FORMULATION AND EVALUATION OF OBETICHOLIC ACID SOLID DISPERSION TABLET

ABSTRACT

Obeticholic acid is farnoside X receptor agonist and recently approved by US FDA. Solubility is less in solvent and it requires improving solubility. Solid dispersion is one of the suitable techniques for solubility enhancement of Obeticholic acid. There are many techniques for preparation of solid dispersion. Fusion (Hot Melting) is one of the simplest and affordable techniques for manufacturing of solid dispersion. Poloxamer is one of the best polymers for manufacturing of solid dispersion. Poloxamer 188 and 407 are easily available in market. Fusion or Hot melting technique is used to manufacture above solid dispersion. Prepared solid dispersion shows improved solubility 0.347 mg/ml. Percent drug release is also better as compare with polymer mixture which is 99.63 %. Precompression parameters observed with in standard range. Post compression parameters such as Hardness, Friability, Uniformity of weight, content uniformity are in standard range. F7 formulation shows 99.63 ± 0.19 in 60 minutes of time. Phosphate buffer 7.4 is used for dissolution test apparatus. All result parameter shows that prepared solid dispersion of Obeticholic acid by using poloxamer gives improved solubility and increased drug release.

Keywords- Obeticholic Acid, Poloxamer 188 and 407, Phosphate Buffer,Solid Dispersion,

INTRODUCTION

For its simplicity and ease of ingestion, the oral route of drug administration is the most common and preferred route of delivery, although it might be problematic if the medication is poorly soluble or has poor membrane penetrability. Although salt manufacture, dissolution rate, and particle size reduction are frequently used to raise dissolution rate and, as a result, oral absorption and bioavailability of low water soluble drugs [1-4], these techniques have limits. One of the promising techniques for improving drug dissolution is solid dispersion of the drug in a water soluble polymer. The solid dispersion (SD) of one or more active ingredients in inert carriers prepared by fusion, solvent or solvent fusion processes is defined as the dispersion of one or more active ingredients in inert carriers at a solid state [5]. Based on in vitro and in vivo permeability data, the Biopharmaceutical Classification system separates medicines into four types. There are four types of compounds: I (high solubility, high permeability), II (low solubility, high permeability), III (high solubility, low permeability), and IV (high solubility, low permeability) (low solubility and low permeability) [6]. Waiving bioequivalence tests is common with Class I drugs. New chemical

compounds with low water solubility and permeability are filtered out during the selection phase since they may cause complications during pharmaceutical development. Oral medication absorption is limited by dissolution/solubility in class II pharmaceuticals and permeability in class III drugs [8-10]. The limited ability of class II medicines to dissolve is clearly a greater limiting factor in their total pace and increased bioavailability than its ability to pass through the gut epithelia. Solid dispersion, surfactant solubilisation, co-solvent use, particle size reduction, hydrotropy, and the use of highly soluble derivatives or salts are some of the pharmacological techniques available for improving the aqueous solubility of poorly soluble pharmaceuticals. Solid dispersion (SD) is the most efficient approach from the dispersion in carrier, more specifically defined as the system has the dispersion of one or more active ingredients in an inert matrix at solid state performed by melting method, solvent evaporation method, and melting solvent [11]. Many researchers have researched SDs of poorly water soluble pharmaceuticals with various pharmacologically inert carriers to improve dissolution and oral absorption of poorly water soluble medications for a long time, but only a few systems are economically viable. Polymer has lately become popular as a surface adsorption excipient as well as a wetting and solubilizing agent. Various strategies have been used to improve the solubility, dissolution, and bioavailability of numerous hydrophobic medications. For some pharmaceuticals, the increase in solubility achieved with Poloxmer was greater than with other meltable polymers like PEGs and complex forming substances like cyclodextrin [12]. Poloxomer was empirically chosen as a polar carrier in this investigation due to its excellent surfactant characteristics and oral safety. According to the analysis, the main ways of improving dissolution are to increase surface area available for dissolution by reducing the particle size of the solid compound and/or optimising the wettability characteristics of the compound surface, to reduce the boundary layer thickness, to ensure sink conditions for dissolution, and last but not least, to improve the apparent solubility of the drug under physiologically relevant conditions.

Obeticholic Acid is a semi-synthetic hydrophobic BA analogue. This one is a highly selective agonist of FXR, Revitalization power similar to that of the endogenous oneBut BA chenodeoxycholic acid is 100 times higherPowerful 5OCA also induces intestinal expression Hormones, especially FGF19. Beneficial effects of OCA on the resulting glucose Lipid metabolism, especially the liverInflammation makes it a potential candidate Pharmacological treatment of various diseasesIncluding PBC and non-alcoholicsteatohepatitis(NASH). Obeticholic acid is a farnesoid X-activated receptor (FXR) agonist that is a modified synthetic bile acid. Human enterocytes and hepatocytes are the main cells that express

farnesoid X-activated receptors. Bile acids, which are found in nature, are the most common ligands for FXRs. FXRs regulate bile acid production and release fibroblast growth factor, notably FGF-19, into the hepatic portal circulation in enterocytes. In hepatocytes, FXRs largely govern hepatic triglyceride synthesis, fibrosis, and a variety of other metabolic pathways. FGF-19 binds to the FGFR-4 receptor on hepatocytes once it is released into the portal vein [13]. The inhibition of cholesterol 7 alpha-hydroxylase (CYP7A1), the enzyme responsible for converting cholesterol to bile acids, is the result of this receptor complex. Obeticholic acid is a farnesoid X-activated receptor (FXR) agonist that is a modified synthetic bile acid. Human enterocytes and hepatocytes are the main cells that express farnesoid X-activated receptors. Bile acids, which are found in nature, are the most frequent ligands for FXRs. FXRs regulate bile acid synthesis and release fibroblast growth factor, notably FGF-19, into the hepatic portal circulation in enterocytes. In hepatocytes, FXRs primarily regulate hepatic triglyceride synthesis, fibrosis, and a range of other metabolic pathways. FGF-19 binds to the FGFR-4 receptor on hepatocytes once it is released into the portal vein. The reduction of cholesterol 7 alpha-hydroxylase (CYP7A1), the enzyme responsible for converting cholesterol to bile acids, is the result of this receptor complex. While Obeticholic acid (OCA) is not approved for use in NASH, current research suggests that OCA's activity in suppressing hepatic triglyceride synthesis and promoting insulin sensitivity and insulin-dependent activities decreases the risk of lipid deposition in hepatocytes, thus also reducing the occurrence and progression of NASH [14].

Advantages

1. Solid dispersion has made it possible to improve drug bioavailability by modifying their water solubility.
2. Increased dissolution rate and absorption extent, as well as a decrease in pre-systemic metabolism.
3. The transformation of a medication from a liquid to a solid state.
4. Solid dispersions are much more efficient than particle size reduction approaches that have a particle reduced size limit of 2-5 mm, which is typically insufficient to improve medication solubility or release in the small intestine significantly.
5. When parameters including carrier molecular weight and composition, drug crystallinity, particle porosity, and wettability are adequately regulated, bioavailability can be improved.

Disadvantages

1. It absorbs moisture which result in phase separation, crystal growth, sometimes there is change in state of material.
2. It has poor Scale up for their manufacturing on large scale.

Applications of Solid Dispersion

1. It make stable drug from un-stabilized drug.
2. Convert liquid or gas into solid form.
3. Get homogeneous mixture of small amount of drug in solid form.
4. To produce fast release drug in slow release formulation.
5. It mask unpleasant taste of drug.
6. It reduces undesirable incompatibility.
7. It reduces presystemic inactivation of drug.

Techniques for Preparation of Solid Dispersion

Different techniques are there to prepare Solid Dispersions are,

1. Kneading Method
2. Co-Milling Method
3. Hot-Melt Method (Fusion Method)
4. Solvent Evaporation Method
5. Solvent Based Method
6. Melting Solvent Evaporation Method
7. Supercritical Fluid

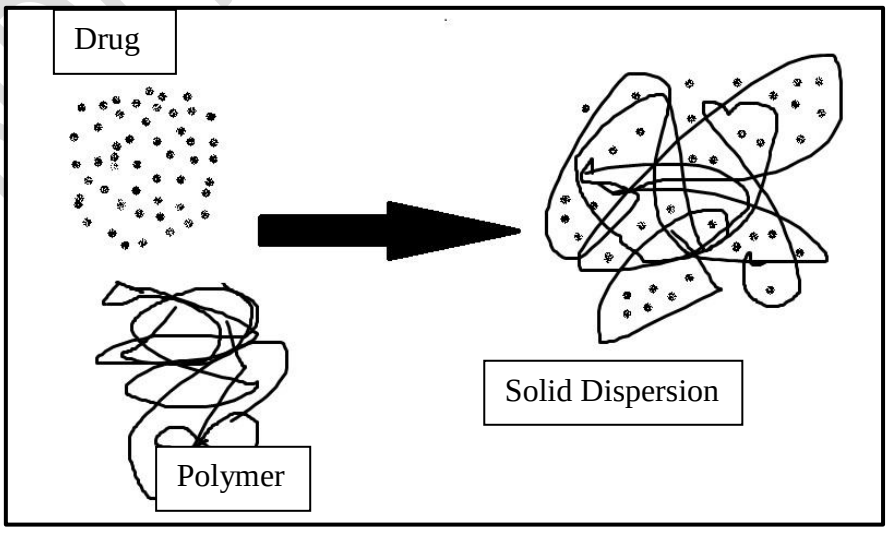

Fig 1:

Material and Method

Obeticholic acid obtained as gift sample from Amneal Pharma, Gujrat. Poloxomer polymer was purchased from Vishal Chemical Supplier Mumbai. Lactose, Mg Stearate was obtained as gift sample from GSK Laboratories, Gujrat.

Drug Profile

Obeticholic Acid

$C_{26}H_{44}O_4$

Molecular Weight- 420.6

Melting Point – 108 -110 ^{O}C

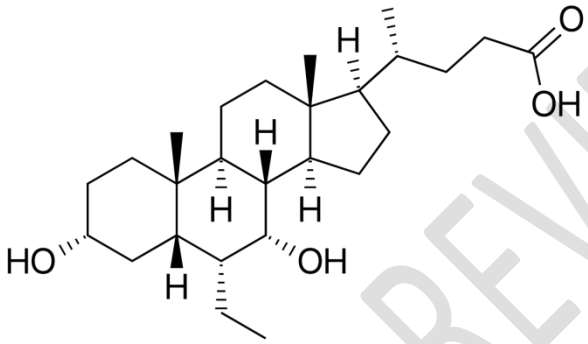

Fig 2:

Mechanism of Action of Obeticholic Acid

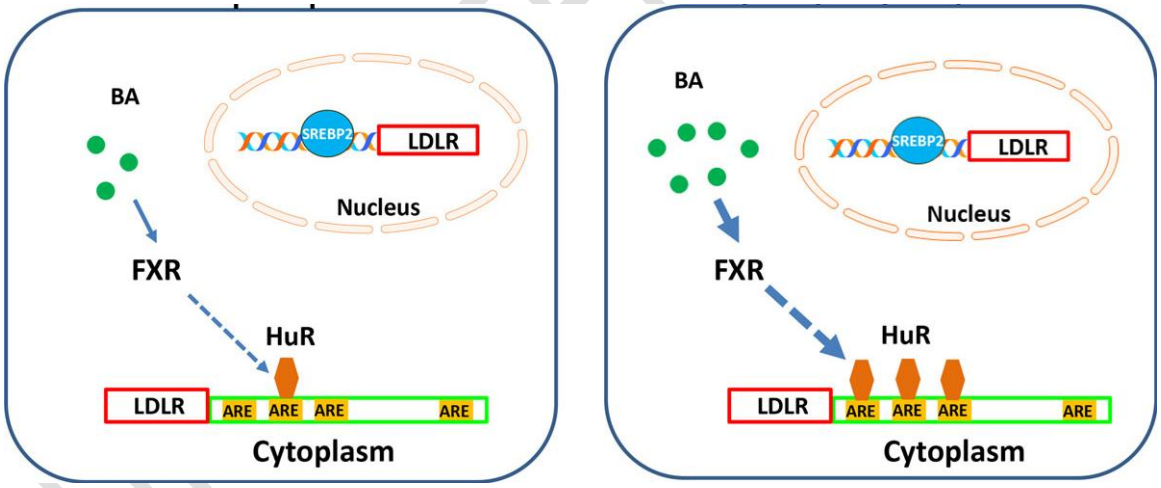

Fig 3:

Poloxamer Profile

Molecular Weight – 162.3

Molecular Formula- $C_8H_{18}O_3$

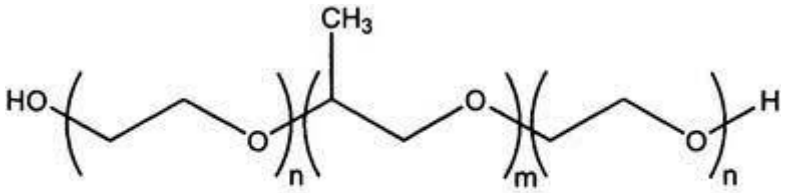

Fig 4:

Preparation of Physical Mixture

A Physical mixture of Obeticholic Acid and Poloxamer in the ratio of 1:1 was prepared by thoroughly mixing accurately weight drug and Poloxamer in glass mortar and pestle. This mixture then pass through sieve no 40 and placed in desiccator for 2 days.

Preparation of Solid Dispersion

Prepared physical mixture is directly heated until it melts. The melted mixture is then rapidly cooled and solidified in ice bath with rapid stirring. The prepared solid mass is then crushed to reduce particle size to be incorporated to convert into suitable dosage form.

Determination of Drug Content

Drug content was calculated by dissolving solid dispersion equivalent to 2 mg drug transfer in 100 ml volumetric flask dissolve in methanol and make up volume up-to 100 ml with phosphate buffer. Filter it and take absorbance by UV spectrophotometer.

***In-Vitro* Drug Release**

2 mg of drug was accurately weighed and added to 900 ml of dissolving media (7.4 phosphate buffer) in USP dissolution apparatus II, which was agitated at a speed of 50 rpm at 370.5°C. At 10, 20, 30, 40, 50, and 60 minutes, five milliliter aliquots were removed and replaced with 5 milliliters of new dissolving media (37°C). The collected samples were evaluated against the blank using a UV-visible spectrophotometer after appropriate dilution at 228 nm. Pure Glimepiride was also dissolved in the same way.

Formulation and Evaluation of Obeticholic Acid Solid Dispersion Tablet

Obeticholic acid 5 mg containing solid dispersion is prepared and by direct compression tablet is prepared. Blend was compressed on 6 station rotary machine using round shape concave punches.

Table 1: Composition of Tablet

Sr. No.	Ingredient	Quantity(mg)
1	Solid Dispersion	10
2	Polyvinyl Pyrollidone	08

3	Lactose	100
4	Sodium Starch Glycolate	18
5	Magnesium Stearate	04

Evaluation of Obeticholic Acid Solid Dispersion Tablet

All prepared tablet were evaluated for content uniformity, friability, hardness, weight variation, *In-Vitro* drug release. Friability test performed on Roche Fraibilator and Hardness tested on Pfizer Hardness tester.

Content Uniformity of Tablets-

Tablet were weighted and crushed in small morter. Fine powder equivalent to 2 mg of drug transfer to 100 ml volumetric flask, containing 10 ml methanol and dissolved, volume made up to 100 ml by NaOH. Solution is filtered and dilute with 100 ml for UV absorbance.

In-Vitro Drug Dissolution –

Prepared Obeticholic acid tablet added to 900 ml of dissolution medium (PH 7.4 Phosphate Buffer) contained in USP dissolution apparatus II and stirred at speed 50 rpm at 37 ± 0.5 ^{0}C. 5 ml sample is withdrawal after 10, 20,30,40,50 and 60 minutes and same quantity of buffer is replaced. Collected sample then send for UV absorbance.

Result and Discussion

The drug content of Obeticholic Acid solid dispersion was found to be in range 98.24 to 99.72 and these values are within the acceptable range. Low values of standard deviation in respect of with respect to drug content, as given in Table below.

Table 2: Indicating uniform drug distribution in all the solid dispersions

Formulation	% Drug Content	Solubility mg/ml
F1	96.15	0.122
F2	97.14	0.186
F3	97.85	0.216
F4	98.26	0.286
F5	98.95	0.292
F6	98.97	0.310
F7	99.63	0.347
F8	99.55	0.298

F9	99.40	0.299

Solubility Studies

Obeticholic Acid's solubility profile was discovered to be 0.0087 mg/ml, indicating a great need to improve its solubility and dissolution. In the current study, a solid dispersion approach utilising Poloxamer was used to improve the solubility and dissolution of Obeticholic Acid. The solubility of all solid dispersions improved with an increase in the weight fraction of surface-active carrier. The Fusion process was used to generate a 1:5 ratio of Obeticholic Acid: Poloxamer 188, which resulted in the greatest increase in solubility. 0.347 mg/ml.

***In-Vitro* Drug Dissolution Studies**

Figure and graph illustrate the in vitro release profile of Obeticholic Acid from Poloxamer 188 and Poloxamer 407 solid dispersions (made using the Fusion Method) and physical mixture formulation. According to the findings, drug dissolution increased progressively as the concentration of both grades of Poloxamer was increased up to a certain point, after which it nearly became constant. The molecular and colloidal dispersion of drug in the hydrophilic carrier matrix of poloxamer was shown to be faster than that of physical mixes and drug. This could be attributed to the drug's molecular and colloidal dispersion in the hydrophilic carrier matrix of poloxamer.

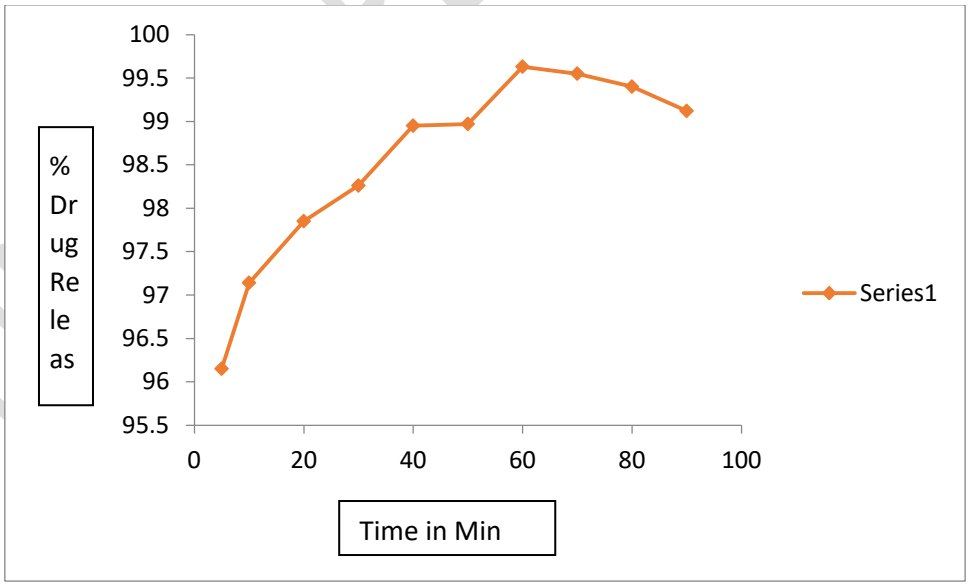

Fig 5: Evaluation of Solid Dispersion Tablet Dosage Form

Pre Compression Evaluation of Drug- Excipient Blend

Table shows the pre-compression results as well as the drug-excipients mix evaluation. The angle of repose was determined to be less than 29, indicating favourable flow properties. It was discovered that the bulk density and tapped density values were both less than one. Similarly, all batches percentage compressibility (Carr's Index) values were less than 15%, indicating that all batches of tablet blend have good flow properties.

Table 3: Parameter

Parameter	**Formulation**
Angle of Repose	24.11
Bulk Density	0.53
Tapped Density	0.56
% Compressibility	6.78
Hausner Ratio	1.04

Table 4: Post Compression Study of Prepared Tablet

Parameter	Prepared Tablet Result
Uniformity of Weight (mg)	148.5 ± 0.45 mg
Content Uniformity %	99.63
Friability %	0.5 ± 0.50
Hardness (kg/cm2)	3.8 ± 0.38(kg/cm2)

Dissolution Study of Prepared Tablet

When the mixture comes into contact with water, the polymeric particles may have hydrated quickly, solubilizing the nearby drug particles and releasing the drug into in the medium. The reason for improved Obeticholic Acid release from solid dispersion as the ratio of Poloxamer 188 and Poloxamer 407 increases is that at low concentrations, similar to those at which more conventional nonionic detergents release from micelles, the poloxamer monomers are thought to form monomolecular micelles through a change in solution configuration. These monomolecular micelles combine to form aggregates of different sizes at higher concentrations, which have a greater ability to solubilize medicines.

Conclusion

Solid dispersions generated by the Fusion Method with poloxamers enhanced the solubility rate of Obeticholic Acid without any physical or chemical interaction. When compared to physical mixes and solid dispersion with poloxamer 407, solid dispersions of Poloxamer 188

with Obeticholic acid demonstrated an improved dissolving profile. In-vitro tests revealed that the Obeticholic Acid :Poloxamer 188,1:5 ratio produced the best outcomes of all formulations. Furthermore, tablets made with that combination had a better dissolving profile and were not impacted by mechanical shocks during compression.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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