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Formulation Aspects of Ezetimibe Lyophilized Dry Emulsion Tablets

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ABSTRACT

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Ezetimibe is the first lipid-lowering drug that inhibits the intestinal absorption of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. After oral administration, ezetimibe is rapidly absorbed and extensively metabolized (>80%) to the pharmacologically active ezetimibe-glucuronide. Total ezetimibe (the sum of 'parent' ezetimibe plus ezetimibe-glucuronide) concentrations reach a maximum 1-2 hours after administration, followed by enterohepatic recycling and gradual elimination. The terminal half-life of ezetimibe and ezetimibe-glucuronide is approximately 22 hours. Consistent with the elimination half-life of ezetimibe, approximately 2-fold accumulation is observed after once-daily dosing. The recommended dose of ezetimibe 10 mg/day can be given in the morning or evening without regard to food.

Keywords: Ezetimibe, lyophilized dry emulsion tablet, and hyperlipidemia, freeze drying, Labrafac

INTRODUCTION

Ezetimibe is an antihyperlipidemic agent capable of lowering blood cholesterol levels. It is the most widely administered oral statin used in terms of increased plasma levels of cholesterol, triglycerides (TG), low-density lipoproteins (LDL) in addition to its ability to increase high-density lipoproteins (HDL). Ezetimibe (EZT) is a lipidlowering drug that inhibits the intestinal absorption of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. According to the Biopharmaceutical Classification System (BCS) ezetimibe is classified as a class II drug, insoluble in aqueous solutions at pH 4 and below, while very slightly soluble in water and ezetimibe shows limited oral bioavailability of about 14% which is attributed to Poor aqueous solubility, crystalline form, hepatic first-pass metabolism and mucosal gastrointestinal presystemic clearance. (1-3)

Hyperlipidemia is an abnormally elevated level of any or all lipids or lipoproteins in the blood. That is the most Dyslipidemia in general (which includes any abnormal lipid levels). (4) In this research work, the importance of freeze dry tablets to enhance the solubility of ezetimibe was explored through the formulation of lyophilized dry emulsion tablets (LDET). The LDET formulation offers the advantages of both emulsion and freeze dry dosage forms. Emulsion is efficient in improving the dissolution rate and bioavailability of poorly water soluble drugs. When freeze-dried dosage forms provide better preservation and stability.(5)

Another distinct advantage of freeze-dried formulations as a final dried product is the density network in the same volume as the initially frozen parent solution, thereby creating a light and porous product that dissolves easily.(6)

The first component consists of water-soluble polymers, such as gelatin, dextrin, alginate, and this component maintains shape and provides mechanical strength to the tablets. There is another factor

Disintegration enhancing agents, such as sucrose and mannitol, which act by cementing the porous framework provided by water-soluble polymers and accelerate the disintegration of tablets. (7-8) In the present work, alginate in combination with gelatin and mannitol was used as a base for the preparation of lyophilized dry emulsion tablets. (9) Gelatin, a mixture of proteins, is an inexpensive polymer that is abundant in nature and can be easily processed into numerous forms and shapes. Being biocompatible, biodegradable, non-toxic and non-immunogenic, both sodium alginate and gelatin have received high consideration and are widely used in various biological applications. The choice of

these excipients can benefit the formulation in several ways. They are expected to form the highly porous matrix structure required for such dosage forms. Also, structural strength was provided by gelatin while crystallinity, stiffness and finesse were provided by mannitol. Sublimation of water, process m
Athyma creates a porous structure during the freeze-drying stage. (10-11) The aim of the present work was the development of fast disintegrating tablets for ezetimibe, exploring the effect of selected excipients through the evaluation of LDET prepared using a combined emulsion-freeze drying technique, which aimed to decrease and increase the disintegration time. Drug dissolution rate.

Properties of the dry emulsions:[2]

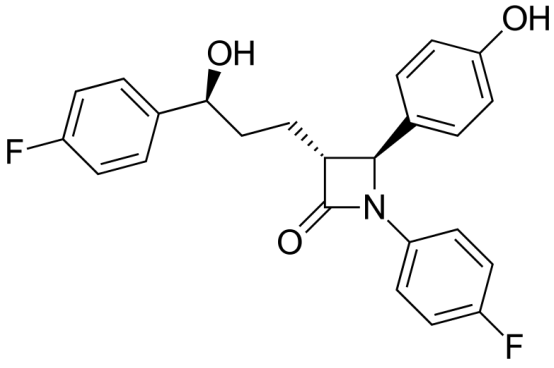
· Rotary atomizer type and rotation rate did not significantly affect the technical properties of dry emulsions containing 40% lipid.
· The reconstitution properties of dry emulsions are affected by the type of rotary atomizer and the rotation rate of the atomizer.
· This may be due to the particle size effect resulting from the increased rotation rate of the atomizer as the particle size decreases.
· Dry emulsions are homogeneous powders that have low flowability due to their low density, particle size and shape. There are technical properties to improve for example by melting our wet granulations. Droplet size distribution of liquid O/W emulsions before spray drying and after reconstitution
· Dry emulsions with less than 50% lipid content improve the original emulsion. As the lipid content increases from 30 to 80%, the droplet size of the dry emulsion decreases. Up to 80% lipid encapsulation is possible with Pharmacot 603 as a solid carrier.
· Dry emulsions with lipid content up to 40% dry powder mass improved the original O/W emulsion when reconstituted. If the liquid viscosity is high, the atomized droplet size increases which makes the powder particle larger.

PHARMACOLOGY

Mechanism of action

Ezetimibe inhibits the absorption of cholesterol from the small intestine and decreases the amount of cholesterol normally available to liver cells. The lower levels of cholesterol in the liver cells leads them to absorb more cholesterol from circulation and thus lowering the levels of circulating cholesterol. It blocks the critical mediator of cholesterol absorption, the Niemann-Pick C1-like 1 (NPC1L1) protein on the gastrointestinal tract epithelial cells, as well as in hepatocytes it blocks aminopeptidase N and interrupts a caveolin 1–annexin A2 complex involved in trafficking cholesterol.[12]

STRUCTURE OF EZETIMIBE



Pharmacokinetics

Within 4–12 hours of the oral administration of a 10-mg dose to fasting adults, the attained mean ezetimibe peak plasma concentration (C_{max}) was 3.4–5.5 ng/ml. Following oral administration, ezetimibe is absorbed and extensively conjugated to a phenolic glucuronide (active metabolite). Mean C_{max} (45–71 ng/ml) of ezetimibe-glucuronide is attained within 1–2 hours. The concomitant administration of food (high-fat vs. nonfat meals) has no effect on the extent of absorption of ezetimibe. However, coadministration with a high-fat meal increases its C_{max} by 38%. The absolute bioavailability cannot be determined, since ezetimibe is insoluble in aqueous media suitable for injection. Ezetimibe and its active metabolites are highly bound to human plasma proteins (90%).[1] Ezetimibe is primarily metabolized in the liver and the small intestine via glucuronide conjugation with subsequent renal and biliary excretion.[24] Both the parent compound and its active metabolite are eliminated from plasma with a half-life around 22 hours, allowing for once-daily dosing. Ezetimibe lacks significant inhibitor or inducer effects on cytochrome P450 isoenzymes, which explains its limited number of drug interactions. No dose adjustment is needed in patients with chronic kidney disease or mild hepatic dysfunction (Child-Pugh score 5–6). Due to insufficient data, the manufacturer does not recommend ezetimibe for patients with moderate to severe hepatic impairment (Child-Pugh score 7–15). In patients with mild, moderate, or severe hepatic impairment, the mean AUC values for total

ezetimibe are increased about 1.7-fold, 3-to-4-fold, and 5-to-6-fold, respectively, compared to healthy subjects.[1]

MATERIALS AND METHODS

Materials:

Ezetimibe was kindly donated by Glenmark, Mumbai. Labrafac® lipophile WL 1349 (caprylic-capric acid triglycerides) was supplied from Fine organics, Mumbai. Gelatin, D-Mannitol and Glycine, Sodium alginate from brown algae was provided from Vishal chemicals Mumbai. Method Preparation of lyophilized dry emulsion tablets Ezetimibe lyophilized dry emulsion tablets were prepared as per Table No. 1
using either gelatin as the matrix former, a sugar alcohol (mannitol) and a collapse

protectant (glycine). The emulsion was first prepared where mannitol and glycine were added to a solution of gelatin or alginate containing the surfactant, thus forming the aqueous phase. On the other hand, the oil
phase was composed of 30 mg of Ezetimibe solubilized in Labrafac® lipophile WL 1349 (6%). The oil phase was then added to the aqueous phase containing matrix former, a sugar alcohol and a collapse protectant, under homogenization at 15,000 rpm for 5 min. Prepared emulsion were then transferred to a freezer at - 22°C and kept for 24 h. The frozen tablets materials were placed for 24 h in a Novalyphe-NL 500 Freeze Dryer with a condenser temperature of -45°C and a pressure of 7x10-2 for 3 days. Then the freeze dried composition should be compressed into tablets by adding croscarmellose sodium, microcrystalline cellulose, and magnesium stearate.

METHOD

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Preparation of Formulation

The ezetimibe raw material (EZ-RM) was used as reference in the dissolution, solubility, pharmacokinetic and biochemical studies. In DSC, SEM and PXRD, EZ-RM samples were used to characterize ezetimibe.

The physical mixture of EZ (PM 1:2.5) was prepared by mixing 100 mg of EZ and 250 mg of croscarmellose sodium in a ceramic bowl using a polymeric spatula, then adding 1000 mg of microcrystalline cellulose (MC) diluent and mixing.

A solid dispersion of EZ was prepared by dissolving 100 mg of EZ in 500 µL of ethanol by vortex (Fisherbrand™; Milan, Italy) at 2500 rpm for 2 min. Two hundred and fifty milligrams of croscarmellose was then added to the EZ solution and mixed in a ceramic bowl using a polymeric spatula. The formulation was dried at 40 °C for 24 h and sieved between 0.297 and 0.850 mm.
The microcrystalline cellulose (1000 mg) was added as a diluent after sieving and mixed with a polymeric spatula.

Micellar systems of EZ MS-I were prepared by dissolving 100 mg of EZ and different proportions of surfactant (Kolliphor® RH40) in 500 µL of ethanol dissolved by vortex (Fisherbrand™; Milan, Italy) at 2500 rpm for 2 min. The following amounts of surfactant were added to the MS-I formulations: 25 mg for MS-I (1:0.25), 50 mg for MS-I (1:0.5) and 75 mg for MS-I (1:0.75). Each solution of EZ and Kolliphor® RH40 in ethanol was added to a ceramic bowl with 250 mg of croscarmellose and 1000 mg of MC and mixed using a polymeric spatula. The micellar systems were then dried at 40 °C for 24 h. The formulations were sieved to isolate the 0.297–0.850 mm fraction.

Micellar systems of EZ MS-II were prepared with 100 mg of EZ and different amounts of Kolliphor® RH 40 for each MS-II formulation: 25 mg for MS-II (1:0.25), 50 mg for MS-II (1:0.5) and 75 mg for MS-II (1:0.75). These proportions of EZ:Kolliphor® RH 40 were dissolved in 500 µL of ethanol using a vortex (Fisherbrand™; Milan,

Italy) at 2500 rpm for 2 min. The solutions of EZ and Kolliphor® RH40 in ethanol were mixed in a ceramic bowl with 250 mg of croscarmellose. The formulations were dried at 40 °C for 24 h and then sieved between 0.297 and 0.850 mm. The microcrystalline cellulose diluent (1000 mg) was then added to each formulation and mixed with a polymeric spatula.

MEDICAL USES

A 2015 review found that adding ezetimibe to statin treatment of high blood cholesterol had no effect on overall mortality or cardiovascular mortality, although it significantly reduced the risk of myocardial infarction and stroke.[11] A 2015 trial found that adding ezetimibe to simvastatin had no effect on overall mortality but did lower the risk of heart attack or stroke in people with prior heart attack.[12][13] Several treatment guidelines recommend adding ezetimibe in select high risk persons in whom LDL goals cannot be achieved by maximally tolerated statin alone.[14][15][16][17][18]

Ezetimibe is indicated in the United States as an add-on to dietary measures to reduce levels of certain lipids in people with:[1]

- Primary hyperlipidemia, alone or with a statin
- Mixed hyperlipidemia, in combination with fenofibrate
- Homozygous familial hypercholesterolemia, in combination with specific statins
- Homozygous sitosterolemia

A 2018 review found that ezetimibe used as sole treatment slightly lowered plasma levels of lipoprotein(a), but the effect was not large enough to be important.[19]

Ezetimibe improves the non-alcoholic fatty liver disease activity score but the available evidence indicates it does not improve outcomes of hepatic steatosis.[20]

CONTRAINDICATION

The two contraindications to taking ezetimibe are a previous allergic reaction to it, including symptoms of rash, angioedema, and anaphylaxis, and severe liver disease, especially when taken with a statin.[21]

Ezetimibe may have significant medication interactions with ciclosporin and with fibrates other than fenofibrate.[1]

DISCUSSION

Binding agent is a important aspect in the formulation of LDET, because of it increases the hardness of tablets and also reduce the surface tension of the drug. In current formulation gelatine is used as a binder for freeze dried tablet and it acts also matrix former. Other excipients like sugar alcohol to produce the porous structure to the lyophilised matrix, which positively increase solubility of formulation. The porous structure of dosage form which leads to difficult to handling, so to influence of freeze dried tablets by evaluating the gelatine as a binder or other excipients. All prepared tablets were acceptable weight variation values as indicated by the relative standard deviation (RSD) of the tablet mass which ranged from 0.42 to 0.55%. Tablet friability was determined by Roche Friabilator and weight loss was calculated and presented in terms of % friability. From table we can say that percentage weight loss of tablets of each formulation was found in the range 0.42 ±0.3 to o.65 ±0.3. It had found that the disintegration time of all tablet batches is ranging from 138±1.6 to 158±0.9. The total Ezetimibe content was found to be uniform along all formulation and ranged from 96±1.3 to 98.34±1.1. Invitro dissolution study of the Ezetimibe freeze dried tablet show significant percentage drug release in the formulation F6, because of higher percentage of gelatine produce the hydrophilicity of drug molecule and also reduce surface tension of same.

CONCLUSION

Ezetimibe lyophilized dry emulsion tablets were successfully fabricated applying the lyophilization technique using Labrafac®, mannitol, glycine and gelatin. The pharmacology of ezetimibe was discussed in detail. The material and methods are also given for formulation of ezetimibe dry emulsion tablets.

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