International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Formulation, Evaluation, And Optimization of Orally Disintegrating Tablets Containing Lipid-Lowering Drug

Kartik Patel[1], Bhavana Patel[2], Jashoda Prajapati[3]

[1]Pg student, Shree Swaminarayan Sanskar Pharmacy college, Ahemdabad
[2,3]Associate Professor, Shree Swaminarayan Sanskar Pharmacy college, Ahemdabad,
[2]bhavanapatel1707@yahoo.com
[3]jesprajapati2000@gmail.com

ABSTRACT: Objective: To formulate and evaluate Orally Disintegrating Tablets containing Ezetimibe by direct compression method. Additionally, formulation optimization utilizing the Factorial design method. To increase patient compliance, the tablet is made with natural superdisintegrants including Emcosoy, Chia seed Mucilage, Guar Gum, and other appropriate excipients for the formulation**. Experimental work:** The Orally Disintegrating Tablet of Ezetimibe is formulated using direct compression method along with different excipients. Disintegrating agents are the main components in the formulation. To achieve the necessary disintegration time for an oral disintegrating tablet, they are utilized in a specific quantity. 32 factorial design is used to optimize the tablet formulation. Pre-post compression parameters were used to evaluate each formulation. **Result:** The Orally Disintegrating Tablet of Ezetimibe formulation containing 20 mg (10%) of Emcosoy (Soy Polysaccharides) exhibit excellent disintegration time of 29.20 seconds. The resulted formulation complies with the desired tablet parameters and all the tests needed. The hardness of tablet was found to be 3.30 kg/cm2 , and the dissolution result complied with a release of 99.99 % of the drug within 30 minutes. Conclusions: The studies indicate that Ezetimibe Orally Disintegrating Tablet was effective using Emcosoy as natural superdisintegrant in proving drug release with acceptable disintegration time.

Key-words: Direct compression, natural superdisintegrant, orally disintegrating tablet, 3 2 factorial design, Ezetimibe, disintegration time.

1. INTRODUCTION

Introduction of Drug Delivery System[1-13]

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (To accommodate various types of drug candidates) and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. The goal of a wide range of pharmaceutical research is to create new dosage forms that may be taken orally. The majority of these initiatives have been directed on either developing new drug delivery systems or improving patient compliance. Scientists working on product development have favored the orally disintegrating systems among the dosage forms created to make it easier to take medication. In similar

fashion the oral cavity is highly acceptable by patients, the mucosa is relatively permeable with rich blood supply and virtual lack of Langerhans cells makes oral mucosa tolerant to potential allergens. Orally disintegrating dosage forms The idea of orally disintegrating dosage forms has emerged from the desire to provide patients with more conventional means of taking their medication. It becomes challenging to swallow the typical solid dosage forms in disease conditions like motion sickness, sudden episodes of attacks of coughing, and repeated emesis. In these circumstances, oral disintegrating dosage forms can be a useful alternative drug delivery method. These dosage forms instantly dissolve when placed in the mouth, releasing the medication, which then dissolves or disperses in the saliva. As the saliva falls down, the drug may then be absorbed from the pharynx, esophagus, or other parts of the GIT. In these situations, bioavailability is considerably higher than what is seen with conventional tablet dosage forms. The novel technology of oral disintegrating dosage forms is called as fast dissolve, rapid dissolve, rapid melt and quick dispersible tablets. However, the function and concept of all are similar. Orally Disintegrating Tablets (ODTs) The technology employed in ODT production affects how well they perform. The rapid infiltration of water into the tablet matrix, which results in porous structure and prompt disintegration, is responsible for the tablets' oral disintegrating ability. So the fundamental methods for creating ODTs are to increase the tablet matrix's porosity, use the proper disintegrating agent, and formulate the drug with highly water-soluble excipients.

Advantages of ODTs • ODT can be given to patients who are unable to swallow tablets or caps, such as the elderly, people who have had strokes, patients who are bedridden, patients who have esophageal problems, and patients who refuse to swallow, such as children, geriatric patients, and patients who are suffering from mental illness. This increases patient compliance. • It includes studies that showed increased bioavailability and demonstrated quick drug absorption through pregastric absorption of medications from the mouth, pharynx, and oesophagus as saliva passes down. • For those who don't always have access to water, such as the disabled, bedridden patients, travelers, and busy people, ODT is most practical. • ODT's pleasant mouth feel helps to change the perception of medication. • By avoiding physical obstructions during oral administration of conventional formulations, the risk of choking or suffocation is reduced, improving safety.

Formulation Aspects of ODTs Faster dissolution should be the result of key ingredients used in the formulation of ODTs that enable quick drug release. This includes both the excipients and the pharmacologically active ingredients (drug) (additives). Selection of Drug candidate: When choosing a suitable drug candidate for the creation of orally disintegrating tablets, a number of criteria may be taken into account. The ultimate characteristics of a drug for dissolution in mouth and pre gastric absorption from fast dissolving tablets include: Bitter taste free 2. lower than 20 mg dose 3. a light to medium molecular weight 4. Suitable water and saliva solubility 5. partial unionization at pH of oral cavity 6. Ability to diffuse and partition in to the epithelium of upper GIT(log >1,or preferably>2) 7. Ability to permeate oral mucosal tissue.

Introduction of Disease[14-16]

Cholesterol is a waxy substance found in your blood. Your body needs cholesterol to build healthy cells, but high levels of cholesterol can increase your risk of heart disease. Hypercholesterolemia is a disorder known for an excess of low-density lipoprotein (LDL) in your blood. Many people can treat it by making changes to their diet and adding exercise to their lifestyles. Others need to take medicine to bring their

LDL level down to a normal level. These treatments lower your risk of heart attacks and strokes. With high cholesterol, you can develop fatty deposits in your blood vessels. Eventually, these deposits grow, making it difficult for enough blood to flow through your arteries. Sometimes, those deposits can break suddenly and form a clot that causes a heart attack or stroke. High cholesterol can be inherited, but it's often the result of unhealthy lifestyle choices, which make it preventable and treatable. A healthy diet, regular exercise and sometimes medication can help reduce high cholesterol. Alternative Names- Cholesterol - high; Lipid disorders; Hyperlipoproteinemia; Hyperlipidemia; Dyslipidemia; Hypercholesterolemia.

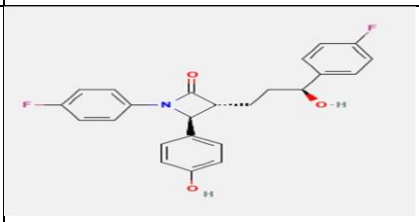
There are many types of cholesterol. The ones talked about most are: ⎪ Total cholesterol -- all the cholesterols combined ⎪ High density lipoprotein (HDL) cholesterol -- often called "good" cholesterol ⎪ Low density lipoprotein (LDL) cholesterol -- often called "bad" cholesterol Medicines such as certain birth control pills, diuretics (water pills), beta-blockers, and some medicines used to treat depression may also raise cholesterol levels. Several disorders that are passed down through families lead to abnormal cholesterol and triglyceride levels. They include: • Familial combined hyperlipidemia • Familial dysbetalipoproteinemia • Familial hypercholesterolemia • Familial hypertriglyceridemia

Types of cholesterol Cholesterol is used by all the cells in your body to keep them healthy. It is carried around your body to the cells that need it by proteins in your blood. Proteins are substances in your body that do most of the work in your cells and help keep your body's tissues and organs working as they should. When cholesterol and proteins combine, they're called lipoproteins. There are two main types of lipoproteins. One is good for your health; the other is bad. High-density lipoproteins or HDL is known as 'good' cholesterol. It gets rid of the 'bad' cholesterol from your blood by taking cholesterol you don't need back to the liver, where it is broken down and removed from your body. Non-high-density lipoproteins or non-HDL is known as 'bad' cholesterol. Too much non-HDL leads to a build up of fatty deposits inside the walls of the blood vessels (channels that carry blood throughout your body). This builds up and narrows blood vessels, increasing the risk of a heart attack or stroke. You may also have heard 'bad' cholesterol being called 'LDL' cholesterol. This used to be the main measure of harmful types of cholesterol, but we now know that other forms of non-HDL cholesterol can also affect your health. examples of precipitating factors cited by patients with epilepsy. In particular, the influence of various provoking factors varies with epilepsy syndrome.

High cholesterol symptoms There are usually no symptoms of high cholesterol. But if left untreated, it can lead to heart attack and stroke. It's often a hidden risk factor which means it can happen without us knowing until it's too late. That is why it's so important to get your cholesterol level checked. However, if you have familial hypercholesterolemia, you may have visible signs of high cholesterol. These include: Tendon xanthomata - swellings made from cholesterol on the knuckles of your hands, your knees or the Achilles tendon at the back of your ankle. Xanthelasmas -small, yellow lumps of cholesterol near the inner corner of your eye. Corneal arcus - this is a pale white ring around the coloured part of your eye, your iris.

Introduction of Drug[17-18]

Parameter	**Description**
Drug / Generic Name	Ezetimibe

Brand Name	Ezetrol, Lypqozet, Nexlizet, Roszet, Vytorin, Zetia
Chemical Formula	C_{24} H_{21} F_{23} NO
Chemical structure	
CAS no	163222-33-1
Chemical Name	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl) azetidin-2-one

PRE-FORMULATION STUDY:

1. Physical properties: The physical properties of the drug sample were characterized on the basis of colour, odour, taste and appearance. All these parameters were recorded and compared with standard shown in table 6.

2. Determination of melting point Capillary melting points, either in an oil bath or with a melting point apparatus, are the most frequent method of determining the melting point. A few quantity of the compound were placed in a 10-15 cm long thin-walled capillary tube with an inner diameter of 1 mm and one end closed. The sample and thermometer were then hung in a capillary, which allowed them to be heated slowly and evenly. The melting point of a sample is defined by the temperature ranges at which it melts. The data of melting point were shown in Table 7.

3. Solubility study: Solubility study of Ezetimibe was determined in different solvents. The operation was carried out using solvents (water, phosphate Buffer pH 6.8, methanol, and ethanol). An excess of the drug was added to 10 ml of media in a small conical flask and was continuously shaken for 24 hours at 37 °C in a conical flask shaker. After 24 hours, sample was filtered through Whatman filter paper no.1, diluted appropriately and the drug was estimated at 234 nm using UV- visible spectrophotometer plot Absorbance vs. concentration curve at room temperature.

2. ANALYTICAL WORK:

1. Determination of λmax of Ezetimibe and preparation of calibration curve38

50 mg of Ezetimibe pure drug was dissolved in 50 ml of Phosphate buffer pH 6.8(stock solution - 1000 µg/ml), from this 5 ml of solution was taken, and the volume was adjusted to 50 ml with Phosphate buffer 6.8(100 µg/ml) and suitable dilutions were made to get the concentrations of 0 to 20µg/ml. • The UV absorption maxima of Ezetimibe was found to be 233 nm, when solution of 100 µg/ml was scanned between 200-400nm by UV visible spectrophotometer. • This λmax was used for preparation of Calibration curve. After taking the absorbance, the calibration curve was prepared by taking the concentration on X-axis and absorbance on Y-axis.

2. Method for obtaining mucilage from chia seeds[27]

The seeds of Salvia hispanica were soaked in water for overnight (seed- solvent ratio was 1:20), boiled for half an hour and mixed on magnetic stirrer for 1 hour so that the mucilage releases completely into water.The resulting mixture was centrifuged at 5000rpm for 50 min, after which three different layers were formed. Only the gel layer was collected and dried in a hot air oven at 50°C. The product was grounded, passed through the sieve no. 80 and then stored at room temperature in desiccators for further use.

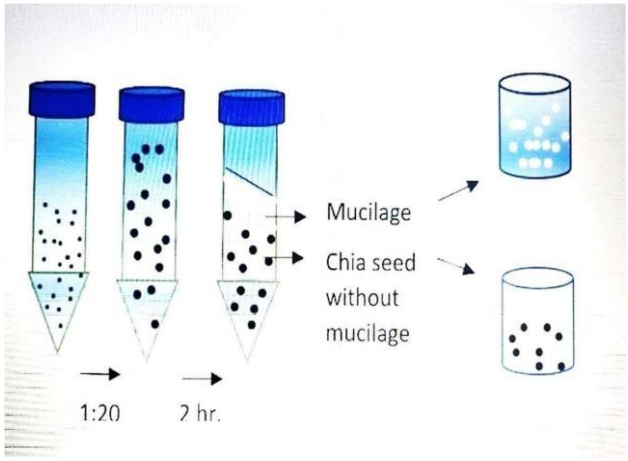


Figure 1: Method for obtaining mucilage from chia seeds

Figure 2: Extraction of Chia seeds Mucilage

3. Optimization of variable using 3^2 Factorial design

Based on the trial batches results, statistical design was applied for optimization of final formulation. It was observed that the amount of super disintegrant and the directly compressible excipient is critical and the physicochemical parameters was depends on the both factors. Hence, factorial design was applied by taking Emcosoy and Mannitol as an independent variable. 3^2 factorial design was applied as per below;

Independent variables		**Dependent variables**	
X1	X2	Y1	Y2
Mannitol(mg)	Emcosoy(mg)	Wetting time (Sec)	Disintegrating time (Sec)

Table 1: Selection of Independent Variables and Dependent Variables

Formulation Table For Factorial Batches

Sr. No.	**Ingredients(mg)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1.	Ezetimibe	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
2.	PEG - 40000	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00

3.	Avicel pH102	104.5	100.5	96.5.	94.5	90.5	86.5	84.5	80.5	76.5
4.	Mannitol	40.00	40.00	40.00	50.00	50.00	**50.00**	60.00	60.00	**60.00**
5.	Emcosoy	12.00	16.00	20.00	12.00	16.00	**20.00**	12.00	16.00	**20.00**
6.	Sodium lauryl sulphate(SLS)	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
7.	Aspartame	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
8.	Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
9.	Flavour	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
10.	Talc	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
11.	Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
12.	**Total**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Table 2 : Formulation Table for Factorial Batches

4. Validation of statistical model:

- Analysis of variance was used to analyse the replies (ANOVA). Different levels of components were chosen at different periods, and the statistical models' predicted responses were calculated. These levels were utilized to create tablets, and responses were recorded in the field. To determine the degree of similarity, the anticipated and observed responses were compared. To determine the accuracy of the design model, one random check point was performed throughout the whole experimental domain. Following that, the experimental data of the response characteristics were quantitatively compared to the expected values. The percentage bias was computed by comparing the predicted values to the actual experimental values.

Table 4: Composition of checkpoint formulation

Ingredients(mg)	**F10**
Ezetimibe	10.00
PEG - 4000	10..00
Avicel pH-102	81.5
Mannitol	55.00
Emcosoy	20.00
Sodium lauryl sulphate (SLS)	8.00
Aspartame	5.00
Magnesium stearate	3.00
Flavor	4.00
Talc	2.00
Aerosil	1.5
Total	**200.00**

Levels	Coded value	Independent variable	
		X1(mg)	X2(mg)
LOW	-1	40	12
INTERMEDIATE	0	50	16
HIGH	1	60	20

Table 3: Factorial Design table

5. Procedure of Direct Compression Method:

- Dispensing and Sifting: Dispensed quantity of Drug, Mannitol, chia seed powder / Guar gum / Emcosoy (Soy polysaccharide), Avicel pH 102, Aspartame and Other excipients were sifted through #40 mesh. Magnesium Stearate were sifted through #60 mesh.Blending and Lubrication: Material of Step-1(a) was transferred to a blender and the material was blended together for 15 minutes at 12 RPM. To the above blended material, sifted Magnesium Stearate was added and the blend was lubricated for 5 minutes at 12 RPM. The blend was then evaluated for pre-compaction parameters.Compression:The blend from step 2.(b) was compressed using Multipunch Tablet compression machine using a 8.0 mm round tip punch sets.

Pre Compression Parameters[39]:

a) Angle of Repose: The angle of repose (θ) was estimated using fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the tip of the heap of the material. The material was allowed to flow through the funnel freely onto the surface. The diameter of the cone was measured and angle of repose was calculated using the following equation. **θ=tan−1 (h/r).**

b) Bulk density: Bulk density was determined by pouring a weighed quantity of material into a graduated cylinder and measuring the volume of the material. Bulk density was calculated using the following equation. **Bulk density =m/v.**

c) Tapped Density:Tapped density is the ratio of the mass of the material to the tapped volume of material. Tablet blend was poured into graduated cylinder. Then, the cylinder was allowed to 100 taps under its own weight onto a hard surface. Tapped density was calculated using following equation. **Tapped density =m/v.**

d) Hausner's ratio: **Hausner's Ratio=Tapped density/bulk density**

e) Carr's compressibility index: **Carr's Index (%) = (Tapped density−Bulk density/Tapped density) x100.**

Post Compression Parameters:

a) Weight Variation: Weight variation was performed to ensure dosage uniformity. The test was carried out by weighing the 20 tablets individually using analytical balance, then calculating the average weight. Not more than two the individual weight deviates from the average weight by more than percentage and none deviates by more than twice that percentage.

b) Thickness: Thickness will affect the physical appearance of the tablet and will be governed by the compressibility of the blend and the target hardness. The thickness of the tablets was determined by using digital vernier caliper. Out of each batch, five tablets are chosen at random. It is expressed from mm and the average values were calculated.

c) Hardness:Hardness is also so called crushing strength. It is the load required to crush the tablet when placed on its edge. Tablets must be able to withstand the rigors of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the field at the hands of the end users (patients/consumers). For these reasons, the mechanical strength of tablets is of considerable importance and is routinely measured. It is measured in Newton or kg/cm^2 or kilo Newton. Hardness governs a balance between Disintegration Time and Friability.

d) Friability:Friability is defined as the %weight loss by tablets due to mechanical action during the test. It refers to the ability of the compressed tablet to avoid fracture and breaking during transport. Friability test from each batch were examined using Friabilator and the equipment was run for 4 min at 25 revolutions per min. Friability of a tablet is calculated by below mentioned formula: **%Friability = (Initial weight - Final weight/Initial weight)*100**

e) Disintegration Time:Disintegration Time is the most important parameter for an Orally disintegrating Tablet. The in-vitro disintegration studies were carried out using a digital tablet disintegration test apparatus. One tablet was placed in each of the 6 tubes of the basket assembly and then disk was added to each tube. This assembly was then suspended in a 1-liter beaker containing water with its temperature being maintained at 37 ± 2°C. The basket was then moved up and down through a distance of 5 to 6 cm, at the frequency of 28 to 32 cycles per minute. The time required for complete disintegration of the tablet was recorded.

f) Wetting Time:A piece of tissue paper (10.75×12 mm) folded twice was placed in a culture dish (d=6.5 c) containing 6 ml of simulated saliva (phosphate buffer pH 6.8). A tablet was carefully placed on the surface of tissue paper and the time required for simulated saliva to reach the upper surface of the tablet was noted as the wetting time.

Figure 3: Wetting Time of Tablet

Water Absorption Ratio

A piece of tissue paper (10.75×12 mm) folded twice was placed in a culture dish (d =6.5 c) containing 6 ml of simulated saliva (phosphate buffer pH 6.8). A tablet was placed on the surface of tissue paper. Initially, the tablet weight was noted before placing in a Petridis. After complete wetting, the wetted tablet was then weighed. The water absorption ratio, r, was determined using equation. R =100×Wa–Wb/Wb Where, Wa= weight of the tablet after water absorption Wb= weight of the tablet before absorption.

Drug content:Tablets were selected randomly, and the average weight was calculated. Tablets were crushed in a motor and accurately weighed the amount of tablet powder was taken from the crushed blend. Then the samples were transferred to 100 ml volumetric flask and diluted with Phosphate buffer 6.8 pH. The contents were shaken periodically and kept for 2 h for solvation of drug completely. The mixture was filtered in Whatmann filter paper and absorbance was measured at 234 nm using Phosphate buffer 6.8 pH as blank.

In-vitro drug release study:In-vitro dissolution of Ezetimibe Orally Disintegrating Tablets was determined for period of 30 min using apparatus II as per USP employing a rotating paddle at 50 rpm using 900 ml of Phosphate buffer 6.8 ph , at 37 ± 0.5 ºC. The sampling of ODT's was done after 5,10,15,20 and 30 min interval in which 5 ml of the sample was withdrawn and replaced with fresh medium to maintain the volume constant. Thenthe absorbance was measured in UV spectrophotometer at λ max **234nm**.

Comparison of optimized formulation with marketed product (Ezedoc 10 Tablet)

➢ Optimized formulation F10 of Ezetimibe was compared with marketed product Ezedoc 50 tablet.

Difference (f1) and similarity (f2) factor in dissolution:

It is a time-dependent measurement of the release of Drug from a dosage form. Results are shown in table.

$$f1 = \left\{ \frac{\{\sum_{t=1}^{n} |Rt - Tt|\}}{\sum_{t=1}^{n} Rt} \right\} \times 100$$

1. Difference (f1): The difference factor (f1), as defined by the FDA, is a measurement of the relative inaccuracy between two curves that estimates the % difference between two curves at each time point.

Where, Rt = % dissolved at time t of reference product (per change) Tt = % dissolved at time t of test product (post change) n = number of time points

2. Similarity (f2):The FDA-defined similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error that measures the similarity in percentage (percent) dissolution between the two curves.

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} x100 \right\}$$

Where,f2 = similarity factor,Rt = mean % drug dissolved (reference product) Tt = mean % drug dissolved (test product)

Difference factor (F1)	Similarity factor(F2)	Inference
0	100	Dissolution Profiles are similar
<15	>50	Similarity or equivalence of two profile

Table 5 : Limits for Difference factor (f1) and Similarity factor (f2)

g) Accelerated stability study (40°C ± 2°C / 75±5% RH): The objective of a stability study is dependent on the stage of development of the product rather than being fixed. At the start of the development process, it is preferable to be aware of the drug substance's stability and potential interactions with excipients. Regarding dosage form and formulation, the stability programme varies. Accelerated stability studies are particularly appealing because they can quickly document good outcomes under challenging circumstances.

RESULT & DISCUSSION

Identification of Drug

1. Physical appearance:

Colour	White
Odour	Odour less
Taste	Bitter
Appearance	Powder

Table 6 : Physical Appearance

2. Determination of Melting point by capillary method:

Melting point of Ezetimibe was found to be 160°-163°C which was in the ranges given in literature, hence the drug could be stated as pure.

Table 7: Melting point

Parameter	Reference(°C)	Test (°C)
Melting point	160°-163°C	161°-162°C

3. Solubility study: Results indicated that Ezetimibe was found to be slightly soluble in distilled water, soluble in phosphate buffer (pH 6.8) and while soluble in methanol.

Solvent	Solubility
Distilled water	Slightly soluble
Phosphate buffer pH 6.8	soluble
Methanol	soluble

Table 8: Solubility of Ezetimibe in different solvents at 37°C

4. Analytical work:

a) λmax of Ezetimibe Phosphate buffer pH 6.8 :

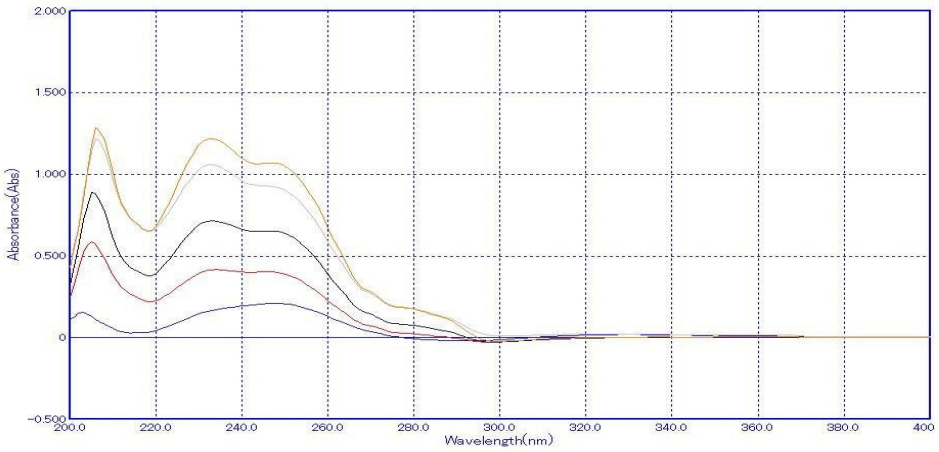


Figure 3: λmax of Ezetimibe in Phosphate buffer pH 6.8

b)Calibration curve of Ezetimibe:

Table 9: Calibration curve of Ezetimibe

Sr.No.	Concentration(µg/ml)	Absorbance
1.	0	0
2.	5	0.108
3.	10	0.219
4.	15	0.334
5.	20	0.44

5. FTIR ((Fourier transform infrared):

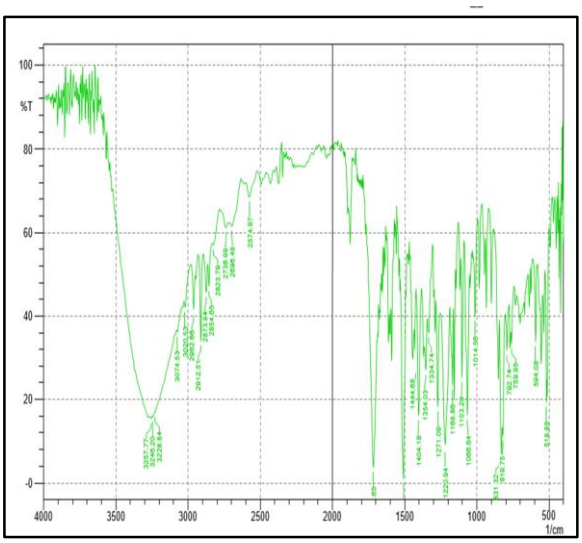


Figure 4: Spectrum of Ezetimibe (API)

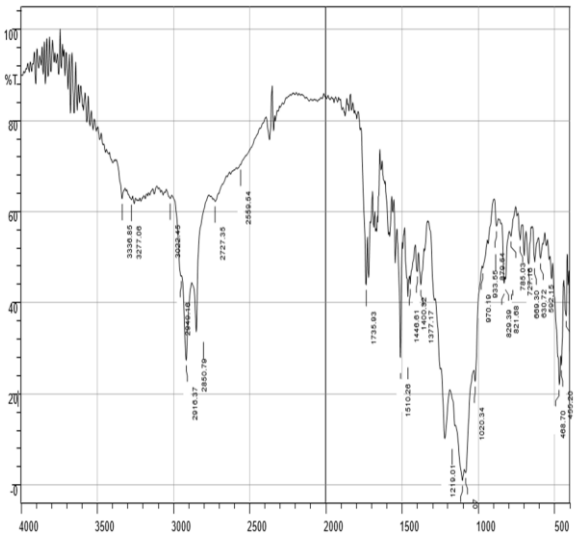


Figure 5: Spectrum of Ezetimibe final formulation

6. Results of Factorial Batches

Factorial batches F1-F9 evaluated for various parameters and the results were tabulated below.

Pre-compression parameters of Ezetimibe Factorial Batches

Table 10**: Pre-compression parameters of Ezetimibe Factorial Batches**

Formulation code	Bulk density (gm/ml) (n=3)	Tapped density (gm/ml) (n=3)	Carr's Index (%) (n=3)	Hausner's Ratio (n=3)	Angle of Repose (n=3)
F1	0.404±0.02	0.480±0.01	15.83	1.18	32.35±0.17
F2	0.408±0.01	0.485±0.01	15.87	1.18	33.34±0.22
F3	0.418±0.01	0.515±0.02	18.83	1.23	36.32±0.21
F4	0.412±0.01	0.490±0.02	15.85	1.18	30.32±0.21
F5	0.430±0.01	0.520±0.02	17.30	1.20	34.35±0.02
F6	**0.420±0.02**	**0.510±0.01**	**17.15**	**1.40**	**30.28±0.25**
F7	0.425±0.01	0.530±0.02	19.81	1.24	29.32±0.17
F8	0.415±0.02	0.490±0.01	15.30	1.18	27.38±0.24
F9	**0.431±0.01**	**0.519±0.01**	**16.96**	**1.20**	**29.36±0.30**

1. Post-compression parameters of Ezetimibe Factorial Batches:

Table 11: Post-compression parameters of Ezetimibe Factori al Batches

Formulation code	Weight Variation (mg) (n=20)	Thickness (mm) (n=3)	Hardness (kg/cm2) (n=3)	Friability (%)
F1	199.2±0.60	3.40±0.01	4.91±0.02	0.48±0.02
F2	200.6±0.70	3.50±0.03	3.95±0.01	0.46±0.03
F3	201.2±0.52	3.40±0.03	3.90±0.03	0.49±0.06
F4	203.5±0.90	3.45±0.05	3.40±0.05	0.45±0.08
F5	204.7±0.83	3.51±0.05	3.50±0.04	0.56±0.05
F6	**201.2±0.60**	**3.57±0.06**	**3.85±0.02**	**0.57±0.02**
F7	199.5±0.54	3.60±0.04	4.03±0.06	0.48±0.10
F8	200.1±1.12	3.50±0.01	3.99±0.04	0.57±0.07
F9	**200.2±1.35**	**3.58±0.02**	**3.12±0.02**	**0.55±0.04**

Table 12: Post-compression parameters of Ezetimibe Factorial Batches

Formulation code	Wetting time (sec) (n=6)	Disintegrating time (sec)(n=3)	Water absorption ratio(%) (n=3)	Drug content (%) (n=3)
F1	72 ± 2.5	76 ± 4.9	69.3 ± 2.5	95.2± 1.3
F2	56 ± 1.7	64 ± 4.8	71.2 ± 3.1	96.4± 1.2
F3	55 ± 2.2	63 ± 6.5	75.3 ± 2.7	98.2± 1.4
F4	42 ± 3.1	47 ± 5.4	81.5 ± 3.2	97.5± 1.5
F5	27 ± 3.1	34 ± 3.6	76.7± 2.5	99.4± 1.4
F6	**26 ± 1.9**	**32 ± 2.3**	**80.3 ± 2.2**	**99.98± 0.5**
F7	42 ± 4.6	44± 4.9	78.4 ± 1.4	98.2 ± 0.3
F8	28 ± 2.8	35 ± 6.1	75.8 ± 2.6	98.3 ± 0.6
F9	**25 ± 3.2**	**32± 4.3**	**81.8 ± 3.2**	**99.9 ± 0.2**

From the above results of factorial batches F1-F9, it was found that the all Nine batches were passed the weight variation limit. The results are well within acceptable range. Thickness was found uniform in all batches. Hardness was good enough to passthe friability test. Friability of all Nine formulations was below 1 hence, found satisfactory.

Further, the disintegration time was observed 32 sec in F6 batch and 32 sec in F9 batch. The Assay results

are also found well within acceptable range. The dissolution study was performed for all 9 batches which were given below along with the graph.

2. Statistical Analysis of Response Y1: Wetting Time

Design expert was used to generate Quadratic equation for Y1 Response

Table 13: ANOVA for quadratic model for Response Y1

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2226.44	5	445.29	751.42	< 0.0001	Significant
A-Mannitol	1290.67	1	1290.67	2178.00	< 0.0001	
B-Emcosoy	416.67	1	416.67	703.12	0.0001	
AB	0.0000	1	0.0000	0.0000	1.0000	
A^2	430.22	1	430.22	726.00	0.0001	
B^2	88.89	1	88.89	150.00	0.0012	
Residual	1.78	3	0.5926			
Cor Total	2228.22	8				

Factor coding is Coded. Sum of square is Type III – Partial .The Model F-value of 751.42 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noice.P-values less than 0.0500 indicate model terms are significant. In this case A, B, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy) model reduction may improve your model.

❖ Quadratic Equation for Response Y1:Wetting Time

$= 27.22 – 15.33A – 8.33B – 0.0000AB + 14.67A^2 + 6.67B^2$

3. Statistical Analysis of Response Y2: Disintegrating time Time

Design expert was used to generate Quadratic equation for Y2 Response

Table 14: ANOVA for quadratic model for Response Y2

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2177.58	5	522.32	203.62	0.0005	
A-Mannitol	1410.67	1	1872.67	659.53	0.0001	

B-Emcosoy	266.67	1	322.67	124.68	0.0015	Significant
AB	0.2500	1	6.25	0.1169	0.7550	
A^2	450.00	1	392.00	210.39	0.0007	
B^2	50.00	1	18.00	23.38	0.	
Residual	6.42	3	2.14			
Cor Total	2184.00	8				

Factor coding is Coded. Sum of square is Type III – Partial The Model F-value of 203.62 implies the model is significant. There is only a 0.005% chance that an F-value this large could occur due to noice. P-values less than 0.0500 indicate model terms are significant. In this case A, B, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy) model reduction may improve your model.

Quadratic Equation for Response Y2: Disintegrating Time

$= 34.00 – 15.33A – 6.67B – 0.2500AB + 15.00A^2 + 5.00B^2$

4. Check Point Batch Analysis

The checkpoint batch was created according to the formula to validate the statistical model. Table 6.17 shows a comparison between expected andexperimental values for check point batch. The results demonstrated a close match between the experimental data from the response surface plot with the calculations from the statistical equation produced via regression. As a result, we may say that the statistical model is mathematically correct. Figure 6.15 shows a Disintegration Time (D.T) and Wetting time (W.T) overlay plot.

Batch Code	Predicted Values (Wetting Time)	Experimental Values (Wetting Time)	Residual	Predicted Values (DT)	Experimental Values (DT)	Residual
F10	21.94	22.40	0.46	28.57	29.20	0.63

Table 15: Comparison of predicted values and experimental values for check point batch

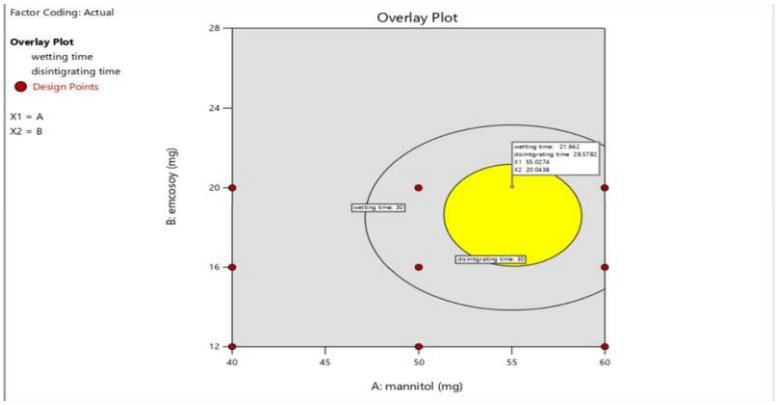


Figure 6: Overlay Plot

Evaluation Parameter	Predicted data	Observed data
Wetting time (Sec)	21.94	22.40
Disintegrating time (Sec)	28.57	29.20

Table 16 : Comparison with Marketed Product

10. Comparison with Marketed Product:

1. Evaluation Parameters of Optimized Batch(F10) and Marketed Product

Parameter	Optimized Batch(F10)	Ezedoc 10
Average Weight(mg)	200.00	130.00
Diameter(mm)	8.00	6.00
Hardness(kg/cm^2)	3.38 ± 0.03	4.00 ± 0.03
Disintegration Time (Sec)	29.20 ± 2.4	135± 3.5

Table 17: Evaluation Parameters of F10 and Ezedoc 10

Time (Min)	Optimized Formulation(F10)	Marketed Product (Ezedoc 10)
5	69.2 ± 0.01	52.4 ± 0.012
10	75.3 ± 0.03	64.6 ± 0.02
15	84.5 ± 0.02	73.7 ± 0.01
20	92.4 ± 0.01	83.4 ± 0.03
30	99.9± 0.03	90.3 ± 0.01
40	-	96.2 ± 0.02
50	-	99.9 ± 0.03
60	-	-

Table 18: Drug Release of Optimized batch F10 and Marketed Product

Parameter	Reference Value	Test Value
Difference Factor(f1)	1-15	12
Similarity Factor(f2)	50-100	51

Table 19: Difference factor (f1) and Similarity factor(f2) values

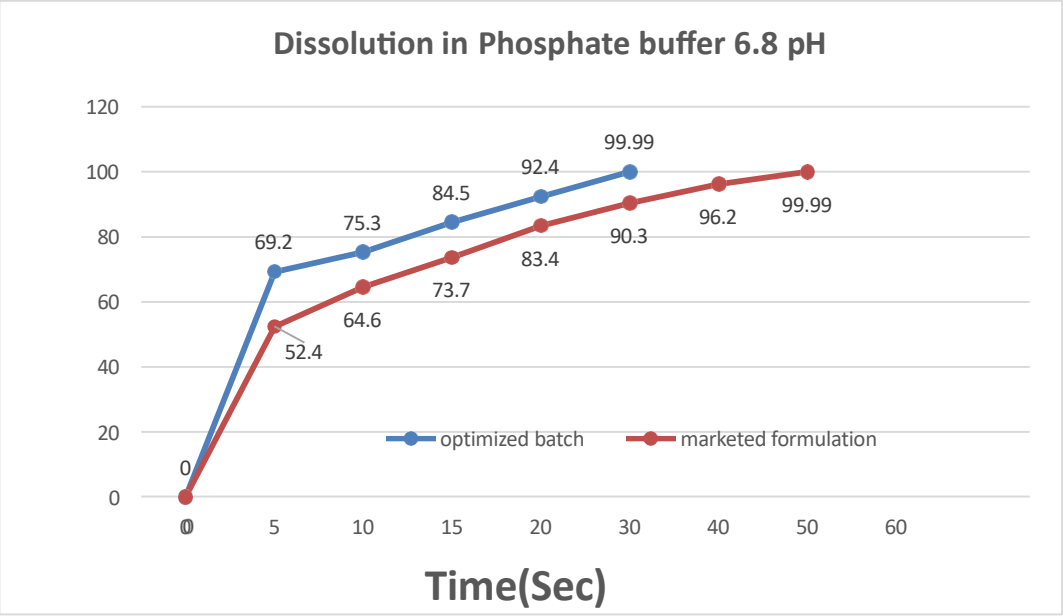
11. Accelerated Stability Study:

Stability tests were conducted for one month at accelerated circumstances of 40°C ± 2°C/75 ± 5% RH in order to assess the stability of this Optimized Batch F10. The formulation's Wetting Time, Disintegration Time, and In-Vitro Drug Release Pattern were all confirmed to be stable, showing no further changes.

Table 20: Accelerated stability study of Optimized batch F10

Parameter	Initial	15 Days	1 Month
Appearance	Complies	Complies	Complies
Wetting time (sec)	22± 3.7	23 ± 2.4	23± 2.5
Disintegration time (Sec)	29 ± 4.8	30 ± 2.2	30± 1.4
In-vitro drug release (%)	99.99 ± 0.03	99.98 ± 0.02	99.99 ± 0.01

Figure 7: %Cumulative drug release comparison of Optimized Batch(F10) and LACOSAM 50



12. Conclusion:

Ezetimibe orally disintegrating tablet was successfully formulated using Emcosoy as natural super disintegrant. The disintegration time was found to be 29.20 seconds which complies with the requirement.

The optimized formulation batch F10 was found to be the best.

References

1. Vollmer, Paolo Galfetti. Rapid Film: Oral Thin Films (OTF) as an innovative Drug Delivery System and Dosage Form, technology overviews http://www.labtec- pharma.com;Acessed on **sept 2007**.
2. Ghosh TK., Pfister WR., Quick dissolving oral dosage forms: Scientific and regulatory considerations from a clinical pharmacology and biopharmaceuticals perspective; In: Drug delivery to the oral cavity: Molecules to market. New York, CRC Press **(2005**), **337-356.**
3. **3.**Fix JA., Advances in quick-dissolving tablets technology employing Wowtab. In IIRConference on Drug Delivery Systems, October, 1998.
4. Devrajan PV., Gore S., Expressp pharm plus. **2003, 7(1):16**.
5. Dobetti L., Fast melting tablets: Developments and technologies. Pharm Technol Drug Deliv Suppl **2001, 44-50.**
6. Allen LV., Wang B., Particulate Support Matrix for making a rapidly dissolving tablet. 1997, US patent 5595761. Bansal AK., Improved excipients by solid-state manipulation. The Industrial Pharmacist**. 2003, 31; 9-12**
7. Priyanka Nagar et al, Orally disintegrating tablets : formulation, preparation techniques and evaluation, Journal of applied pharmaceutical science **2011, 01 (04); 35-45.**
8. Brown D., Orally disintegrating tablets: Taste over speed. Drug Deliv Technol **2001, 3: 58-61**.
9. Meyers GL., Battist GE., Fuisz RC., Process and apparatus for making rapidly dissolving dosage units and product Thereform**. 1995**, PCT Patent, WC **95/34293** A1.Seager H., Drug delivery p
10. roducts and the Zydis fast-dissolving dosage form.J Pharm Pharmacol **1998, 50: 375-382.**V.V.
11. Potnis et al, A Review on Epilepsy and its Management, Journal of Drug Delivery & Therapeutics**. 2020; 10(3):262-264**
12. Reddy LH., Fast dissolving drug delivery system: A review of the literature Indian J.Pharm Sci. 2002, 64: 331-336.
13. Robertson MI., Regulatory Issues with Excipients, Int. J. Pharm. **1999,187: 273-276.**
14. Gupta A., Mishra AK., Gupta V., Bansal P., Singh R., Singh AK., International Journal of Pharmaceutical & Biological Archives 2010, 1(1): 1-10.
15. https://my.clevelandclinic.org/health/diseases/23921-hypercholesterolemia
16. https://www.mayoclinic.org/diseases-conditions/high-blood-cholesterol/symptoms-causes/syc 20350800.
17. https:// information/conditions-treated-a-to-z/high-cholesterol
18. https://go.drugbank.com/
19. https://pubchem.ncbi.nlm.nih.gov/#query=Ezetimibe
20. Manish Khadka et al, "Formulation and evaluation of oral disintegrating tablets of furosemide" World J Curr Med Pharm Res. **2021**;3(6),149-156.
21. Shahinaze A. Fouad et al, "Development of orally disintegrating tablets containing solid dispersion of a poorly soluble drug for enhanced dissolution: In-vitro optimization/in-vivo evaluation" Plos One **2021**,15(12): e0244646.
22. Gamal M. Mahrous et al, "Formulation and evaluation of orally disintegrating clopidogrel tablets" BJPS **2016**, vol. 52, 309-409.P.A.
23. Ravi Sheshala et al, "Formulation and Optimization of Orally Disintegrating Tablets of Sumatriptan

Succinate" Chem Pharm Bull 2011, 59(8); 920-928.
24. B. P. Patel et al, "Formulation and Evaluation of Mouth Dissolving Tablets of Cinnarizine" IJPS **2010**, 522-525.
25. Darshan Pradhan et al, "An overview on FDA approved natural super disintegrants efficacy in a fast dissolving drug delivery system" JOAPR **2021,** 01-07.
26. Femi Joseph et al, "Natural Superdisintegrants for the Formulation of Orally Disintegrating Tablets" IJRR, **2021**, Vol. 8, 123-128.
27. Mohammadali Poursharifi Ghourichay et al 2021, "Formulation and quality control of disintegrating tablets(ODT):Recent Advance and Perspectives."Hindawi BioMed Research International Volume **2021**,Article ID 6618934,12 Pages.
28. Reecha Madaan et al, "Formulation and Characterization of Fast Dissolving Tablets Using Salvia Hispanica (Chia Seed) Mucilage as Superdisintegrant" Acta Pharm. Sci. **2020**, Vol 58.
29. T. Neelima Rani, Y. Indira Muzib, " Design and Evaluation of Ezetimibe Rapid melts by Direct Compression and Sublimation Methods" Asian Journal of Pharmaceutics **2016,** vol.10(4), S518.
30. Puneeth J. et al, "Formulation and Evaluation of Nano Co-Crystal Based Oral Disintegrating Tablet of Ezetimibe" Indian Journal of Pharmaceutical Education and Research, Vol 57, Issue 3, Jul-Sep, **2023**.
31. Reddy PS, Murthy KVR. Formulation and Evaluation of Oral Fast Dissolving Films of Poorly Soluble Drug Ezetimibe Using Transcutol Hp. Indian J of Pharmaceutical Education and Research. **2018**;52(3):398-407.
32. Vemula et al.; Formulation and Evaluation of Ezetimibe Liquid solid Tablets: An Approach to Enhance the Dissolution Rate BJPR, 7(6): 440-450, **2015;** Article no.BJPR.2015.124.
33. BH. CH. NARASIMHARAJU. et al. Spectrophotometric method for the determination of ezetimibe in pharmaceutical formulations Biomedical & Pharmacology Journal Vol. 1(2), 413-416 **(2008).**
34. Patil Dhananjay et al/ Formulation and Evaluation of Ezetimibe Lyophilized Dry Emulsion Tablets. Journal of Drug Delivery & Therapeutics**. 2019**; 9(3-s):630-635.
35. B. Venkateswara Reddy, et al. Formulation and Evaluation of Ezetimibe Immediate Release Tablets. J. Pharm. Bio. Res., **2015**, 3(1): 205-210.
36. Raymond C Rowe, Pual J Sheskey and Marian E Quin, Handbook of Pharmaceutical Excipients, 6th Edn; Pharmaceutical Press, USA.
37. Bahl, B. S., and Arun Bahl. A textbook of organic chemistry, Purification of organic compound, S. Chand Publishing**, 2017**.
38. Dr. Siraj N., Prof. Tanvir Y, Practical book of physical pharmaceutics-I,published by Nirali prakashan, **2018**.
39. Mohammad Imran, Md. Rageeb, Tushar A. Deshmuk, Practical instrumental analysis, published by P.V. prakashan, **2017**.
40. Bhowmik, Debjit, B. Chiranjib, Pankaj Krishnakanth, and R. Margret Chandira. "Fast dissolving tablet: an overview." Journal of chemical and pharmaceutical research 1, **2009,** no. 1: 163-177.