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MELT GRANULATION AND LIQUISOLID TECHNIQUE APPROACH FOR THE ENHANCEMENT OF SOLUBILITY OF EDOXABAN

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ABSTRACT

The objective of the present work is to obtain improve the solubility and dissolution profile of poorly soluble drug, Edoxaban using liquid solid compacts and melt granulation techniques. The solubility studies of Edoxaban were studies in non-liquid vehicles, Liquisolid system of Edoxaban was prepared by using Maisine CC, Avicel pH, Aerosil, SSG and by melt granulation technique using Gelucire 48/16 pellets, Polyox WSR N-80. The formulations were evaluated for drug excipient interactions, flow properties, and general quality control tests of tablets using Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC). In vitro dissolution studies were performed at 37°C ± 0.50°C, taking 900 ml of 0.1N HCl as a dissolution medium at 50rpm measured at 296nm. Stability studies were performed at 40°C and 75% RH for three months. Solubility data obtained that Maisine CC (744.2327µg/mL) & Tween 80 (668.0290 µg/mL) were found to have good solubility with Edoxaban. The FT-IR spectra of the drug and polymer showed that there was no shift in the major peaks. The formulation was found to comply with Indian pharmacopeial limits, Disintegration of all the capsules occurred within 73 sec and 85 sec. LSF5 and MGF4 showed the better results. No significant difference was seen in the tablet properties, and drug release profile after storage for 3 months.

Keywords: Edoxaban, Maisine CC,Avicel pH,Aerosil, Gelucire 48/16 pellets, ,Liquidsolid system, melt granulation.

1. INTRODUCTION:

One of the major challenges of present pharmaceutical research is to enhance the dissolution profile, absorption efficiency and bioavailability of water insoluble drugs (Yalkowsky and Rubino, 1985; P.K.Lakshmi et al., 2011). The solubility dissolution behaviour of a drug is frequently the rate-limiting step to absorption of drugs from the gastrointestinal tract for orally administered drugs (Sugawara et al., 2005; Youn et al., 2006). It reports that over 70% of drugs and active entities are poorly water-soluble compounds (BCS II or BCS IV) (Goke,K et al., 2018), these drugs often suffer from formulation challenges because of limited dissolution and/or low permeability(Zhiguo Ma et al., 2018).

A variety of formulation strategies have been explored to overcome the poor aqueous solubility of drugs, including micronization (Leleux J and Willliams R.O, 2014), nanocrystalization (Scholz, P. and Keck, C.M,2015), cyclodextrin inclusion (Zhang X et al.,2016), cocrystallization (Gadade, D.D. and Pekamwar, S.S,2016),solid dispersion (Vo, CL et al., 2013), liquisolid technique (Vranikova, B.; Gajdziok, J. 2013), and

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encapsulation in nanoparticles (Kalepu, S.; Nekkanti, V 2016).Recently, liquisolid technique has shown promising approach for the dissolution enhancement. Liquisolid systems are described as dry, non-adherent, free-flowing and compressible powder mixtures acquired by conversion of liquid drugs, drug suspensions or drug solution (Vemula SK et al 2015). The approach was reported by Spireas et al. and applied to water insoluble drugs which were then formulated as rapid release systems. This method involves absorption of liquid medication onto a carrier that are subjected to instant adsorption onto coating materials resulting in a free flowing, dry, compressible powder mixture. In general, biologically safe, non-volatile solvents are employed as liquid vehicle like propylene glycol (PG), Polyethylene glycol 400 (PEG400) etc. cellulose, lactose, starch and their different grades are used as carriers. But when it comes to coating material, silica dioxide like material with high adsorption capacity are used. The principle of enhanced dissolution by liquisolid compacts owes to presence of solid drug in partially dispersed state that results in increased aqueous solubility and wetting properties (Patil U et al., 2012).

Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a melt able binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed (Yang D et al., 2007) Maisine CC, Avicel pH 102, Aerosil, Tween 80, Gelucire 48/16 pellets, Polyox WSR N-80 are used as carrier materials and vehicles along with sodium starch glycolate.

Edoxaban is a member of the Novel Oral Anti-Coagulants (NOACs) class of drugs, and is a rapidly acting, oral, selective factor Xa inhibitor. By inhibiting factor Xa, a key protein in the coagulation cascade, Edoxaban prevents the stepwise amplification of protein factors needed to form blood clots. Edoxaban is predominantly absorbed from the upper gastrointestinal tract, and oral bioavailability is approximately 62 %. Food does not affect total exposure to Edoxaban (Parasrampuria, D. A., & Truitt, K. E. (2016).)

2. MATERIALS AND METHODS:

2.1. Materials:

Edoxaban was purchased from Aurobindo Pharma Pvt Ltd, Hyderabad. Maisine CC and Brig 35 were obtained as a gift sample from Dr.Reddy's laboratories Pvt. Ltd. Avicel pH 102 and Aerosil were purchased from Sigma-Aldrich, Germany. Tween 80 was purchased from Sigma Aldrich Bangalore, India. PEG 400, PEG 600 and Span 80 were obtained from Sysco Research Laboratories Pvt. Ltd., Mumbai.

2.2. Methodology:

2.2.1. Preparation of Standard Graph of Edoxaban:

50mg of Edoxaban was dissolved in 50ml of Citrate/Phosphate Buffer pH 6.0 in volumetric flask to obtain 1000 µg/ml. From stock solution-I, 10 ml solution was

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transferred in 100ml volumetric flask and volume was made up to 100ml with Citrate/Phosphate Buffer pH 6.0 to obtain 100 µg/ml. From stock solution-II aliquots of 1, 2, 3, 4 and 5ml were taken and volume was made adjusted to 50ml with Citrate/Phosphate Buffer pH 6.0 to get 2, 4, 6, 8, 10µg/ml solution. The absorbances of solutions were determined against blank. A 10 µg/ml standard solution of Edoxaban in Citrate/Phosphate Buffer pH 6.0 was scanned on a double beam UV spectrophotometer. From UV spectrum, Edoxaban λ max was obtained. A standard graph showing the absorbance vs. different concentrations was plotted and correlation coefficient (R^2) was also calculated.

2.2.2. Solubility Studies:

The solubility of Edoxaban in non-volatile liquid vehicles, which are being used to prepare the liquisolid systems, were studied by preparing saturated solutions of the drug in these solvents and analysing their drug content spectrophotometrically. Specially, Edoxaban was mixed in 7ml screw capped vials with such amounts of each of the above solvents in order to produce systems containing an excess of drug. The mixtures were shaken on an automatic test tube shaking machine for 24 hours and then settled for another 2 hours. The screw capped vials were centrifuged at 2500 Rpm for further settling of undissolved crystalline material and thereby obtaining a clear supernatant. After centrifugation, accurately measured quantities of the filtered supernatant solutions were further diluted with methanol and analysed spectrophotometrically at 296 nm for their drug content.

2.2.3. Flowable Liquid Retention Potential:

The success of liquisolid system with an acceptable flow rate and compressibility depends on liquid load factor (Lf) and excipient ratio (R). Hence, the powder excipients ratio and liquid load factor of the formulations are related as follows:

$$Lf = \mathbf{\Phi CA +} \Phi\mathbf{Co}\ (1/R)$$

2.2.4. Compatibility study of drug and polymer using FTIR:

The compatibility between the pure drug and excipients was detected by FTIR spectra.

2.2.5. Liquisolid Compacts Preparation Technique for Edoxaban:

Drug and Solvent were weighed in calculated amounts and transferred in to a mortar and dispersed, to it carrier and coating material was added and blended. Sodium starch glycollate was added to the above blend to obtain a uniform mixture. This mixture is made in to plugs and filled in to capsules given in table 1.

Table 1: Formulation of Liquisolid Systems of Edoxaban

Formulations	**LSF1**	**LSF2**	**LSF3**	**LSF4**	**LSF5**	**LSF6**	**LSF7**	**LSF8**
Drug: Liquid	1:2	1:4	1:2	1:4	1:2	1:4	1:2	1:4

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Ca: Co (R)	20	20	40	40	20	20	40	40
Lf	0.28	0.28	0.198	0.198	0.351	0.351	0.261	0.261
Drug (mg)	30	30	30	30	30	30	30	30
Maisine CC(mg)	60	120	60	120	-	-	-	-
Tween 80 (mg)	-	-	-	-	60	120	60	120
Avicel pH 102 (mg) Q	375	624.9	545.2	757.4	908.88	512.16	413.20	688.70
Aerosil (mg) q	18.74	31.248	13.63	22.72	15.36	25.63	10.32	17.21
SSG (mg) 5%	24.16	40.31	32.44	54.07	20.63	34.368	25.65	42.79
Capsule size '0'	163	163	163	163	163	163	163	163
Unit weight of blend (mg)	**507.916**	**846.518**	**681.36**	**1135.6**	**433.370**	**722.136**	**539.193**	**898.716**
Total weight of filled capsule (mg)	**703.516**	**1042.11**	**876.96**	**1331.27**	**628.970**	**717.736**	**734.79**	**1094.31**

R = Carrier:Coating (Q:q)-[Microcrystalline Cellulose: Aerosil)

Liquidload Factor: Lf = W (Weight of Liquid medication)/Q (Carrier material)

LV: Liquid Vehicle (Maisine CC & Tween 80)

2.2.6. Melt Granulation Technique for Edoxaban:

Procedure: The polymer was weighed and transferred into porcelain dish and this was placed on hot and heated (55ºC for Gelucire 48/16 pellets and 65ºC for Polyox WSR N-80) until the polymer was melted. Porcelain dish was removed from the hot plate and to it weighed quantity of drug was added and stirred to get a uniform mixture. After solidification of this mixture, it was broken into pieces and passed through #40 mesh. To this Avicel pH 102 and SSG was passed through #40 and were added and blended. Aerosil and Magnesium stearate was passed through #60 and blended. Finally, this blend was filled into capsules given in Table 2.

Table 2: Formulation of Edoxaban by Melt Granulation Technique

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Formulations	**MGF1**	**MGF2**	**MGF3**	**MGF4**	**MGF5**	**MGF6**	**MGF7**	**MGF8**
Drug: Polymer	1:0.25	1:0.5	1:1	1:2	1:0.25	1:0.5	1:1	1:2
Drug (mg)	30	30	30	30	30	30	30	30
Gelucire 48/16 pellets(mg)	7.5	15	30	60	-	-	-	-
Polyox WSR N-80 (mg)	-	-	-	-	7.5	15	30	60
Avicel pH 102 (mg)	18.6	11.1	52.2	22.2	18.6	11.1	52.2	22.2
SSG (mg) 5%	3	3	6	6	3	3	6	6
Aerosil (mg) 0.5%	0.3	0.3	0.6	0.6	0.3	0.3	0.6	0.6
Magnesium stearate (mg) 1%	0.6	0.6	1.2	1.2	0.6	0.6	1.2	1.2
Capsule size	Size 2	Size 2	Size 2	Size 2	Size 2	Size 2	Size 2	Size 2
Capsule weight (mg)	63	63	63	63	63	63	63	63
Weight of blend (mg)	60	60	120	120	60	60	120	120
Total weight of filled capsule (mg)	123	123	183	183	123	123	183	183

3. Evaluation: Determination of Flow Properties& Disintegration Time

3.1. Angle of repose: The angle of repose of powder blend was determined by the funnel method. The diameter of the powder cone was measured and angle of repose (θ) was calculated using the following equation:

$\theta = \tan^{-1} h/r$

Where, h and r are the height and radius of the powder cone

3.2. Determination of bulk density & tapped density: An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after

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that the volume (Vf) was measured and continued operation till the two consecutive readings were equal (Lachman et al., 1987). The bulk density and the tapped density were calculated using the following formulae:

Bulk density = W/V_0 Tapped density = W/V_f

Where, W= Weight of the powder

V_0 = Initial volume V_f = final volume.

3.3. Compressibility Index (Carr's index): Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. The less compressible material is the more flowable. (Lachman et al., 1987).

CI = (TD-BD) x 100/TD

Where, TD is the tapped density and BD is the bulk density.

3.4. Hausner's Ratio: It is the ratio of tapped density and bulk density. Generally, a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index (S. D Mankar and M.S.Bho,2019)

3.5. In vitro disintegration time: The disintegration time was measured using Disintegration test apparatus in water (37± 2°C). The time in seconds taken for the complete disintegration of the tablet/capsule with no palpable mass in the apparatus was measured in seconds (Sahil M,2011).

3.6.In vitro dissolution profile: Dissolution studies were carried out by USP paddle method Type II apparatus at 37± 0.50 ° c, taking 900 ml of 0.1N HCl as a dissolution medium. Speed of rotation of paddle was set at 50 rpm. Absorbance of sample was measured at 296 nm by using UV spectrophotometer (Shinde Anilkumar J et al., 2010).

3.7. DSC Studies: DSC thermogram of pure drug and mixture were recorded using Diffraction scanning calorimeter (DSC 60, Shimadzu, Japan). The measurement was performed between 30 and 350^{o}C at heating rate 10^{o}C/min. The obtained DSC graphs were interpreted and compared for any presence of interactions (J. L. Ford and T. E. Mann, 2012).

3.8. Stability Studies: The formulations were loaded for stability as per ICH guidelines into stability chambers which were maintained at 40 oC and 75% RH. Stability studies were conducted for 3 months. Samples were withdrawn at 1 month, 2 months and 3 months. Third month samples were analyzed and results are tabulated (Skelly, P. J. and Tighe, B. J,1979)

4. RESULTS and DISCUSSION:

Standard graph of Edoxaban was constructed using concentration 2, 4, 6, 8, 10 (µg/ml) in Citrate/Phosphate Buffer pH 6.0. It is evident from the figure 1 & 2 that the graph is linear with regression coefficient value of R^2 = 0.9993 and slope = 0.02887 at λ max of 296nm.

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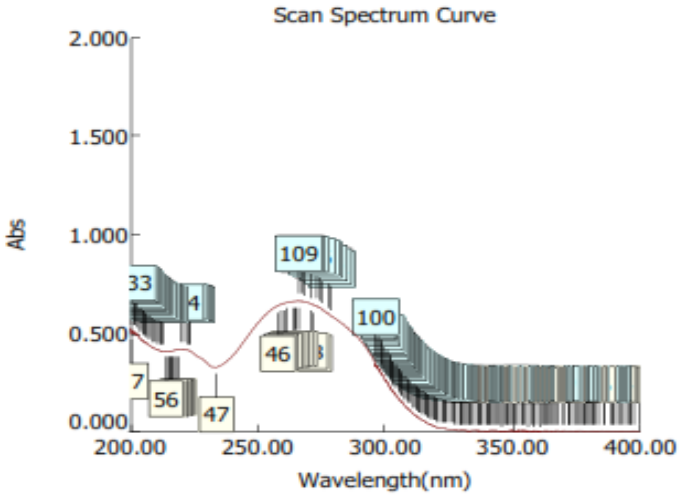
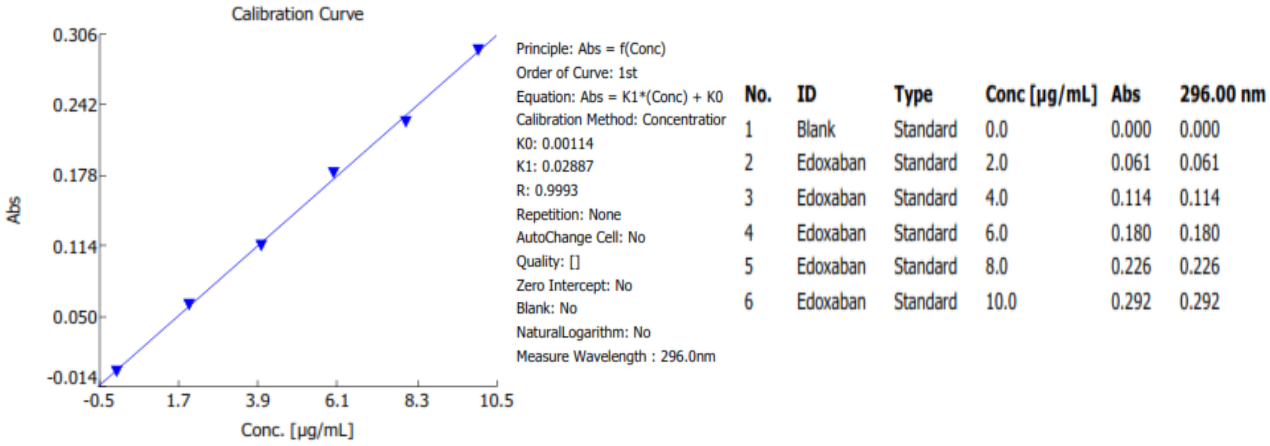


Figure 1: Spectrum Scan of Edoxaban (µg/ml)



No.	ID	Type	Conc [µg/mL]	Abs	296.00 nm
1	Blank	Standard	0.0	0.000	0.000
2	Edoxaban	Standard	2.0	0.061	0.061
3	Edoxaban	Standard	4.0	0.114	0.114
4	Edoxaban	Standard	6.0	0.180	0.180
5	Edoxaban	Standard	8.0	0.226	0.226
6	Edoxaban	Standard	10.0	0.292	0.292

Figure 2: Calibration Curve for Edoxaban

4.1. Solubility Studies:

Solubility studies of Edoxaban in non-volatile liquid vehicles were studied and the results were extrapolated to determine the percent mg/ml of Edoxaban in its saturated solution with the solvents under investigation. Results are shown in Table 3.

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Table 3: Solubility Studies

S.No	Non-Volatile Liquid Vehicles	Absorbance at 296.00 nm	Solubility (µg/mL) at 296.00 nm
1	PEG 400	0.051	172.7052
2	PEG 600	0.086	293.9383
4	MAISINE CC	0.216	744.2327
6	BRIG 35	0.072	245.4450
7	TWEEN 80	0.194	668.0290
8	SPAN 80	0.120	441.7076

Observation: From the above data obtained, Maisine CC (744.2327µg/mL) & Tween 80 (668.0290 µg/mL) were found to have good solubility with Edoxaban.

4.2. Flowable Liquid Retention Potential:

The flowable liquid-retention potential of carrier and coat material results are depicted in the table 4

Table 4: Flowable Liquid Retention Potential

Material	Maisine CC	Tween 80
Avicel pH 102	0.135	0.1842
Aerosil	3.6	3.6

4.3. Compatibility study of drug and polymer using FTIR

The FT-IR spectrophotometer was used to identify as well as determine the possibilities of any interaction between the formulation components at the optimized composition. As showed there was no substantial differentiation in the FT-IR spectra of the drug when compared to the spectra of the physical mixture of drug and polymers. The FT-IR spectra of the drug and polymer showed that there was no shift in the major peaks. This further revealed that there was no variation in the properties of the drug and polymers in the formulation. Hence, the drug and polymers were compatible with each other.

IR spectrum of Edoxaban shows a peak at 1614.41 cm^{-1} due to C=O stretching, 1503.28 cm^{-1} N-H stretching, 1378.41 cm-1 may be due to-CH3, 683.79 cm^{-1} may be due to C-H stretching. The IR spectrum of the drug along with individual excipients and mixtures, it is clear that, there is no appreciable change in the positions of the characteristic bands of the drug along with the IR spectrum of the formulation derived during the present investigation as shown in Figures 3 and 4. Since there is no change

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in the nature and position of the bands in the formulation, it can be concluded that the drug maintains its identity without going any chemical interaction with the polymers used.

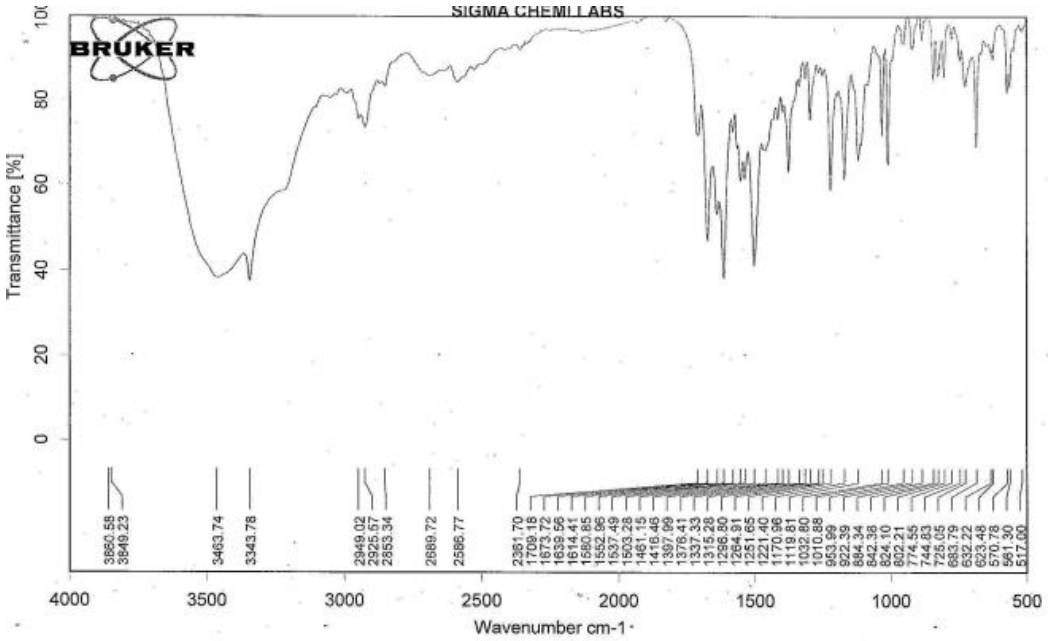

Figure 3: FTIR Spectra of Pure Drug Edoxaban

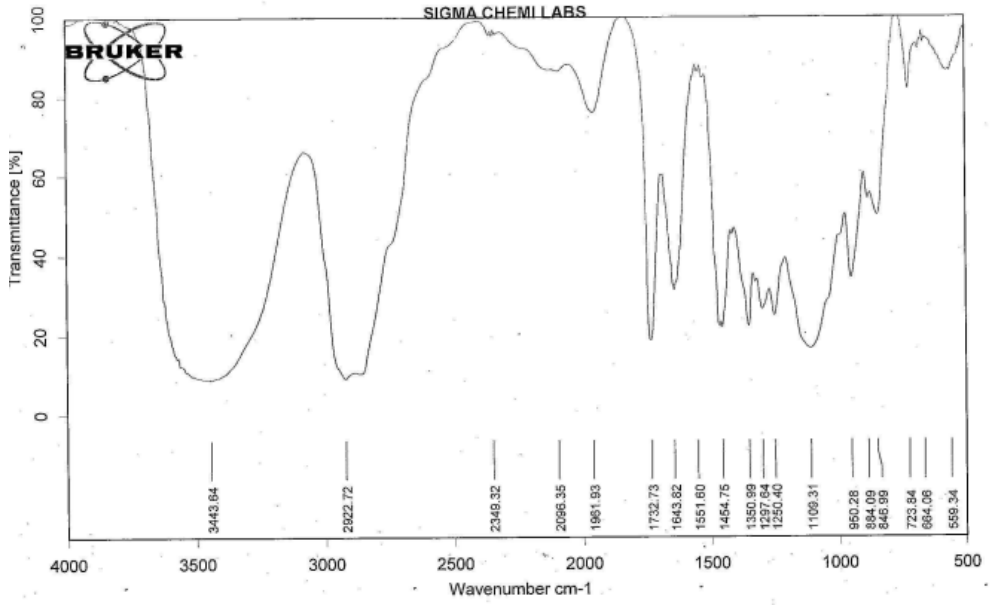

Figure 4: FTIR Spectra of Pure Drug Edoxaban + Formulation Mixture

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4.4. Evaluation:

The angle of repose values of all the formulations are ≤ 35 implying all are having good flow. The lower ratio of Drug: Liquid are showing good flow at a particular excipient ratio. This might be due to lower amount of liquid in the formulation due to which cohesive forces might be less. Powders showing Carr's index (Ci) up to 11.21 are considered of acceptable flow properties. The CI values of all the formulation are between 11.21 – 15.36 and Hausner ratio values are between 1.121 – 1.302 indication fair to passable flow. The CI and Hausner value of LSF8 is lowest which might be due to the lower are ratio of Drug: Liquid and excipient ratio of 20. Disintegration of all the capsules occurred within 73 sec values given in Table 5.

Table 5: Flow Properties of Formulations LSF1-LSF8 (Liquid solid Compacts Technique for Edoxaban)

Formulations	**LSF1**	**LSF2**	**LSF3**	**LSF4**	**LSF5**	**LSF6**	**LSF7**	**LSF8**
Angle of repose	34	35	32.1	33	31	30	33	29.5
Bulk density	0.259	0.268	0.254	0.266	0.251	0.236	0.241	0.230
Tapped density	0.348	0.366	0.301	0.309	0.328	0.315	0.306	0.314
CI	14.99	13.55	15.36	12.98	14.12	11.98	13.36	11.21
Hausners ratio	1.265	1.276	1.286	1.302	1.299	1.289	1.267	1.121
DT (min: sec)	1:07	1:01	0:59	1:05	0:55	1:05	1:04	1:13

4.5. In Vitro Drug Release:

The drug particles in liquid solid formulations were dispersed in selected hydrophilic liquid vehicle, after liquid solid capsule was disintegrated, the primary particles of liquid solid suspended in the dissolution medium contained drug particles in a state of molecular dispersion. All the formulations showed almost entire drug release within 15 min. because of the drug being in solubilized state. LSF2, LSF5 and LSF8 showed higher release immediately which might be due to the higher excipient ratio since more coating of liquid medicament is possible given in the table 6 and Figure 5.

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Table 6: Percentage Cumulative Drug Release for the Formulations LSF1-LSF8

	% Cumulative drug release							
Time (in min.)	**LSF1**	**LSF2**	**LSF3**	**LSF4**	**LSF5**	**LSF6**	**LSF7**	**LSF8**
0	0	0	0	0	0	0	0	0
5	34.11	39.44	42.97	49.44	61.77	52.37	53.77	50.17
10	42.19	45.77	58.44	60.17	72.11	62.77	64.77	61.77
15	56.77	59.44	64.77	69.22	80.11	70.11	71.22	73.77
20	62.11	68.11	71.44	79.33	89.77	80.17	81.22	82.77
30	79.22	89.44	91.22	92.77	96.77	93.77	94.77	92.17
45	92.77	96.22	99.79	100.03	100.45	99.89	99.98	100.35

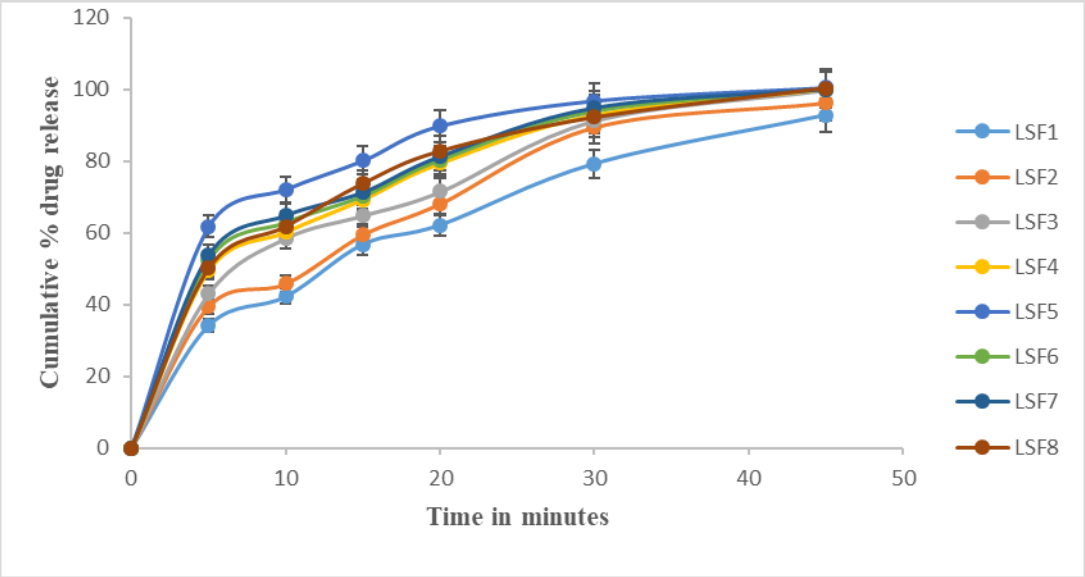

Figure 5: Percentage Cumulative Drug Release for the Formulations LSF1-LSF8

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4.6. Evaluation:

Determination of flow properties and disintegration time:

Table 7: Flow Properties of Formulations MGF1-MGF8 (Edoxabane by Melt Granulation Technique)

Formulations	MGF1	MGF2	MGF3	MGF4	MGF5	MGF6	MGF 7	MGF8
Angle of repose	30	29	21.6	18	25.3	28	29	23.2
Bulk density	0.495	0.467	0.458	0.358	0.396	0.413	0.425	0.443
Tapped density	0.594	0.574	0.556	0.451	0.498	0.512	0.536	0.541
CI	19.36	21.87	25.6	12.64	18.66	21.67	22.47	23.98
Hausner ratio	1.354	1.199	1.298	1.112	1.254	1.287	1.279	1.654
DT (in minutes)	1:12	0:58	1:12	1:25	1:11	1:01	1:18	1:03

Angle of repose values indicate excellent to good flow ranging from 18 - 30. Difference between bulk density and tapped density is formulations indicating good flow. The CI and Hausner values are less for this is again in correlation with the properties of the polymer used for melt granulation. Disintegration of all the capsules occurred within 85 sec given in the table 7.

4.7. In Vitro Drug Release:

Dissolution of all the formulations was carried out using 900ml of 0.1N Hcl at 50rpm and it showed entire drug release. And as polymer concentration is increased dissolution has increased but at higher concentration of polymer, harder granules are formed due to which initial release of drug is less is less for MGF6 and MGF7.Polyox formulations showed lower initial drug release compared to Gelucire formulation. Polyox is a water swellable polymer due to this drug diffusion is lower whereas Gelucire is a water-soluble excipient. Based on the drug release MGF4 formulation showed better results given in table 8 and figure 6.

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Table 8: Percentage Cumulative Drug Release for the Formulations MGF1-MGF8

	% Cumulative Drug Release							
Time (in minutes)	**MGF1**	**MGF2**	**MGF3**	**MGF4**	**MGF5**	**MGF6**	**MGF7**	**MGF8**
0	0	0	0	0	0	0	0	0
5	30.44	37.99	38.99	49.66	33.49	38.11	40.19	43.66
10	44.11	49.33	52.19	62.11	53.77	59.11	57.44	56.11
15	55.22	59.11	62.44	71.55	67.22	65.44	64.22	60.11
20	65.78	69.77	71.33	85.66	79.44	76.88	79.11	80.11
30	87.17	90.44	91.77	96.77	91.77	86.33	89.55	85.22
45	98.47	99.01	97.44	100.98	100.01	99.66	100.04	99.98

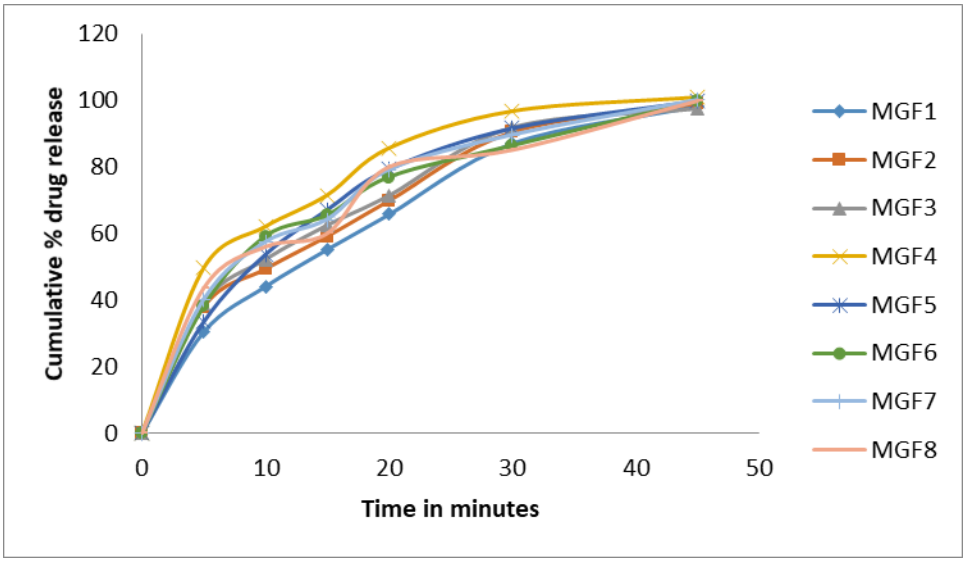

Figure 6: Percentage Cumulative Drug Release for the Formulations MGF1-MGF8

4.8. Stability data of Edoxaban:

DSC Studies: DSC is conducted for Formulation mixture before and after stability both for liquid solid and hot granulation method as showing in the figures 7 to 10.

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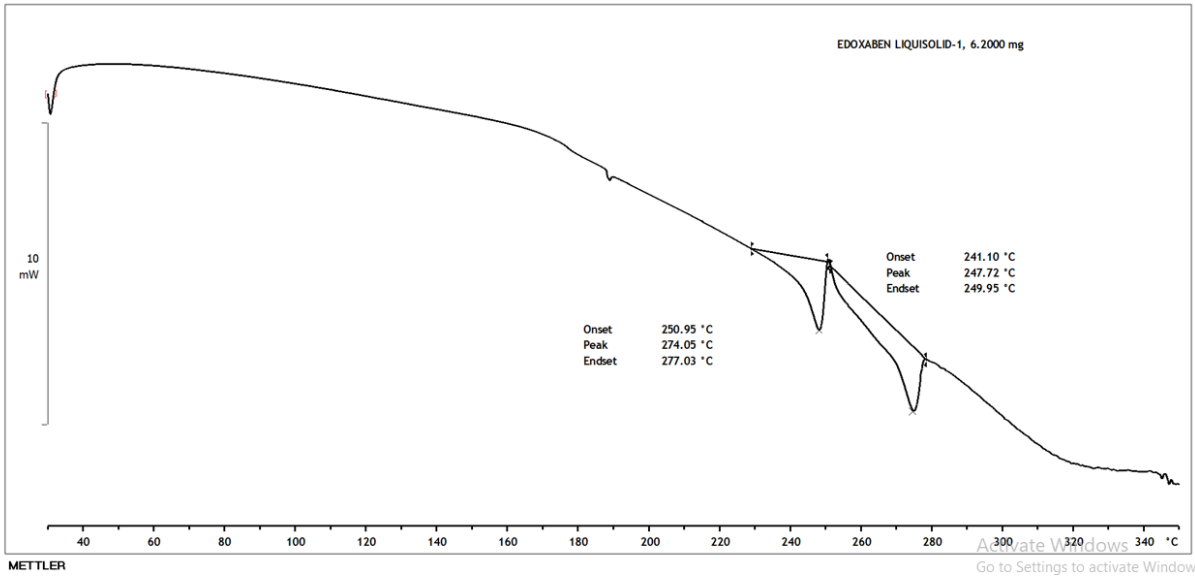

Figure 7: DSC Spectra of Liquid Solid method before stability

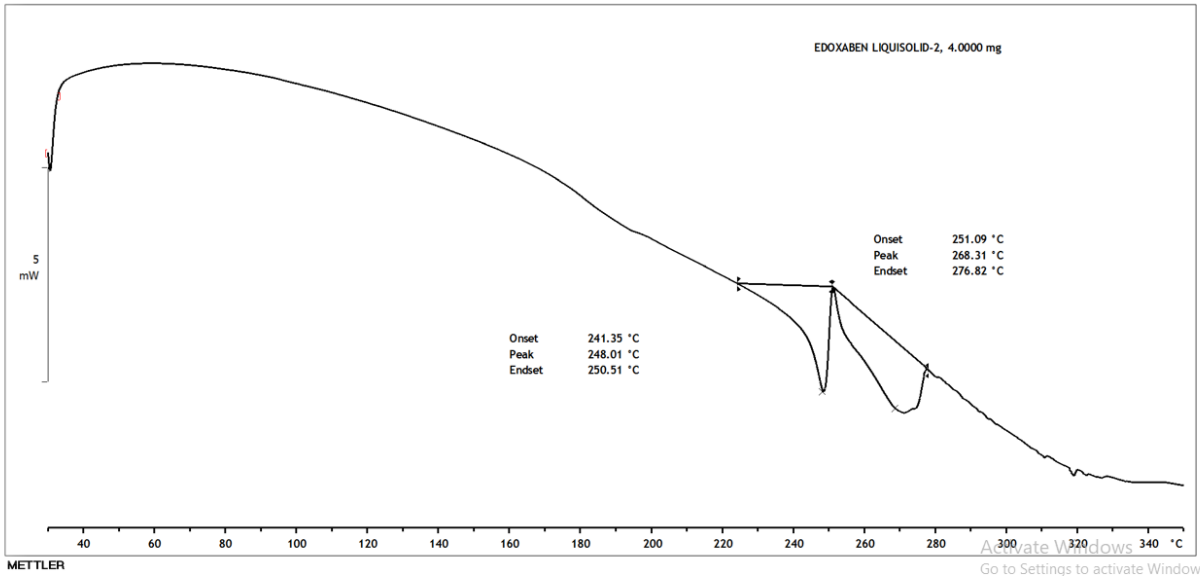

Figure 8: DSC Spectra of Liquid Solid method after stability

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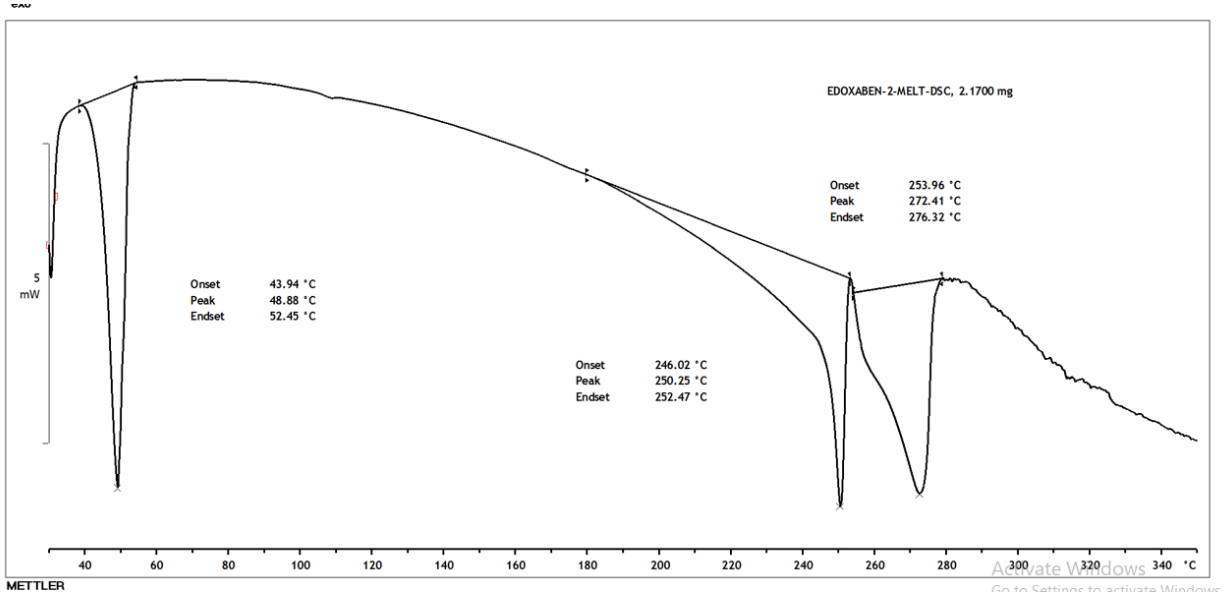

Figure 9: DSC Spectra of hot-granulation method before stability

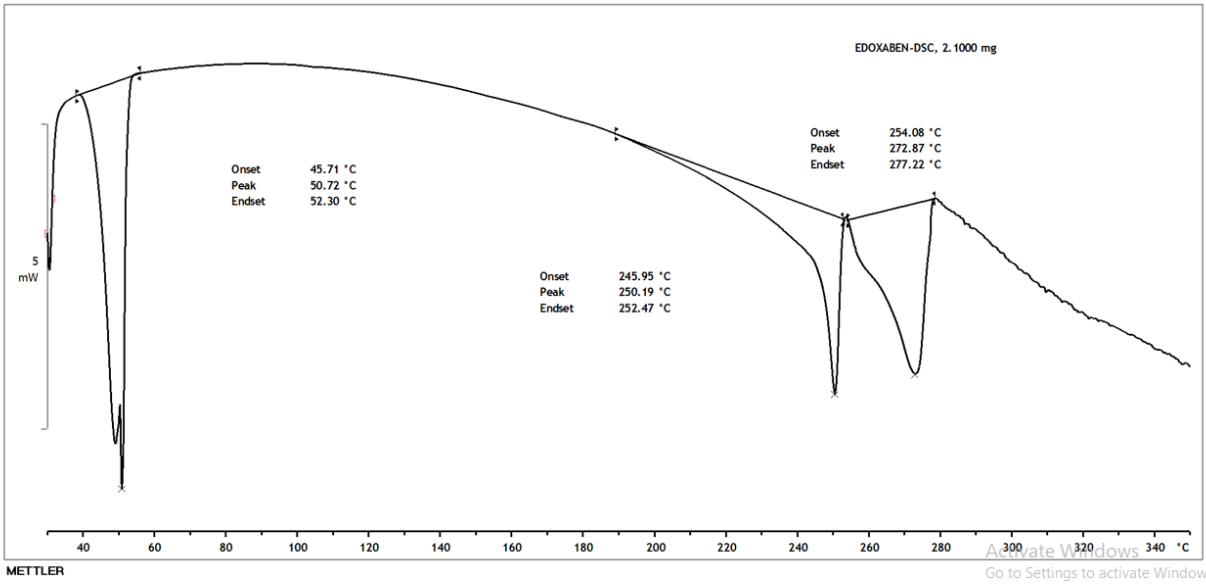

Figure 10: DSC Spectra of hot-granulation method after stability

The optimized formulation was subjected to stability studies at 40 C ± 2 º oC/ 75%±5 RH for 3 months, LSF5 and MGF4 were selected as optimized formulation evaluated in vitro dissolution studies stability given in the table 9.

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Table 9: Stability data of Edoxaban

		Initial	**After 3 months**
Formulation			
Liquid solid Systems	LSF5	100.45	100.99
Melt-Granulation Technique	MGF4	100.98	101.06

5. Conclusion:

In the present study, the potential of liquisolid systems and Melt granulation techniques to improve the dissolution properties of water-insoluble drug was investigated using Edoxaban as the model drug. Among the various mechanisms used for improving the solubility and thereby the dissolution of these drugs, liquisolid technique and melt granulation is gaining much attention and importance in recent years.

FT-IR spectra of the drug revels that no variation in the properties of the drug and polymers in the formulation. In the flow properties Drug: Liquid are showing good flow at a particular excipient ratio. the higher dissolution rates observed in liquisolid formulations may be attributed to significantly larger surface area of the molecularly dispersed drug particles. LSF5 and MGF4 was selected as optimized formulations.

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