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Formulation and Evaluation of Ezetimibe Lyophilized Dry Emulsion Tablets

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ABSTRACT

This article presents the development of lyophilized dry emulsion tablets prepared with the dry emulsion technique to enhance the in-vitro dissolution and in-vivo performance of the poorly bioavailable drug Ezetimibe. Ezetimibe (EZT) is a lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. Ezetimibe has a very low solubility and dissolution rate resulting in highly variable bioavailability, which is also in part due to extensive efflux by p-glycoprotein (P-Gp). Tablets were fabricated by freezedrying o/w emulsions of Ezetimibe. The Emulsions were prepared using a matrix former solution (alginate or gelatin, 2 or 4%) containing a sugar alcohol (mannitol), as the water phase and Labrafac® as the oil phase under proper homogenization. In the present study friability, disintegration time, and *in-vitro dissolution*of lyophilized dry emulsion tablets were done. Results showed the significant influence of the matrix former and emulsifier type on the disintegration time. *In-vitro dissolution* studies revealed the enhanced dissolution rate of Ezetimibe from the lyophilized tablets compared to the plain drug. DSC studies proved presence of the drug in the amorphous form in the fabricated tablets. The obtained results suggest a promising, easy-to-manufacture and effective dosage form for the treatment of hyperlipidemia.

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

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1. INTRODUCTION

Ezetimibe is an antihyperlipidemic agent capable of lowering blood cholesterol levels. It shows one of the most widely administered oral statins used in case of elevated plasma levels of cholesterol, triglycerides (TG), low-density lipoproteins (LDL) in addition to its ability to elevate the high-density lipoproteins (HDL). Ezetimibe (EZT) is a lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. Ezetimibe is classified according to the biopharmaceutical classification system (BCS) as a class II drug , insoluble in aqueous solutions of pH 4 and below, while being very slightly soluble in water and ezetimibe shows limited oral bioavailability of about 14% which is attributed to its poor aqueous solubility, crystalline nature, hepatic first-pass metabolism and mucosal gastrointestinal presystemic clearance. [1-3]

Hyperlipidemia is abnormally elevated levels of any or all lipids or lipoproteins in the blood. It is the most common form of dyslipidemia (which includes any abnormal lipid levels). [4]

In this research work, the importance of freeze dried tablet for enhancing the solubility of Ezetimibe was explored through the formulation of lyophilized dry emulsion tablet (LDET). The LDET formulation offers the advantages of both emulsions and freeze dried dosage forms. By preparing emulsion is efficient in improving dissolution rate and bioavailability of the poorly water-soluble drugs. When the freeze-dried dosage forms offer, good preservation and stability.[5]

Another specific advantage of freeze-dried formulations as a final dry product being a network of solid occupying the same volume as the original solution that was initially frozen, whereby, a light and porous product readily soluble is produced.[6]

The first component consists of water-soluble polymers, such as gelatin, dextrin, alginate and this component maintains the shape and provides mechanical strength to the tablets. The second component is the disintegration-enhancing agents, such as sucrose and mannitol, which act by cementing the porous framework provided by the water-

soluble polymer and accelerate the disintegration of tablets.[7-8]

In the present work, gelatin and alginate in combination with mannitol were used as the base for the formulation of lyophilized dry emulsion tablet. [9] Gelatin, a mixture of proteins, is an inexpensive polymer abundantly available in nature, can be readily processed into numerous forms and shapes. Being biocompatible, biodegradabile, non-toxic and non-immunogenic, both sodium alginate and gelatin have attracted high consideration and are extensively used in various biological applications. The selection of these excipients can potentially benefit the formulation in many ways. They are expected to form the highly porous matrix structure necessary for such dosage form. Also, the structural strength was provided by the gelatine whilst the crystallinity, hardness and elegance were provided by mannitol. Sublimation of water, the process media, induces the porous structure during the freeze drying stage. [10-11]

The purpose of the present work was the development of fast disintegrating tablets for Ezetimibe formulated using combined emulsion-freeze drying techniques exploring the impact of the selected excipients through evaluation of the LDET produced, aiming at reducing the disintegration time and enhancing the dissolution rate of the drug.

2. 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.

Table 1: Composition of Lyophilized Ezetimibe freeze dried tablet

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Ezetimibe (mg)	10	10	10	10	10	10
2	Gelatin (%)	3	3.2	3.4	3.6	3.8	4
3	Sodium alginate(%)	2	1.8	1.6	1.4	1.2	1
4	Mannitol (%)	0.886	0.886	0.886	0.886	0.886	0.886
5	Labrafac (%)	6	6	6	6	6	6
6	MCC (mg)	4	4	4	4	4	4
7	CCS (mg)	10	10	10	10	10	10
8	Magnesium Stearate (mg)	5	5	5	5	5	5

3. RESULTS AND DISCUSSION

Compatibility studies – FTIR:

The FTIR spectra of the Ezetimibe and physical mixture of polymer were recorded to check interaction between drug and polymers. The characteristic peaks of Ezetimibe appeared in the spectrum of physical mixture without any significant change in the position. It indicates that there was no interaction between Ezetimibe and physical mixture of polymers.

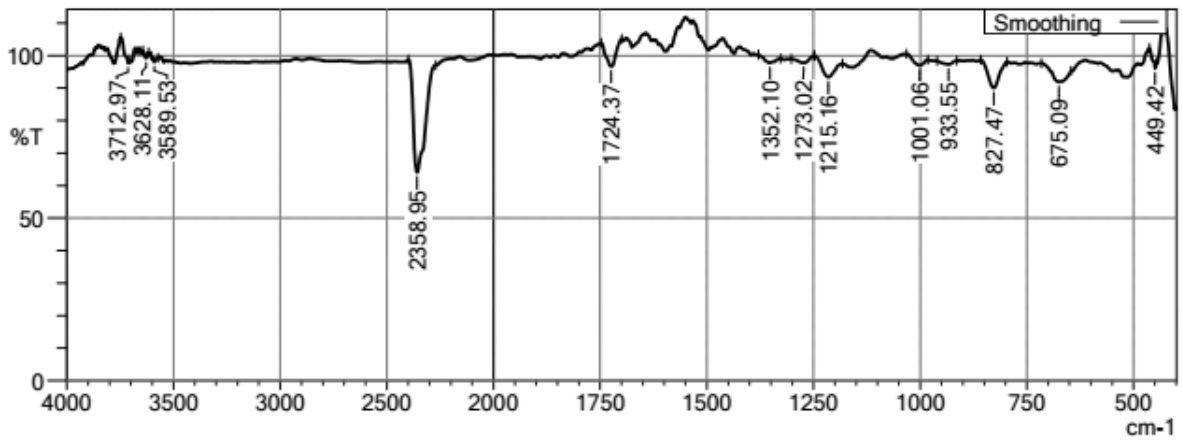

Figure 1: FTIR spectra of Ezetimibe pure drug

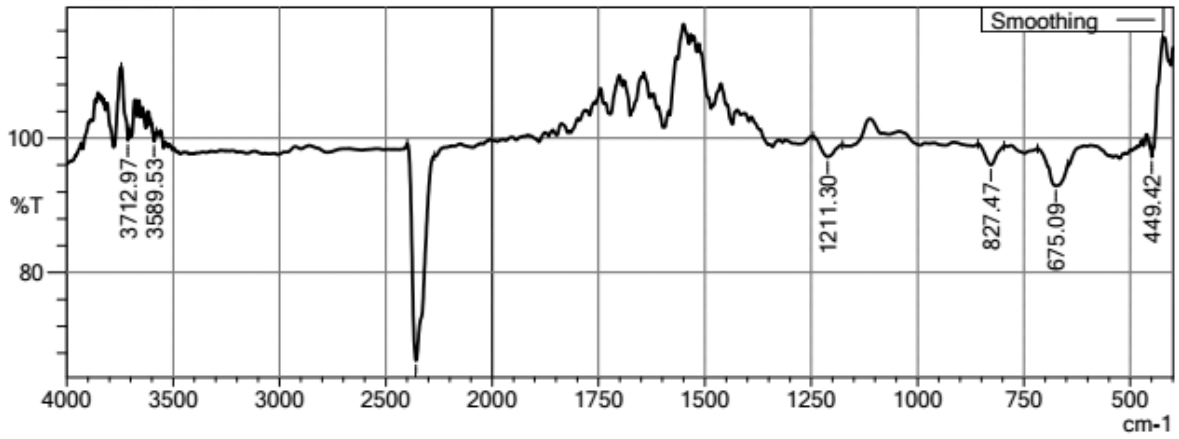

Figure 2: FTIR spectra of physical mixture

Differential Scanning Calorimetry (DSC):

DSC thermograms of pure Ezetimibe and drug excipient mixture are shown in Fig. and Fig. respectively. Results have shown that the sharp exothermic peak was observed of the drug individually at 164.2^{0}C, corresponding to its melting point (162^{0}C -164^{0}C). For the sample containing the drug and selected excipient mixture, sharp peak was observed of the drug at 164.9^{0}C with reduction in peak intensity. Thus as there was not a significant shift in exothermic peak of drug as that obtained from individual drug sample, it can be concluded that there was no interaction occurred between the excipient and drug Ezetimibe. Thus the Ezetimibe was found to be compatible with the selected excipient.

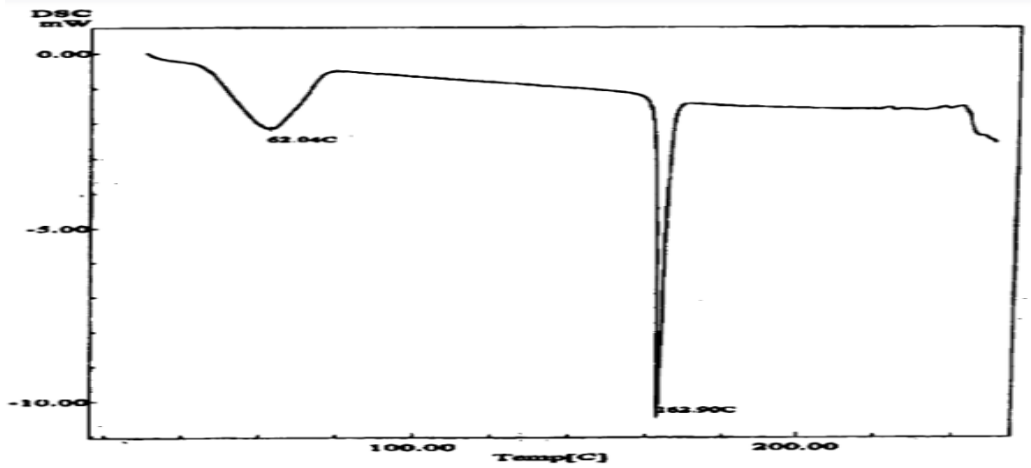

Figure 3: Differential Scanning Colorimetry of Ezetimibe Pure Drug.

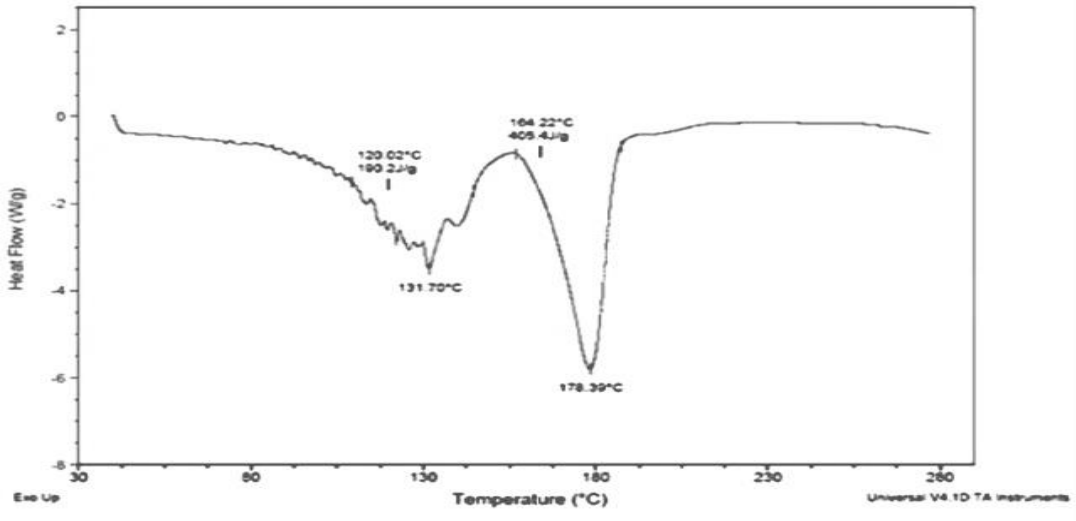

Figure 4: Differential Scanning Colorimetry of Physical Mixture

Table 2: Evaluation parameters of tablets

Formuation	Uniformity of weight(%RSD)	Friability (%)	Total ezetimibe content (%)	Disintegration time(s)
F1	0.55±0.17	0.65±0.30	98.06±1.4	158±0.94
F2	0.45±0.1	0.64±0.27	96.00±1.3	154±1.6
F3	0.44±0.1	0.63±0.25	97.70±1.3	150±1.88
F4	0.52±0.17	0.44±0.1	98.34±1.1	150±1.88
F5	0.42±0.3	0.69±0.06	98.04±1.2	140±1.24
F6	0.45±0.1	0.42±0.3	97.70±1.3	138±1.6

The data is presented as (n=3) mean value ±S.D.

Table 3: Dissolution profile of various batches of tablets in 4.5pH acetate buffer

Time (min.)	% drug release					
	F1	F2	F3	F4	F5	F6
00	00	00	00	00	00	00
15	5.4	7.65	20.7	7.9	15.3	7.8
30	17.55	15.3	32.45	18.5	34.7	26.35
45	25.25	29.3	41.58	47.3	43.8	59.4
60	42.85	60.9	53.75	74.0	67.7	96.4
90	56.9	62.4	74.95	77.3	85.85	97.5
120	64.2	72.75	86.8	89.9	94.95	98.0

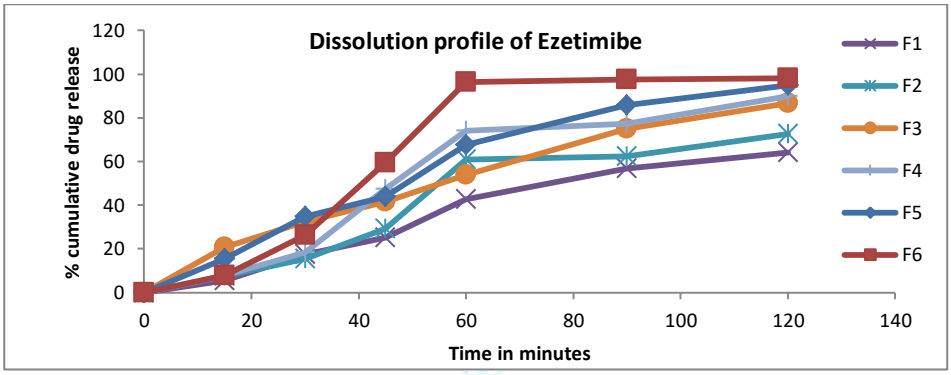

Figure 6: Dissolution profile of various batches of tablets in 4.5pH acetate buffer.

Kinetics of Drug Release

The value of coefficient of regression for different models of different mouth dissolving film formulations is given in Table No. 4

Table No. 4: Kinetic parameters of Ezetimibe dry emulsion tablets.

FC	Zero r^2	First r^2	Higuchi r^2	Peppas r^2
F1	0.9761	0.9895	0.9899	0.9820
F2	0.9298	0,8984	0.9524	0.9697
F3	0.9943	0.9898	0.9948	0.9979
F4	0.9220	0.9759	0.9587	0.9615
F5	0.9715	0.9899	0.9892	0,9869
F6	0.8698	0.9115	0.9203	0.9208

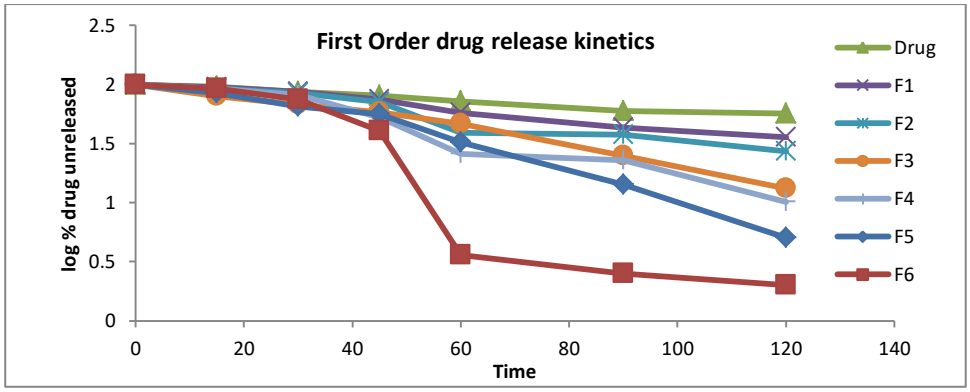

Figure 7: first order drug release kinetics

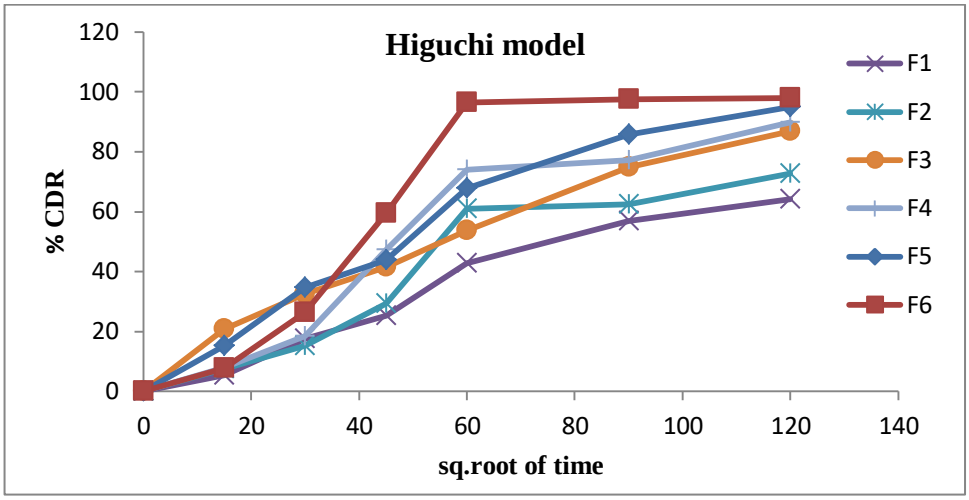

Figure 8: Higuchi model

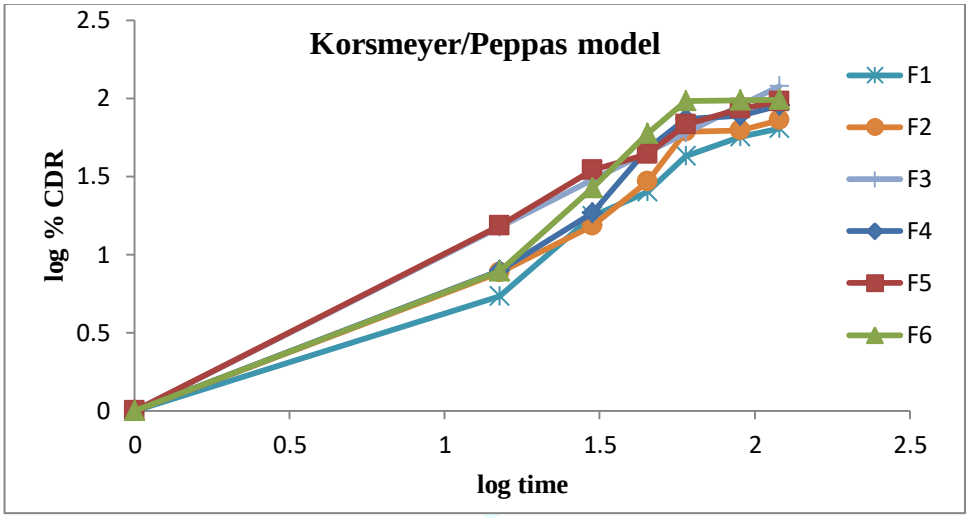

Figure 9: Korsmeyer/Peppas model

4. 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. *In-vitro* 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.

5. CONCLUSION

Ezetimibe lyophilized dry emulsion tablets were successfully fabricated applying the lyophilization technique using Labrafac®, mannitol, glycine and gelatin.The poorly water soluble drug Ezetimibe used in the preparation was characterized for preformulation and spectral analysis by UV spectroscopy and FTIR spectroscopy. The physical characteristics and spectra of Ezetimibe were found to be identical with standard given in analytical profile of drug substance. Polymer and drug were checked for compatibility by FTIR and DSC. It was evident that there was no probable unnecessary interaction found between drug and polymer. Preferable tablet properties were obtained regarding friability and uniformity of weight in addition to enhanced drug release properties and excellent disintegration characteristics which are showed in formulation F6.

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