations of batch SD1-SD4.

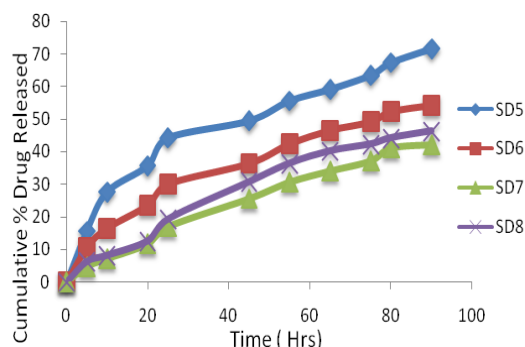


Figure 2: Dissolution profile of Ezetimibe solid dispersion formulations of batch SD5-SD8.

The drug content was found to be minimum (98.15%) for SD7 whereas SD6 have shown maximum (99.66%) drug content. PEG 6000 containing formulations showed better results than PEG 4000 formulations because of its high molecular weight which are responsible for the formation of fine microcrystal and absence of drug clusters. Dissolution data of Ezetimibe solid dispersion formulations are reported in Figure 1 and Figure 2. From the result, it can be seen that all the prepared solid dispersion showed an enhancement in the dissolution rate of the drug compared to plain drug. Solid dispersions prepared by using PEG 4000 showed enhanced dissolution when compared to other PEG 6000. The rank order of dissolution rate improvement for various carriers are; PEGS 4000>PEG 6000.

CONCLUSIONS

Eight formulations were prepared by the solvent evaporation method and fusion method. All prepared solid dispersion formulations showed significantly higher drug dissolution in comparison with pure drug. In the solid dispersion there are many mechanism are responsible for exhibiting faster release like the decrease in particle size, partly to the wettability and to some extent to increase in the solubility of the drug due to the solubilising effect of carrier used or to the increase in surface area of the drug in the product. From the obtained results it can be concluded that solid dispersions improved the dissolution rate of poorly soluble drug Ezetimibe. The results of the Ezetimibe solid dispersion was indeed promising although more evaluation is needed before it can be finally recommended for capsule or tablet dosage form of Ezetimibe.

AUTHOR'S CONTRIBUTION

Jajere UM: writing original draft, methodology, investigation, formal analysis, conceptualization.
Achadu AE: writing, review and editing, methodology, formal analysis, conceptualization. Final version of manuscript is approved by all authors.

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DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTERESTS

None to declare.

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