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Formulation and Evaluation of Poorly Aqueous Soluble Drug by Solid Dispersion Method

Omprakash G. Bhusnure*[1], Mohite Yogita[2], Sachin S. Gholve[1], Giram P. Sidram[3],Thonte S.S.[3]

Channabasweshwar Pharmacy College, Department of Quality Assurance, Maharashtra- 413512, India
Channabasweshwar Pharmacy College, Department of Pharmacutics, Maharashtra- 413512, India
Channabasweshwar Pharmacy College, Department of Pharmacology, Maharashtra- 413512, India

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ABSTRACT

Development of solid dispersions of poorly water soluble drugs is one of the most widely used approaches to enhance the solubility as well as dissolution rate. In the current investigation, Ezetimibe is selected as model drug to improve the solubility and dissolution rate by solid dispersion method. Solid dispersions were prepared using solvent evaporation method by incorporating sol plus as carriers in different ratios and evaluated for solubility studies, FT-IR, X-Ray, DSC studies and *in vitro* dissolution studies. Based on the solubility and drug release studies, formulations different disintegrates are used and the best natural disintegrating agent i.e. Guar gum was selected to prepare the tablets and *in vitro* dissolution study is done, tablets containing Guar gum showed almost complete drug release within the 12 min. The percent drug release in 12 min (Q12) and initial dissolution rate for formulation F3 was 94.22±1.08%, 9.26%/min. These were very much higher compared to conventional tablets containing pure drug (23.87±1.13%, 2.38%/min). The relative dissolution rate was found to be 2.14 and dissolution efficiency was found to be 67.52 and it is increased by 4.0 fold with F3 formulation compared to conventional tablets. Thus, it is concluded that the formulation of guar gum as disintegrating agent is a suitable approach to improve the solubility and dissolution rate of Ezetimibe than pure form of drug.

KEYWORDS: Solid Dispersion, Super Disintegrating Agent, Guar gum, Ezetimibe.

INTRODUCTIONS:

Many newly developed drugs are of synthetic origin and posses poor aqueous solubility which leads to poor bioavailability after oral administration. This is because the oral absorption is rate limited and enhancement in solubility & dissolution rate is required for improvement in oral bioavailability[1] . It remains a challenge for the formulation scientists to improve the oral bioavailability of such drugs when given as solid dosage forms. Formulation development of new chemical entities has the major problem of low aqueous solubility. Also, poorly aqueous soluble APIs tend to get eliminated from gastrointestinal tract getting fully dissolved and absorbed into systemic circulation[2].

Most of the new drug candidates entering drug development pipeline fail because of non-optimal biopharmaceutical properties i.e. rate and extent of absorption, rate of distribution, dose to achieve minimum effective concentration and to avoid side effects can exert a sig nificant influence on the drug's absorption, distribution, metabolism,excretion, and toxicity. Over the years, tools of drug discovery have caused a perceptible shift in bio-pharmaceutical properties. So these properties have significant role in the bioavailability of the drugs[3].

Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased oral bioavailability and subsequently to clinically relevant dose reduction[4].

The dissolution properties of a drug and its release from a dosage form have a basic impact on its bioavailability. Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products, since nearly half of the active substances being identified through the new paradigm in high throughput screening are either insoluble or poorly soluble in water. The dissolution rate of a drug is a function of its intrinsic solubility and its particle size[5].

Ezetimibe, selected in the present work is chemically 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone belonging to the lipid lowering agents category. It inhibits the intestinal absorption of cholesterol[6]. Ezetimibe is a white crystalline powder having poor aqueous solubility characteristics which leads to its limited dissolution resulting in poor bioavailability

***Corresponding author.**
Dr. Bhusnure O.G., M. Pharm, Ph.D.
Professor and Department Head Of Quality Assurance,
Channabasweshwar Pharmacy College(Degree),
Kava Road, Latur-413512, Dist. Latur. (MS)

(35–65%). The dissolution is a rate limiting step for the absorption of poorly water-soluble drugs and hence drugs showing limited dissolution give poor therapeutic out come as a result of poor oral bioavailability[7].

Solubility:

Solubility is a in quantitative term which defines the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute and solute both are in equilibrium. Solubility is an important determinant in drug liberation and absorption which plays a key role in its bioavailability.

Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure[8]. The drug solubility in saturated solution is a static property whereas the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate[9].

Noyes-Whitney's equation illustrates how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral bioavailability:

$$dC/dt * h = AD.(Cs - C) \quad \ldots\ldots (1)$$

Where, dC/dt is the rate of dissolution,
A is the surface area available for dissolution,
D is the diffusion coefficient of the compound,
Cs is the solubility of the compound in the dissolution medium,
C is the concentration of the drug in the medium at time t,
h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound[10].

Importance of Solubility:

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraint and flexibility in the design of dosage forms. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products. However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first pass metabolism, pre-systemic metabolism and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability.

Solubility is one of the important parameters to achieve the desired concentration of drug in the systemic circulation for achieving required pharmacological response. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered in formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having a poor aqueous solubility.

More than 40 % NCEs (new chemical entities) developed in Pharmaceutical Industry are practically insoluble in water[11]. For orally administered drugs solubility is most important one rate limiting parameter to achieve their desired concentration in the systemic circulation in pharmacological response. Poor solubility results into poor bioavailability of drug after oral administration[12]. The improvement of drug solubility thereby its oral bio-availability remains one of the most challenging aspects of the drug development process, especially for oral drug delivery system.

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility, high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. As for BCS class II drugs, the rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drugs[13].

MATERIAL & METHODS:

Calibration curve observations for EZT in - A) Methanol and D/W at 232 nm B) Methanol and acetate buffer pH 4.5 at 232 nm.

Table . A

Sr. no.	Concentration (µg/ml)	Absorbance
1	10	0.185
2	15	0.347
3	20	0.559
4	25	0.725
5	30	0.908
6	35	1.097

Table . B

Sr.no.	Concentration (µg/ml)	Absorbance
1	0	0
2	4	0.113
3	8	0.234
4	12	0.451
5	16	0.659
6	20	0.88
7	24	1.098

2.1. Materials used in the experimental study:

Table No. 1: List of chemicals along with grades and their sources

Sr. No.	Name	Company
1.	Ezetimibe	Indoco Remidies, Mumbai.
2.	Soluplus®	BASF, Mumbai.
3.	Methanol	Loba Chemie, Mumbai.
4.	Guar Gum	Meher Chemie, Mumbai.
5.	Sodium Starch Glycolate	Meher Chemie, Mumbai.
6.	Cross Carmilose Sodium	Ozone Int. , Mumbai.
7.	Avicel – pH 101	Ozone Int. , Mumbai.
8.	Mg. Sterate	Meher Chemie, Mumbai.
9.	Xanthin	Meher Chemie, Mumbai.
10.	Lactose	Ozone Int. , Mumbai.
11.	Talc	Meher Chemie, Mumbai.
12.	Sodium acetate	Loba Chemie, Mumbai.
13.	Sodium lauryl sulphate	Loba Chemie, Mumbai.
14.	Acetic acid	Loba Chemie, Mumbai.
15.	Distilled water	……..

Table No. 2 : List of Instrumentsalong with grades and their company

Sr. No.	Name of instrument	Make & Model
1	Digital balance	A & D Company Ltd. Mumbai
2	Ultrasonicator	Pci Mumbai
3	UV spectrophotometer	UV-VIS Shimadzu, 1800, Japan
4	Spray dryer	Model-LU-222 Aavanced Labultima,India.
5	pH meter	Labtronics Model LT-11
6	Dissolution test apparatus	Disso 2000, Lab India, India.
7	Fourier Transformer-IR Spectroscopy	Shimadzu IR Affinity 1 Model, Japan.
8	Differential scanning colorimeter	Mettler Toledo Pvt. Ltd. Switzerland
9	X-ray diffraction spectrophotometer	X-ray diffractometer (PW 1729, PHILLIPS, the Netherland)
10	Scanning Electron Microscopy	SEM-JEOL Instruments,JSM-6360,Japan.
11	Rotary shaker	Lab HOSP Mumbai.
12	KBR Press	-
13	Vernier Caliper	-
14	Hardness Tester	-
15	Friability Test apparatus	Labindia FT1020

Ezetimibe was obtained as a gift sample from IPS Pharma Indoco Remidies, Mumbai, India. Soluplus® was purchased from BASF, Mumbai. Methanol, Sodium acetate, Sodium lauryl sulphate, Acetic acid etc purchased from Loba Chemie, Mumbai. Guar Gum, Sodium Starch Glycolate, Mg. Sterate, Xanthin, Talc purchased from Meher Chemie, Mumbai. Cross Carmilose Sodium, Avicel pH 101, Lactose was purchased from Ozone Int, Mumbai. All other remaining materials used were of analytical grade.

Table no. 3 : Peak intensities of pure Ezetimibe at various diffraction angle ($2Q^0$) in their XRD patterns

EZT	
$2Q^0$	Intensity
17.19	1077
18.28	1878
19.66	1941
23.23	2373

Table No. 4 : Formulations by using Diff. conc. Of Disintegrates

Contents	Weight in mg F1	F2	F3	F4
Ezetimibe	10	10	10	10
Guar Gum	8	8	8	16
Mg. Sterate	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5
Micro Crystaline Cellulose	9	18	36	9
Sucrose	5	5	5	5
Lactose	135	126	108	127
Total weight	170	170	170	170
Disintegration Time (sec.)	**178**	**102**	**100**	**126**
% Drug Release	87.89	95.78	98.95	97.89

Contents	Weight in mg F5	F6	F7	F8	F9
Ezetimibe	10	10	10	10	10
Guar Gum	16	16	4	4	4
Mg. Sterate	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5
Micro Crystaline Cellulose	18	36	9	18	36
Sucrose	5	5	5	5	5
Lactose	118	100	139	130	112
Total weight	170	170	170	170	170
Disintegration Time (sec.)	**177**	**145**	**184**	**390**	**347**
% Drug Release	86.95	97.89	87.42	72.63	83.16

Table No. 5: Practical yield of spray dried batches

Sr. No.	Codes	Drug/Drug + Polymer	Production yield
1	EZT	Pure Ezetimibe	-
2	EZT-1	EZT with Soluplus® by spray drying method (0.5:1)	28.13%
3	EZT-2	EZT with Soluplus® by spray drying method (1:1)	26.13%
4	EZT-3	EZT with Soluplus® by spray drying method (1:0.5)	26.68%

Table No.6 : Percentage Drug content of spray dried batches.

Sr. No.	Batch Code	% Drug Content
1	EZT	-
2	EZT-1	92.33 ± 0.81
3	EZT-2	93.51 ± 0.79
4	EZT-3	97.17 ± 0.74

Table No.7 : Saturation solubility of pure Ezetimibe and solid dispersions

Sr. No.	Batch Code	Saturation Solubility (µg / ml)
1	EZT	12.00 ± 2.51
2	EZT-1	142.85± 0.39a
3	EZT-2	136.87 ± 0.29a
4	EZT-3	135.71 ± 0.75 a

Table No. 8 : Dissolution data of EZT solid dispersions acetate buffer (pH 4.5)

Batch code	DP_2±S.D.	DP_{15} ±S.D.	DP_{25} ±S.D.	DP30[a] ±S.D.
EZT	9.91±2.28	33.24±1.3	49.13±2.26	52.48±3.19
EZT-1	71.45±2.77	99.85±2.68	-	-
EZT-2	65.72±3.2	89.81±2.09	99.15±3.54	-
EZT-3	47.84±3.47	75.32±2.41	93.14±2.43	98.8±3.53

2.2. Preformulation studies

2.2.1. Procedure for Fourier Transform Infrared (FTIR) spectral analysis:

The compatibility for pure drug Ezetimibe, polymers and their physical mixtures used in this experimental procedure was evaluated by recording of spectra using FT-IR Spectrophotometer (Perkin Elmer, spectrum-100, Japan). The spectra were recorded by taking 5% of sample in potassium bromide (KBr) and after this mixture was grounded into a fine powder it was compressed into KBr pellets at 4000 Psi compaction pressure for a period of 2 min. The resolution was 1 cm^{-1} and the range of scanning was 400–4000 cm^{-1} [14,15].

2.2.2. Procedure for diffraction scanning calorimetric (DSC) studies:

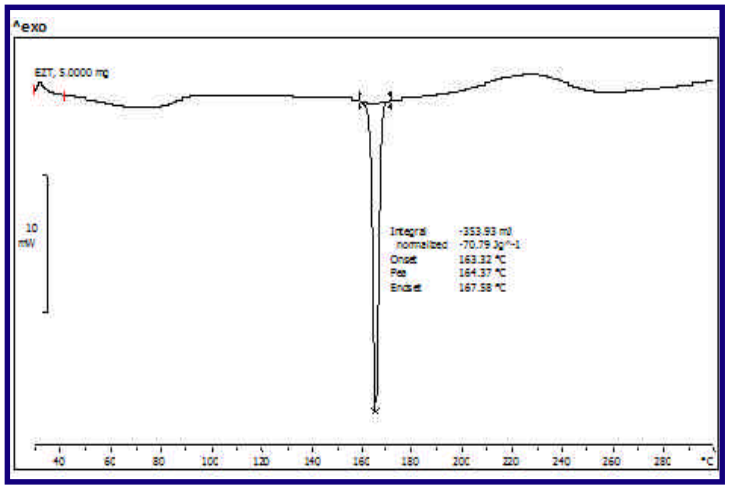

Figure No. 1 : DSC thermograms of Ezetimibe

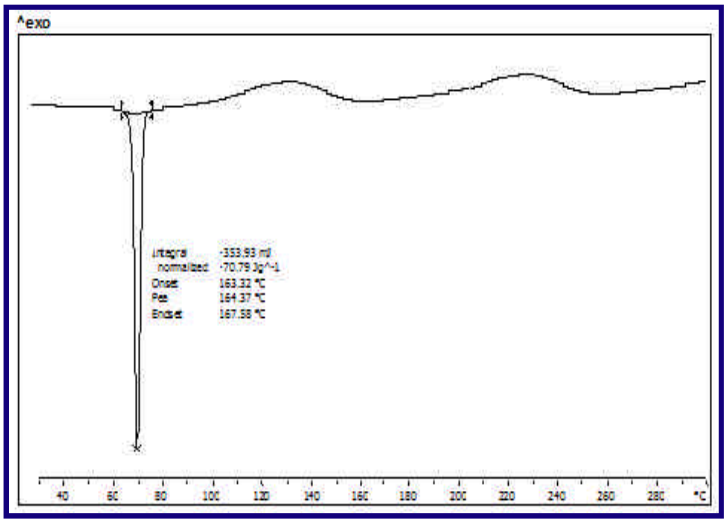

Figure No. 2 : DSC thermograms of Guar gum

The DSC thermograms of pure drug Ezetimibe were recorded using Diffraction scanning calorimeter (DSC 60, Shimadzu, Japan). Their measurement was taken 164.37 ^{0}C at a heating rate of 10^{0}C/min (Hadi et al., 2014a,b).

2.2.3. X-ray powder diffractometry (XRPD):

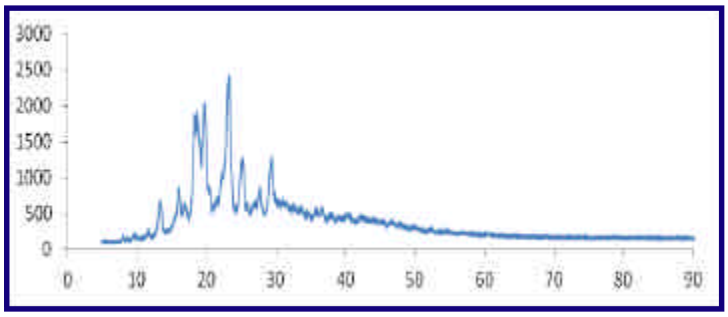

Figure No. 3 : XRPD Patterns of Ezetimibe

Table no. 9 : Peak intensities of pure Ezetimibe at various diffraction angle (2Q^0) in their XRD patterns

EZT	
2Q^0	**Intensity**
17.19	1077
18.28	1878
19.66	1941
23.23	2373

The XRD pattern of drug Fig. no. crystalline nature of Ezetimibe is depicted in XRPD analysis (Fig no.). The XRD scan of plain Ezetimibe showed intense peaks clearly indicate crystalline nature of the pure drug.

2.3. Formulation methods:

2.3.1. Procedure for preparation of solid dispersion method by

2.4. Evaluation Methods

2.4.1. Pre compression parameter:

2.4.1.1 Angle of repose:

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation[16].

Tan= H / R .....Equation I
Where, H = Pile height and
R = Radius of Pile
Therefore; = tan^{-1} H / R

2.4.1.2. Bulk density:

The sample equivalent to 25g was accurately weighed and filled in a 100 ml graduated cylinder and the powder was leveled and the

unsettled volume, Vo was noted. The bulk density was calculated by the formula

Bulk density (ρo) = M/Vo .....Equation II
M = mass of powder taken
Where, Vo = Apparent unstirred volume

2.4.1.3. Tapped density:

The tapped density was determined by mechanically tapping the measuring cylinder and the volume was noted

Where, ρt = tapped density

Tapped density (ρt) = M / Vt .....Equation III
M = weight of granules
Vt = tapped volume of granules in cm^3

2.4.1.4. Compressibility index:

The bulk volume and tapped volume was measured and compressibility index was calculated using the formula (Aulton, 2003).

Compressibility index =100 (Vo-Vf)/Vo .....Equation IV
Where,Vo = Bulk volume
Vf = Tapped volume

2.4.1.5. Hausner's ratio:

Tapped volume and bulk volume were measured and the hausner's ratio was calculated using the formula

Hausner's ratio = Vo/Vf.....Equation V

Where,
Vo = Bulk volume
Vf = Tapped volume

2.4.2. Post compression parameter:

2.4.2.1. Friability test:

Six tablets were weighted and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. After revolutions the tablets were dedusted and weighted again. The percentage friability was measured using the formula,

%F = {1- W / W0} X 100

Where, %F = Friability in percentage.
W0 = Initial weight of tablets.
W = Weight of tablet after revolution.

2.4.2.2. Thickness:

Three tablets selected randomly from each batch and thickness was measured by using vernier caliper.

2.4.2.3. Hardness:

Hardness was measured by using Pfizer hardness tester; hardness values are given in Kg.[2, 3]

2.4.2.4. Disintegration study:

Disintegration test was carried out as in acetate buffer (pH 4.5) uncoated tablets in USP.

2.4.2.5. In-Vitro Dissolution Test:

Evaluation of prepared tablet formulation:

The evaluation parameters and their result of prepared tablet and marketed tablet (EZEDOC 10 mg) are given in the table . The result of the evaluation revealed that all quality control parameters such as crushing strength, weight variation, friability and disintegration test of compressed tablets with excipients remained within the desired limits as per USP standards and also nearly similar to the marketed tablet.

The dissolution curve of prepared tablet and marketed tablet in acetate buffer (pH 4.5) with 0.45% SLS are shown in the figure. The table 9 shows % drug dissolved in 5 min. (DP_5), % drug dissolved in 45 min. (DP_{45}) for prepared tablet and marketed tablet. Thus the the reference as well as the test formulation are similar and hence were found to be comparable.

The result indicates the dissolution profile of prepared tablet was almost comparable with that of marketed tablet. The prepared Ezetimibe tablet release 95.36% drug and marketed tablet release 98.65% drug in 45 min. The result obtained from all evaluation parameters of the prepared tablet of Ezetimibe is similar to the parameters of a marketed tablet. This rapid release from the tablets may be due to rapid disintegration due to disdintegrants and solubilization of Ezetimibe from solid dispersion due to hydrophilic carriers.

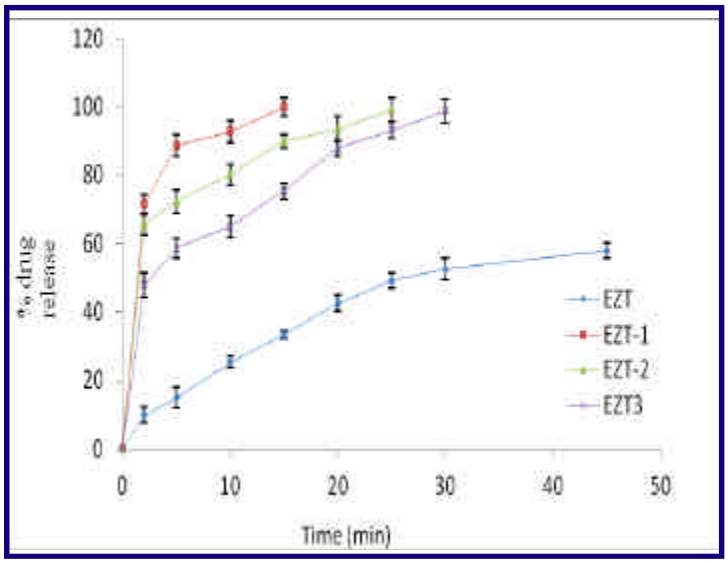

Figure No. 4: Drug release profile of EZT and solid dispersions acetate buffer (pH 4.5)

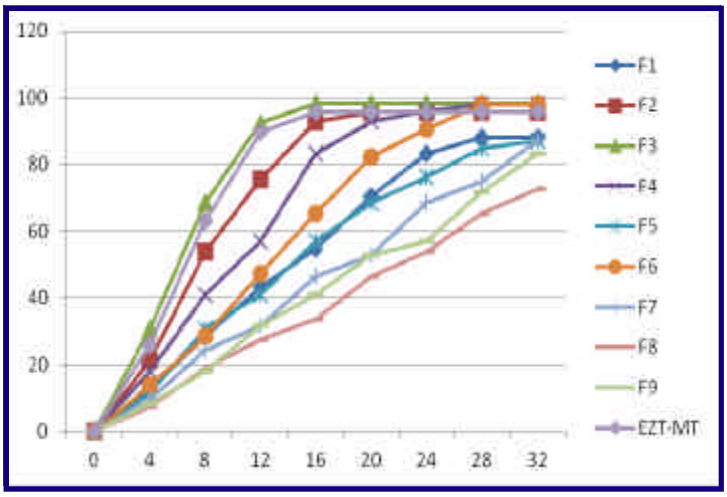

Figure No. 5 : Dissolution of Ezt with diff. Conc. of Guar Gum

RESULT AND DISCUSSION:

3.1. Evaluation of Pre compression Parameter:

The angle of repose of the powder mixture for all formulations (F1–F5) ranged from 25.9 to 27.7 indicating excellent flow properties (Couto et al., 2013). Bulk and tapped density of the powder mixture for all formulations varied from 0.358 to 0.455 gm/cm3 and from 0.432 to 0.581 gm/cm3, respectively. Hausner's ratios and compressibility indices ranged from 1.2 to 1.27 and 18.54% to 21.68%, respectively. The results of flow properties are acceptable for granules[17]. The values of compressibility indices further confirmed the good compressibility of the prepared granules[18,-20].

3.2. Evaluation of Post compression Parameter:

The hardness of the tablets prepared was determined by Monsanto Hardness tester and found to be within the range of 2.5 kg/cm^2 to 3.2 kg/cm^2.

The friability was found in all designed formulations in the range 0.36% to 0.44% to be well within the approved range (<1%). The weight variation was found in all designed formulations in the range 0.094 to 102.1 mg and % deviation was in a range of 0.03 to 1.22. All the tablets passed weight variation test as the average percentage weight variation was within 7.5 % i.e. in the pharmacopoeia limits. The mean thickness was (n=3) almost uniform in all the formulations and values ranged from 3.0 mm. to 3.35 mm. The standard deviation values indicated that all the formulations were within the range.

The *in-vitro* disintegration time was measured by the time taken to undergo complete disintegration. Rapid disintegration within 3 minutes was observed in all the formulations. The disintegration time of all the formulations is checked & is found within the range of 30 sec-57 sec.

3.3. FT-IR Study:

Table no. 10 : Interpretation of IR spectra of Ezetimibe

Functional group	Wave number (cm^{-1})
Broad, intermolecular hydrogen bonded, O-H stretch	3222.400 cm^{-1}
Aromatic C-H stretch	2966.166 cm^{-1}
Weak combination and overtone band of ring	1881.263 cm^{-1}
C-O of lactam	1714.505 cm^{-1}
Ring skeletal vibration band	1614 cm^{-1}
C-N stretch	1445.420 cm^{-1}
In plane O-H bend	1354.672 cm^{-1}
C–F stretch	1217.403 cm^{-1}
C-O stretch of secondary alcohol	1065.6 cm^{-1}
Ring vibration due to para-disubstituted benzene	813 cm^{-1}

Evaluation of prepared tablets

Pre-formulation study:

Table no. 11A : Pre-compressional Study

Formulation Code	Angle of Repose	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner Ratio	Carr's Index (%)
F1	25.49	0.214	0.251	1.17	14.74
F2	29.05	0.364	0.364	1.18	15.38
F3	26.97	0.276	0.322	1.16	14.28
F4	29.25	0.341	0.388	1.13	12.11
F5	32.27	0.324	0.376	1.16	13.82
F6	26.57	0.320	0.397	1.24	19.39
F7	26.24	0.313	0.356	1.13	12.07
F8	28.31	0.332	0.312	1.12	13.05
F9	27.12	0.286	0.352	1.15	14.21

Table no. 11B : Post compression Study

Formulation Code	Hardness (kg/cm^2)±SD	Friability (%) ±SD	Weight variation (mg) ± SD	Drug content (%) ± SD
F1	4.50 ± 0.44	0.36 ± 0.001	165 ± 1.48	97.54 ± 1.37
F2	4.30 ± 0.31	0.39 ± 0.003	169 ± 0.54	98.25 ± 0.80
F3	4.08 ± 0.40	0.33 ± 0.002	172 ± 0.41	95.27 ± 2.47
F4	4.66 ± 0.55	0.12 ± 0.003	158 ± 1.64	99.12 ± 0.98
F5	4.25 ± 0.57	0.34 ± 0.005	180 ± 1.14	97.32 ± 1.25
F6	4.08 ± 0.30	0.48 ± 0.007	162± 0.83	100.05 ± 1.87
F7	4.01 ± 0.61	0.54 ± 0.006	175 ± 0.67	101.22 ± 1.23
F8	4.16 ± 0.46	0.37 ± 0.0	178 ± 1.21	100.54 ± 0.74
F9	4.25 ± 0.57	0.44 ± 0.004	160 ± 1.34	100.24 ± 0.54

Table No. 12 : Evaluation parameters of tablet

Sr. No.	Evaluation Parameters	EZT-SDT	EZT- MT	USP standards
1	Thickness (mm)	2.98±0.02	3.30±0.01	-
2	Hardness (kg/cm^2)	5.2±0.26	5.4±0.1	-
3	Diameter (mm)	8	6.61	-
4	Tensile Strength	0.138 ± 0.006	0.157 ± 0.002	-
5	Weight variation (%)	130 ± 2.11	130 ± 1	10%
6	Friability (%)	0.22±0.02	0.20 ± 0.015	Less than 1.2%
7	Disintegration Time(Min.)	10±2.82	8±1.41	< 15 min
8	Uniformity of content	98.81 ± 0.37	99.54 ± 0.27	90% -110%

Table No. 13: Dissolution data of EZT with diff. conc. of guar gum

Time (min)	% Drug release F1	F2	F3	F4	F5
0	0	0	0	0	0
4	12.63	21.05	30.53	17.89	11.58
8	28.42	53.68	68.42	41.05	30.53
12	43.16	75.53	92.45	56.84	41.05
16	54.73	92.78	98.36	83.16	56.84
20	70.53	95.78	98.36	92.89	68.41
24	83.16	95.78	98.36	95.89	76.32
28	87.89	95.78	98.36	97.89	84.95
32	87.89	95.78	98.36	97.89	86.95

Time (min)	% Drug release F6	F7	F8	F9	EZT-MT
0	0	0	0	0	0
4	13.68	9.47	7.37	8.42	25.87
8	28.42	24.21	18.95	17.89	63.05
12	47.37	31.58	27.37	31.58	89.46
16	65.26	46.32	33.68	41.05	95.65
20	82.1	52.63	46.32	52.63	95.65
24	90.53	68.41	53.68	56.84	95.65
28	97.89	74.74	65.26	71.58	95.65
32	97.89	87.42	72.63	83.16	95.65

The infrared spectrum of pure EZT was recorded and spectral analysis was done using FTIR spectroscopy (FT-IR Affinity, Schimadzu).

3.4. DSC:

DSC thermograms of Ezetimiibe shown in Fig.No.10. The DSC thermograms of pure Ezetimibe showed sharp endotherm at 164.37°C . This clearly indicates crystalline nature of the pure drug.
Figure No. 11 : DSC thermograms of Ezetimibe

3.5. XPRD:

The XRD pattern of drug Fig. No. crystalline nature of Ezetimibe is depicted in XRPD analysis . The XRD scan of plain Ezetimibe showed intense peaks clearly indicate crystalline nature of the pure drug. Table No. 6: Peak intensities of pure Ezetimibe at various diffraction angle ($2Q^0$) in their XRD patterns. Figure No.10: XRPD Pattern of Ezetimibe

3.6. In-Vitro Dissolution:

The dissolution medium of EZT and prepared solid dispersions was optimized and the 500 ml acetate buffer (pH 4.5) with 0.45% sodium Lauryl Sulphate (SLS) was selected as a dissolution medium. The dissolution studies were performed in triplicate in dissolution apparatus (Lab India, Model Disso 2000, India) using the paddle method, according to USP Type II. Samples were placed in a dissolution vessel containing 500 ml of acetate buffer (pH 4.5) at 50 rpm maintained at 37 ± 0.5°C according to USFDA guidelines. 20 mg of drug or its equivalent amount of prepared solid dispersions were added to dissolution medium and the samples were withdrawn at time intervals of 2, 5, 10, 15, 20, 25, 30, 45 min. respectively. The volume of dissolution medium was adjusted to 500 ml by replacing it with fresh dissolution medium. The samples were immediately filtered through 0.45µm membrane filter, suitably diluted and analyzed spectrophotometrically at 232 nm. The dissolution curve of pure Ezetimibe and its solid dispersions in acetate buffer (pH 4.5) with 0.45% SLS are shown in the fig. . The result reflected high improvement in solid dispersions as compared to pure Ezetimibe. Table 3 shows % drug dissolved for all systems. In acetate buffer (pH 4.5) with 0.45% SLS solid dispersions EZT-2 and EZT-3 showed 99.15±3.54 and 98.8±3.53 drug release at 25 and 30 mins respectively. While EZT-1, containing highest ratio of Soluplus® released 99.85± 2.68 drug within 15 min only. Where, pure EZT showed only 57.92 ± 0.42% release at 45 min. The factors that might be contributing in enhancing the dissolution rate are greater hydrophilicity and solubilizing property of the Soluplus® that resulted in greater wetting and dispersing drugs in their molecular state into hydrophilic carrier matrix [1] and due to increase in surface area was occurred by spray drying.[2]

During dissolution experiments, it was noticed pure drug floated on the surface of dissolution medium for a longer period of time and showed only 57.92 ± 0.42% release at 45 min. Solid dispersions sank immediately in dissolution medium. This showed increased wettability of formulation particles, which enhances dissolution by reducing interfacial tension between the hydrophobic drug and dissolution medium.

On the basis of this dissolution data of spherical agglomerates among the different formulation EZT-1 was selected for further development and its evaluation properties compared with marketed formulation.

Table No.14: Practical yield of spray dried batches

Sr. No.	Codes	Drug/Drug + Polymer	Production yield
1	EZT	Pure Ezetimibe	-
2	EZT-1	EZT with Soluplus® by spray drying method (0.5:1)	28.13%
3	EZT-2	EZT with Soluplus® by spray drying method (1:1)	26.13%
4	EZT-3	EZT with Soluplus® by spray drying method (1:0.5)	26.68%

Table No.15 : Percentage Drug content of spray dried batches.

Sr. No.	Batch Code	% Drug Content
1	EZT	-
2	EZT-1	92.33 ± 0.81
3	EZT-2	93.51 ± 0.79
4	EZT-3	97.17 ± 0.74

CONCLUSION

Solubilization of poorly aqueous soluble drug continues to be a challenging task for formulation experts. Poor aqueous solubility of drug frequently results in poor dissolution which is the prime determinant of the rate and extent of absorption of the drug. An improvement in aqueous solubility/dissolution can overcome this problem. So attempt was made to prepare and optimize solid dosage form tablet by using spray drying techniques with different ratio of drug/polymer.

Among the evaluation results of prepared three SD of API with three different ratios with Soluplus i.e. (0.5:1, 1:1 & 1:0.5 for solid dispersion EZT-1, EZT-2, EZT-3 respectively) EZT-1 shows enhanced solubility parameter as compare to others. On the basis of dissolution data of spherical agglomerates among the different SD formulations EZT-1 was selected for further development (with various synthetic & natural super disintegrate) & it's evaluation properties compared with marketed formulation.

The evaluation results of prepared tablet SDT and marketed tablet (EZEDOC 10 mg result revealed that all quality control parameters such as weight variation, friability and disintegration test of compressed tablets with excipients remained within the desired limits as per USP standards and also nearly similar to the marketed tablet.

The dissolution curve of prepared tablet and marketed tablet in acetate buffer (pH 4.5) are shown in the figure. The table No. 15 shows % drug dissolved in 5 min. (DP_5), % drug dissolved in 45 min. (DP_{45}) for prepared tablet and marketed tablet. Thus the reference as well as the test formulation are similar and hence were found to be comparable.

The result indicates the dissolution profile of prepared tablet was almost comparable with that of marketed tablet. The prepared Ezetimibe tablet release 98.36% drug and marketed tablet release 95.65% drug in 45 min. The result obtained from all evaluation parameters of the prepared tablet of Ezetimibe is similar to the parameters of a marketed tablet. This rapid release from the tablets may be due to rapid disintegration due to disintegrates and solubilization of Ezetimibe from solid dispersion due to hydrophilic carriers.

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