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FORMULATION AND EVALUATION OF LIQUISOLID COMPACTS OF DABIGATRAN ETEXILATE MESYLATE

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Abstract:

The term 'liquisolid systems' (LS) is a powdered form of liquid drug formulated by converting liquid or solid lipophilic drug in suitable non-volatile solvent systems into dry looking, non-adherent, free-flowing, and readily compressible powdered mixtures by blending with selected carrier and coating materials. The aim of the present study is to improve the solubility of poorly water soluble drug, dabigatran etexilate mesylate a BCS class II drug. Dabigatran Etexilate Mesylate is an inactive pro-drug that is converted to dabigatran, the active form used as an anti-coagulant. Various non-volatile solvents (PEG 600, PEG 400, Castor oil, Span 80, Tween 80, Glycerine, Transcutol, Olive oil, Liquid Paraffin) were used and maximum solubility was observed in combination of span80 and castor oil (400.96ug/ml). Selection of carrier materials like Maize starch, MCC, Avicel pH 101 and 102 and Prosolv SMCC 50 with a loading factor of 0.72, 0.75, 0.77, 0.87 and 1.75 respectively were optimized. To this admixture, coating material Aerosil 200 in different ratios (R=5, 10, 15, 20, 25) was added to enhance the flow property. Finally the powdered material is compressed to tablets by direct compression using 11.9mm. The tablets were evaluated for physicochemical properties, and dissolution studies. Among all formulations, dabigatran etexilate mesylate liquisolid compacts containing Prosolv SMCC 50 (LSP) showed higher dissolution rate (99.8% in 30 min) than the pure drug (11.15% in 45 min). FTIR studies and DSC studies revealed that there is no significant interaction between the drug and excipients. The XRD analysis confirmed formation of a solid solution inside the compact matrix. Formulations were stable. From this study it can be concluded that the liquisolid technique is a promising alternative for improvement of dissolution property of water-insoluble drugs. Hence Span80+Castor oil (non-volatile solvent) and Prosolv SMCC 50 were optimized in enhancing the dissolution rate of dabigatran etexilate mesylate.

Keywords: *Dabigatran Etexilate Mesylate, Non- Volatile solvents, Liquisolid compacts, Liquid load factor.*

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INTRODUCTION:

One of the major challenges of present pharmaceutical research is to enhance the dissolution profile, absorption efficiency and bioavailability of water insoluble drugs. The solubility & the dissolution behaviour of a drug, is the rate-limiting step to absorption of drugs from the gastrointestinal tract for orally administered drugs. During the past few years, many techniques have been developed such as drug micronization, solid dispersions [1], co-precipitation, lyophilization, microencapsulation, use of the prodrug, drug derivatization processes and inclusion of drug solutions into soft gelatin capsules to improve the solubility and bioavailability have been developed.

Formulation of liquisolid (LS) compact is a novel "powder solution technology," which makes use of liquid medications admixed with suitable carriers and coating materials which are formulated into a moderately flowing, dry looking, non-adherent and compressible powder forms that have an increased drug dissolution rate profiles [2,3]. Due to their significantly increased wetting properties and surface of drug available for dissolution, LS compacts of water insoluble substances may be expected to display enhanced drug release properties, and consequently, improved bioavailability [4,5]. Rapid release rates are obtained in liquisolid formulations. These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs [6].

Dabigatran Etexilate Mesylate (DEM) is an oral prodrug that is metabolized by Serum Esterase to Dabigatran, the active form. It is a synthetic, competitive and reversible direct thrombin inhibitor. Inhibition of thrombin disrupts the coagulation cascade and inhibits the formation of clots. DEM may be used to decrease the risk of venous thromboembolic events in patients who have undergone total hip or knee replacement surgery, or to prevent stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation therapy is indicated.

The aim of the present study is to improve dissolution rate, absorption efficiency of poorly water soluble drug DEM using liquisolid (LS) technology. LS can be achieved by using various non-volatile solvents like Tween 80, polyethylene glycol 400, propylene glycol, glycerin, Span80 and Castor oil to dissolve the drug. Acceptable flow properties can be achieved by changing carrier and coating material ratio using different type of carriers like Avicel pH 101, 102 and Aerosil 200 as coating material. Co-processed excipient Prosolv SMCC50, used as carrier and coating material is also used. The formulations were optimized based on dissolution rate.

MATERIALS AND METHODS:

Dabigatran Etexilate Mesylate (DEM), Avicel pH 101 & 102, Aerosil 200, and Prosolv SMCC 50 were received as a gift sample from Dr Reddy's Laboratories, India. Tween 20, Tween 80, Polyethylene glycol (PEG200, PEG400) and Propylene glycol (PG) were purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). All other chemicals, reagents and solutions used were of analytical grade.

Saturation Solubility Studies

To select the best non-volatile solvent to dissolve DEM, solubility studies of DEM were carried out in different non-volatile solvents like Propylene glycol, PEG400, Tween 80, Span 80, castor oil, transcutol, glycerine, olive oil, liquid paraffin and combination of non-volatile solvents. Saturated solutions were prepared by adding excess drug to the vehicles containing 10 ml of solvent in a screw capped vial. The vials were sealed and rotated for 72hr at ambient temperature under constant shaking in orbital shaker. Then subsequently the solutions were centrifuged at 10,000 rpm for 5 min and the supernatant was filtered through a 0.2µm Whatmann filter [7,8]. The filtered solution was diluted and the drug concentration was analyzed using UV spectrophotometer at 324 nm.

Holding capacity of the carrier material

The capacity of each excipient to hold liquid and behave like dry powder (holding capacity) was determined by adding different weights of non-volatile solvents. The addition of powder and the trituration was continued until mortar contents start to look non adherent, free flowing dry powder [9].

Calculation of Load factor (Lf)

In an LS system, the amount of liquid retained by the carrier and coating materials depends on the excipient ratio (R), while maintaining acceptable flow and compression properties. The excipient ratio R of a powder is defined as the ratio between the weights of carrier (Q) and coating materials (q) present in the formulation. Preparation of an LS system with an acceptable flow rate and compressibility is possible when a maximum amount of retained liquid of the carrier material is not exceeded. This characteristic amount of liquid is termed as liquid load factor. The liquid Lf is defined as the weight ratio of the liquid medication (W) and carrier powder (Q) in the system. To calculate the loading factor, non-volatile solvent (480 mg to 961mg) was added to 1g carrier material and blended for 1 minute. The above procedure was repeated until a powder with acceptable flow rate was obtained [10].

Selection of coating material ratio based on flowability

A carrier material after holding maximum amount of solvent maintaining good flow property has to increase its flowability further by addition of coating material (Aerosil 200) in different ratios. Different ratios of coating materials are selected for a particular carrier material based on increased flowability which is the Excipient ratio R (carrier: coating ratio).

Evaluation of flowability (Φ-value) and compressibility (Ψ-value) of Liquisolid powders:

The flowability of the obtained mixtures, after determining the holding capacity of the excipients, was calculated by measuring the angle of repose, Hausner's ratio and the compressibility index.

Angle of repose:

The angle of repose was determined by the funnel method suggested by Newman. Angle of repose (θ) was determined by the following formula.

$$\theta = \text{Tan}^{-1} h/r \ldots\ldots (1)$$

Where, θ is Angle of repose, h is height of the cone and r is radius of the cone base

Compressibility index:

Carr's index was calculated from the following equation using the values of bulk density (ρ_b) and tapped density (ρ_t).

$$C = (\rho_t - \rho_b / \rho_t) \times 100 \ldots\ldots (2)$$

Hausner's ratio: Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's Ratio} = \rho_t / \rho_b \ldots\ldots\ldots (3)$$

Preparation of Liquisolid tablets

Desired quantity of DEM was dissolved in non-volatile solvent to prepare the drug solution. The mixture of carrier-coating materials (maize starch, MCC, Avicel PH 101, Avicel PH 102 and Prosolv SMCC 50 as the carrier materials and aerosol 200 as the coating material) was added to the liquid medication and blended in a mortar. The mixing procedure was conducted in three stages. In the first stage, drug was mixed slowly to allow uniform distribution of liquid medication. In the second mixing stage, carrier materials was added to the system and blended for 2 min and the liquid powder admixture was left undisturbed for approximately 5 min to allow the drug solution to be absorbed into the interior of the powder particles then the calculated quantities of coating material (Aerosil 200) was added. In the final stage, diluent Di-phosphate calcium (DCP) and 2% of talc and magnesium stearate as lubricants was added to the powder and mixed. The final mixture was compressed into tablets. Formulation of LSP compacts were prepared by using Prosolv SMCC 50 (co-processed excipient) as both carrier material and coating material. The mixture was directly compressed into tablets [11,12].

Table 1: Formulation of LS compacts of DEM

Formulation Code	Drug (mg)	Solvent (mg)	Carrier Material (Q)				Aerosil 200 (q)	Prosolv SMCC 50	DCP	Loading Factor (Lf)	Excipient ratio (R) (Q/q)	Tablet Wt. (mg)
			Maize Starch	MCC	Avicel pH 101	Avicel pH 102						
LS 1	75	175	241.8	-	-	-	48.36	-	9.83	0.72	5	550
LS 2	75	175	241.8	-	-	-	24.81	-	33.3	0.72	10	550
LS 3	75	175	241.8	-	-	-	16.1	-	42	0.72	15	550
LS 4	75	175	241.8	-	-	-	12	-	46.1	0.72	20	550
LS 5	75	175	241.8	-	-	-	9.6	-	48.6	0.72	25	550
LS 6	75	175	-	232.8	-	-	46.56	-	20.6	0.75	5	550
LS 7	75	175	-	232.8	-	-	23.2	-	44	0.75	10	550
LS 8	75	175	-	232.8	-	-	15.52	-	51.7	0.75	15	550
LS 9	75	175	-	232.8	-	-	11.6	-	55.6	0.75	20	550
LS 10	75	175	-	232.8	-	-	9.3	-	58	0.75	25	550
LS 11	75	175	-	-	225	-	45	-	30	0.77	5	550
LS 12	75	175	-	-	225	-	22.5	-	52.5	0.77	10	550
LS 13	75	175	-	-	225	-	15	-	60	0.77	15	550
LS 14	75	175	-	-	225	-	11.2	-	63.8	0.77	20	550
LS 15	75	175	-	-	225	-	9	-	61	0.77	25	550
LS16	75	175	-	-	-	200	40	-	60	0.87	5	550
LS 17	75	175	-	-	-	200	20	-	80	0.87	10	550
LS 18	75	175	-	-	-	200	13.3	-	86.7	0.87	15	550
LS 19	75	175	-	-	-	200	10	-	90	0.87	20	550
LS 20	75	175	-	-	-	200	8	-	92	0.87	25	550
LSP	75	175	-	-	-	-	-	100	45	1.75	-	400

Evaluation of LS compacts

The prepared LS compacts were evaluated for various tests such as weight variation, hardness, thickness and friability according to standard procedures [13,14].

Disintegration time

Disintegration time of tablets was determined in a tablet disintegration test apparatus, using 0.01 N HCl, 1000ml as disintegration medium at 37±2º C.

Drug content

20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 75 mg was weighed and dissolved in 10 ml of methanol and the volume was made to 100 ml with distilled water in a 100 ml volumetric flask. Dispersions were filtered and 1 ml aliquot was taken and diluted to 10 ml with 0.01 N HCl respectively. The concentration of the resultant solution was 10µg/ml. The absorbances of these solutions were determined at 327 nm against the blank. The percentage assay was calculated from the standard curve.

Content uniformity

The content of drug in each of 10 tablets taken at random was determined. Each tablet was powdered and transferred to 100 ml volumetric flasks containing solution of methanol. The flask is shaken to mix the contents thoroughly. The volume is made up to the mark with solution and filtered. One ml of the filtrate is suitably diluted and drug content is estimated at 327 nm using a double beam UV-visible spectrophotometer. This procedure is repeated thrice and the average value was calculated.

***In vitro* drug release study**

Dissolution studies of LS tablets were carried out in USP Apparatus II (Paddle type) (Electro Lab). Tablets were placed in the dissolution vessel containing 900 ml of 0.01NHCL maintained at 37±0.5°C and stirred at 50 rpm. Aliquots of 5 ml were withdrawn at specified time intervals for 60min and replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 327 nm.

Drug Excipient Interaction Study

The drug excipient interaction study was carried out by Fourier transform infrared (FTIR) (Shimadzu, India). Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} in a scan time of 12 minutes. The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in the compound.

Thermal analysis by DSC

DSC analysis was performed using TA Instruments Perkin-Elmer pyris differential scanning calorimeter (DSC). The instrument was calibrated with indium standard. 3-5 mg samples were weighed and placed in a closed, hermetic sample pans with pin hole. Thermograms were obtained by heating the sample at a constant rate 10ºC /min. A dry purge of nitrogen gas (50 ml/min) was used for all runs. Samples were heated from 0ºC to 210.0ºC. The melting point, heat of fusion, disappearance of the crystalline sharp peak of the drug and appearance of any new peak and peak shape were noted. The thermogram of the LSP optimized formulation was superimposed with that of pure drug.

Powder X-Ray diffraction analysis

The crystallinity of the prepared LSP optimized mixture was studied by XRD. The change in amount of crystallinity was studied. XRD analysis was performed using D-5000 Siemens X- ray diffractometer using Copper K α (λ = 1.5406 A°) radiation. The data were recorded over a scanning 2θ range of 5^0 to 50^0 at a step time of 0.045 steps/0.5 sec. The pure drug is analyzed by XRD in same manner and the peak intensity and presence of new peaks were noted. The diffractograms of the optimized LSP mixture was superimposed with that of pure drug.

Accelerated stability studies

The optimized formulation was subjected to stability studies at 40°C±2°C/75%±2% RH for period of one month. Each tablet was individually wrapped in aluminum foil and packed in ambered colored bottle and put at above specified condition in a humidity chamber for one month [9]. The tablets were analyzed for the hardness, disintegration time, drug content and in-vitro drug release.

RESULTS AND DISCUSSION:

Solubility Studies

The solubility study results given in Table 2 revealed that the solubility of drug was high in Span 80 (78.26 mg/ml) and Castor oil (67.63 mg/ml), based on that the combination of both the non-volatile liquids were used for studies and the solubility was found to be 400.96 mg/ml with the combination of these solvents.

Table 2: Solubility study of DEM

SI.No	Solvent	mg/ml
1	Distilled Water	0.187
2	PEG 600	11.42
3	PEG 400	11
4	Castor oil	67.63
5	Span 80	78.26
6	Tween 80	18.8
7	Glycerine	13.0
8	Transcutol	34.78
9	Olive oil	2.60
10	Liquid paraffin	2.12
11	Sesame oil	14.78
12	Castor oil + Span 80	400.96

Note: Values are expressed as Mean ±SD, n=3

Holding capacity of carrier material and determination of liquid load factor (L_f):

From the Table 3 flowability and load factor of a particular carrier material like Maize starch, MCC, Avicel PH 101, Avicel PH 102 and Prosolv SMCC 50 were used in different amounts until every carrier material exhibits required flowability. However a constant weight (175 mg) of combination of solvents (Span80+Castor oil) was used based on the solubility of 75mg dose of DEM. The drug was dispersed in the solvent and carrier material was added at a different amount until a required flowability was achieved. Maize starch, Micro Crystalline cellulose, Avicel PH 101 and Avicel PH 102 had a flowability of 35, 34, 32, 30 at a carrier weights of 241.81 mg, 232.8 mg, 225 mg and 200 mg respectively indicating good flow property and with Prosolv SMCC 50 at a weight of 100 mg had flowability of 23 indicating excellent flow were optimized.

Table 3: Holding capacity, Flow Property and Liquid Load factor of carrier materials with combination of Liquids

S.no	Carrier Material (Q)	Solvent (W) (mg)	Carrier Weight (Q) (mg)	Flowability (Φ)	Lf= W/Q
1	Maize Starch	Span 80 + Castor oil (175)	210.2	36	0.74
2	Maize Starch	Span 80 + Castor oil (175)	241.81	35	0.72
3	MCC	Span 80 + Castor oil (175)	199	35	0.76
4	MCC	Span 80 + Castor oil (175)	232.8	34	0.75
5	Avicel PH 101	Span 80 + Castor oil (175)	200.8	33	0.78
6	Avicel PH 101	Span 80 + Castor oil (175)	225	32	0.7
7	Avicel PH 102	Span 80 + Castor oil (175)	178	31	0.87
8	Avicel PH 102	Span 80 + Castor oil (175)	200	30	0.87
9	Prosolv SMCC 50	Span 80 + Castor oil (175)	79	24	1.80
10	Prosolv SMCC 50	Span 80 + Castor oil (175)	100	23	1.75

Evaluation of flow properties of LS formulations

From the table 4 the particles with high absorption properties due to a porous surface should be used as carrier material, such as Maize starch (LS1-LS5), MCC (LS6- LS10), Avicel PH 101 (LS11-LS15) and Avicel PH 102 (LS16- LS20). Increasing the moisture content of carrier materials may result in decreased powder flowability [15]. The coating material is required to cover the surface, and further maintain the powder flowability. Accordingly, the coating material should be a very fine and highly adsorbent silica powder, thus Aerosil 200 was selected as a coat material [16]. DEM liquisolid compacts were prepared with different excipient ratios (R= 5, 10, 15, 20 and 25). All the formulations (LS1-LS20) were studied for their flow properties like angle of repose, bulk density, tapped density, hausner's ratio and compressibility index. Angle of repose < 30^0 indicate free flow property while angles > 40^0 indicate poor flow [17]. From the above formulations it was observed that the LS16 formulation has least flow property (25.20±0.25) having free flow property when compared to the other formulations, from the table it was found that there is a relationship between powder excipient ratio (R) and the angle of repose. The powder excipient ratio (R) is directly proportional to the angle of repose i.e., when the excipient ratio increased the angle of repose increased. The bulk and tap densities of DEM liquisolid powders were found to be 0.29±0.28 to 0.45±0.25 g/cm^3 for bulk density and 0.34±0.18 to 0.53±0.15 g/cm^3 for tap density. The powder has a good flowability when the hausners ratio is lower than 1.2 while if the ratio is more than 1.2 indicates bad. From table 4 it was observed that formula LS17 has 1.1±0.78 Hausner ratio indicating good flow when compared to other formulations. Compressibility index was found to be least for LS8 formulation (11.2±0.16) indicates good flow property when compared to other formulations. All the formulations were within the Pharmacopoeial limits.

These formulations were compressed into tablets using 11.9mm punch. The tablets were evaluated for Physico-chemical parameters.

Table 4: Flow property evaluation studies

Formulation no.	Angle of repose (θ)	Bulk density (gm/c^3)	Tapped density (gm/c^3)	Hausner ratio	Compressibility index (%)
LS1	30.19±0.34	0.35±0.37	0.41±0.35	1.12±0.32	14.6±0.26
LS2	31.28±0.29	0.35±0.12	0.39±0.29	1.11±0.28	11.4±0.19
LS3	32.6±0.44	0.32±0.25	0.36±0.37	1.12±0.27	12.5±0.34
LS4	33.20±0.53	0.31±0.28	0.35±0.35	1.12±0.31	12.9±0.21
LS5	34.8±0.51	0.31±0.10	0.35±0.25	1.12±0.21	12.9±0.34
LS6	30.22±0.59	0.30±0.14	0.34±0.37	1.13±0.34	13.3±0.29
LS7	31.18±0.32	0.29±0.29	0.35±0.33	1.13±0.38	15.6±0.26
LS8	32.21±0.29	0.35±0.12	0.38±0.36	1.12±0.24	11.2±0.16
LS9	33.19±0.34	0.34±0.27	0.41±0.25	1.13±0.30	13.6±0.24
LS10	33.01±0.38	0.29±0.10	0.37±0.16	1.14±0.27	13.3±0.34
LS11	28.8.17±0.3	0.36±0.36	0.43±0.10	1.15±0.28	14.4±0.33
LS12	29.22±0.22	0.38±0.10	0.46±0.39	1.15±0.39	15.0±0.28
LS13	29.8.18±0.2	0.41±0.29	0.48±0.22	1.16±0.33	14.0±0.18
LS14	30.21±0.36	0.45±0.25	0.53±0.15	1.15±0.26	15.7±0.21
LS15	30.92±0.35	0.42±0.25	0.48±0.25	1.14±0.48	12.5±0.14
LS16	25.20±0.25	0.33±0.25	0.39±0.74	1.18±0.74	15.38±0.2
LS17	26.06±0.15	0.32±0.14	0.38±0.15	1.10±0.78	15.7±0.24
LS18	27.85±018	0.35±0.17	0.42±0.15	1.20±0.12	16.66±0.2
LS19	28.95±0.54	0.37±0.25	0.46±0.74	1.24±0.32	13.56±0.3
LS20	29.89±0.74	0.29±0.28	0.34±0.18	1.17±0.38	14.70±0.2
LSP	18.8±0.25	0.30±0.14	0.37±0.4	1.23±0.5	10.12±0.35

Note: *Values are expressed as Mean ±SD, n=3*

Evaluation of Liquisolid tablets

All the formulations were evaluated for weight variation, hardness, disintegration time, friability, drug content and content uniformity. The tablets should have sufficient hardness to resist the breakage during handling and at the same time it should disintegrate after swallowing. From table 5 formulation LS5 has the highest hardness (4.5±0.23 kg/cm^2) and lowest was (3.7±0.34 kg/cm^2) for LS3. Thickness of the tablets ranged from 3.2±0.0.65mm to 3.9±0.24mm. Disintegration time ranged from 2-3 mins. Friability for all the formulations was within 1.12% which is acceptable for disintegrating tablets, drug content was 96% to 98% and content uniformity is 95% to 99%. It was observed that, all the formulations were as per official requirements (Indian Pharmacopoeia 1996).

Table 5: Evaluation parameters of liquisolid compacts

Formulation code	Weight variation (mg)	Hardness (Kg/cm^2)	Thickness (mm)	Disintegration time (min)	Friability (%)	Drug content (%)	Content uniformity (%)
LS1	549.5±1.33	3.7±0.33	3.63±0.46	2.46±0.44	0.64±0.01	97.78±0.65	97.5±0.35
LS2	548.9±1.27	3.9±0.38	3.45±0.35	2.38±0.37	0.72±0.03	96.66±0.86	95.8±0.24
LS3	549.02±1.14	3.7±0.34	3.82±0.26	3.03±0.37	0.65±0.02	98.72±0.58	97.4±0.26
LS4	547.98±1.18	3.8±0.19	3.63±0.38	3.07±0.45	0.83±0.02	95.69±0.60	96.2±0.19
LS5	549.63±1.38	4.5±0.23	3.54±0.25	2.39±0.42	0.76±0.02	96.54±0.58	95.2±0.37
LS6	548.35±1.23	4.2±0.21	3.83±0.44	2.48±0.49	0.86±0.03	98.84±0.39	99.4±0.32
LS7	548.52±1.11	4.2±0.24	3.52±0.33	2.55±0.45	0.78±0.01	97.56±0.48	98.7±0.16
LS8	548.23±1.14	3.9±0.22	3.44±0.34	2.57±0.36	0.87±0.03	97.47±0.73	98.2±0.18
LS9	548.28±1.32	4.1±0.36	3.57±0.28	2.49±0.42	0.12±0.02	98.56±0.63	96.4±0.21
LS10	547.94±1.24	4.0±0.29	3.52±0.39	2.56±0.38	0.95±0.04	98.88±0.55	98.7±0.24
LS11	546.91±1.43	3.9±0.31	3.54±0.28	2.29±0.39	0.96±0.02	96.56±0.57	97.4±0.26
LS12	547.73±1.36	4.2±0.25	3.54±0.33	2.38±0.34	0.85±0.03	98.54±0.67	96.5±0.31
LS13	551.09±1.24	4.1±0.29	3.42±0.39	2.46±0.31	0.96±0.02	98.59±0.75	99.5±0.28
LS14	547.81±1.43	3.9±0.41	3.53±0.17	2.41±0.29	0.88±0.01	98.58±0.84	95.6±0.22
LS 15	550.28±1.05	4.2±0.52	3.8±0.12	2.41±0.19	0.78±0.02	97.23±0.52	99.22±0.78
LS16	548.65±0.95	4.4±0.65	3.6±0.39	2.43±0.33	0.79±0.04	97.52±0.98	98.65±0.14
LS17	549.33±0.99	3.9±0.58	3.2±0.24	2.48±0.28	0.88±0.08	98.52±0.14	97.95±0.23
LS18	549.29±1.02	4.0±0.74	3.8±0.85	2.47±0.52	0.88±0.01	98.65±0.12	98.75±0.85
LS19	547.38±1.05	4.2±0.84	3.2±0.65	2.45±0.26	0.92±0.03	98.47±0.74	99.85±0.45
LS20	549.68±0.20	4.1±0.57	3.9±0.24	2.45±0.71	0.79±0.04	97.24±0.96	99.65±0.52
LSP	399.98±0.1	4.1±0.29	3.2±0.52	3.10±0.26	0.52±0.18	99.87±0.27	99.45±0.74

Note: *Values are expressed as Mean ±SD, n=3*

***In vitro* Drug release Study**

Comparison of Optimized Liquisolid Compacts with Pure Drug and LS Formulations

Dissolution studies were carried out with USP apparatus II (paddle type). All the formulations were subjected to *in vitro* dissolution studies in 900ml of 0.01 N HCl. The dissolution studies of pure drug and LS compacts were performed and compared. Dissolution rate of pure DEM was less because of hydrophobic nature of drug as it falls in to BCS class II. With each carrier the formulations with excipient ratio (R= carrier/ coating material) of 25 showed better drug release in 45 min when compared to other excipient ratios. As the excipient ratio with coating material was increased the flow property enhanced, but increments of coating material results in lesser dissolution rate due to its hydorophobic nature. With starch as carrier material LS1, LS2, LS3, LS4 and LS5 releases were 34.1±0.85%, 39.4±0.69%, 45.7±0.25%, 58.5±0.36% and 65.8±0.21% respectively. With liquisolid tablets containing MCC as carrier material (LS6-LS10), LS10 was considered as best formulation to produce better release (78.9±0.14% in 45 min) when compared to other formulations. With Avicel PH102 as carrier material (LS11-LS15), formula LS14 and LS15 showed the highest percent drug release 75±0.28 % and 86±0.34 % in 45min respectively. The drug release profiles from LS16 to LS20 containing Avicel PH102, the dissolution rate was found to better with LS20 (95.1±0.18 % in 45 min) with a excipient ratio of 25, when compared to other formulations [18].

Formulation LSP showed 99.8±0.45% of drug release in 30 min. Hence these optimised formulations from each carrier material were compared with pure drug release. The comparative dissolution release of pure drug, LS5, LS10, LS15, LS20 and LSP are shown in figure 1. All the formulations showed maximum release in 45 min but LSP showed in 30 min. The pure drug release was 11.15±0.4% in 45 min.

The reason behind this is that when the powder excipient ratio increased the release will increase as the coating material decreased. LSP containing Prosolv SMCC 50 is a unique combination of MCC and Colloidal Silica thus having enough flowability and does not require coating material for further flowability. Thus LSP was optimized. Thus, *in vitro* dissolution studies indicated the importance of liquisolid compacts to enhance the solubility and dissolution rates.

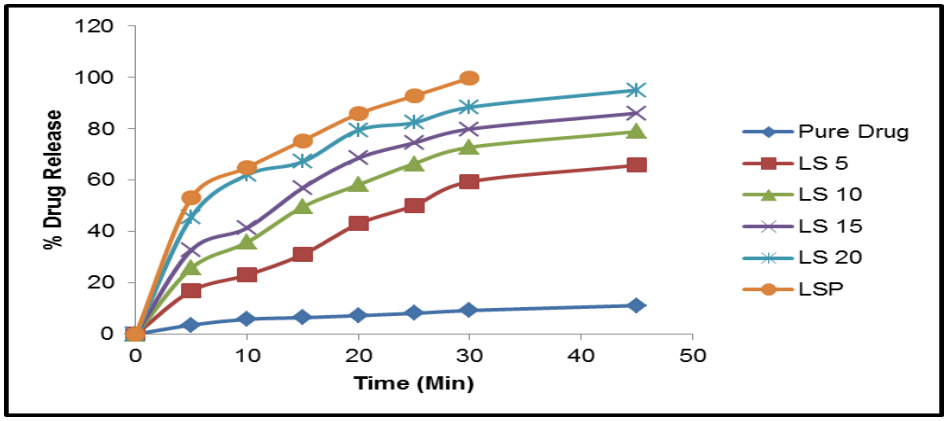

Fig.1: Comparison Of Optimized Liquisolid Compacts with Pure Drug

Drug- excipient compatibility study by FTIR

DEM compatibility with excipient was studied by FTIR. The FTIR spectra of pure drug (shown in figure 2), peaks (3200cm^{-1}, -N=H vibration indicating presence of amine group; 2800cm^{-1}, C-H vibration indicating presence of alkane; 1740 cm^{-1}, C=O vibration indicating presence of ketone) were similar in formulation (LSP) spectra (shown in figure3) suggesting that there is no interaction and the pure drug is not altered functionally. The FTIR studies from the spectra confirmed the absence of any chemical interaction between the drug and excipients.

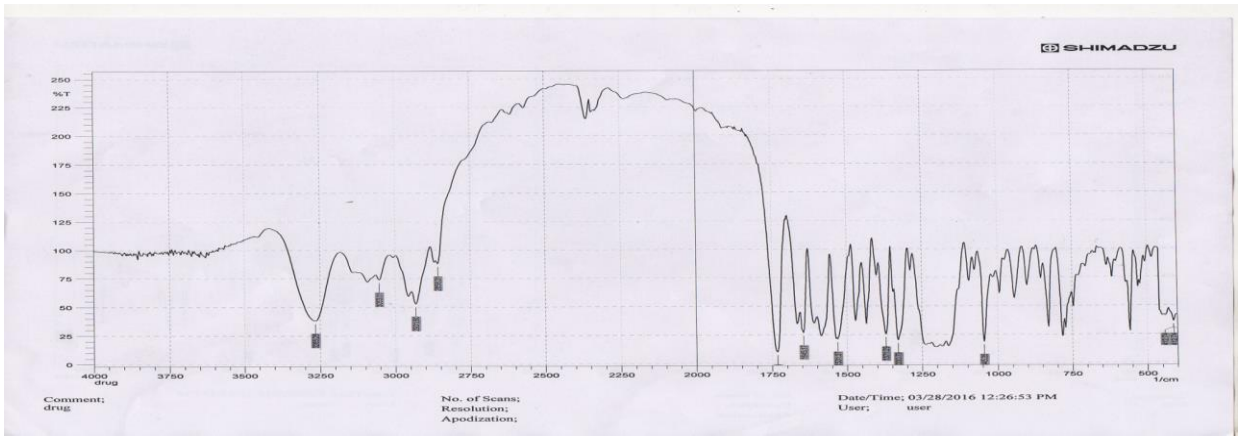

Fig. 2: FTIR graph of pure drug

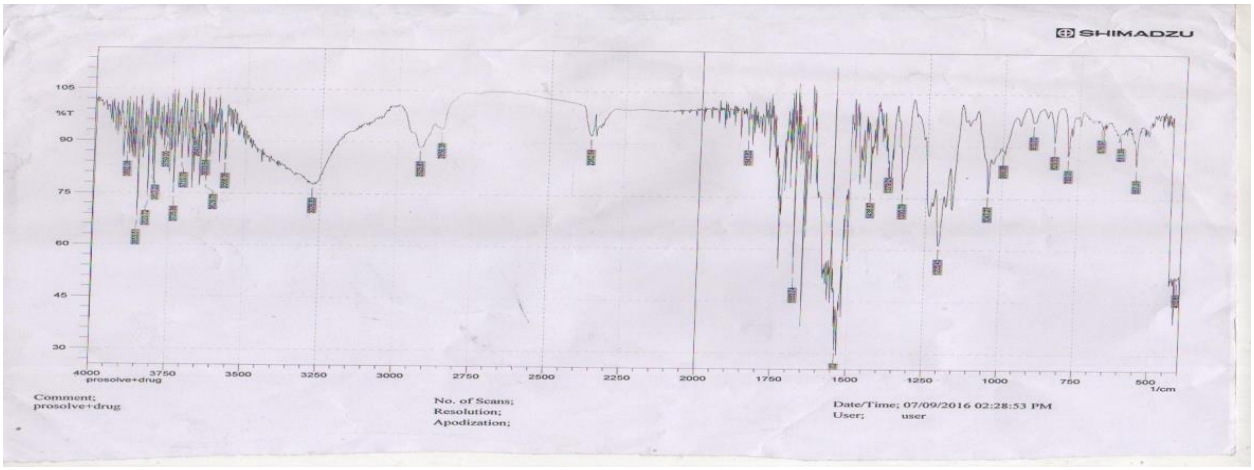

Fig. 3: FTIR graph of optimized formulation (LSP)

Powder X-Ray diffraction analysis

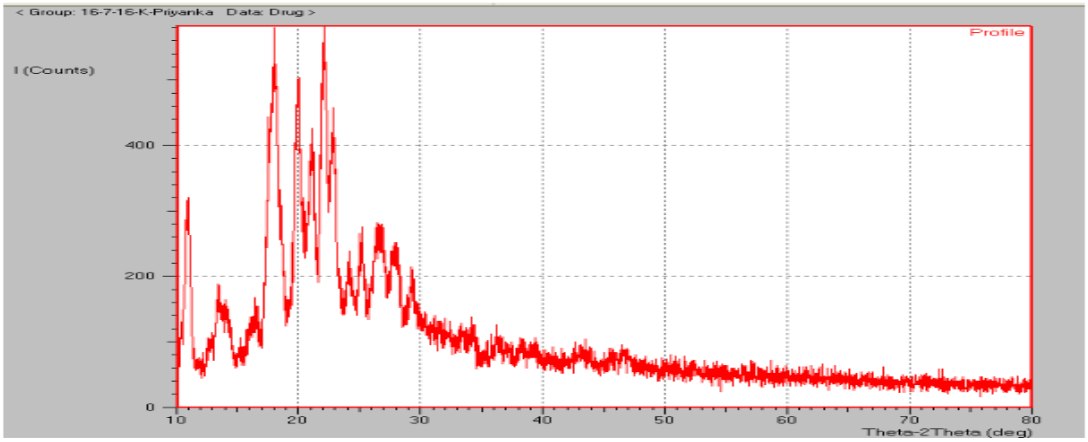

Fig.4: XRD studies of pure drug

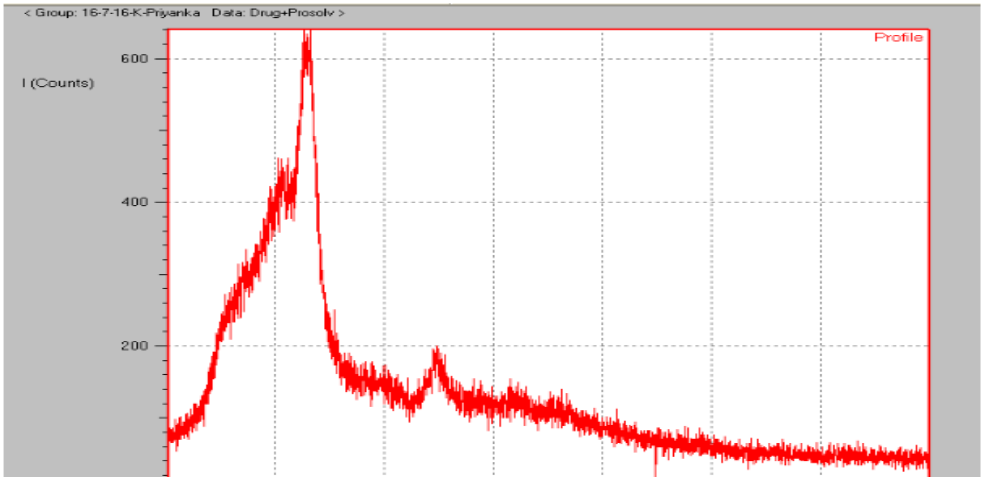

Fig.5: XRD graph of LSP

From the XRD studies shown in figure 4 for pure drug and figure 5 for optimised formulation LSP, revealed a reduction in peak intensity of LSP formulation when compared with XRD of pure drug. The characteristic peaks identified in the drug XRD was not detected in formulation. Decrease in the intensities and less number of peaks was probably due to change in crystal habit or conversion to an amorphous form. Reduced crystalline properties when compared to pure drug could account for increased dissolution.

THERMAL ANALYSIS BY DSC

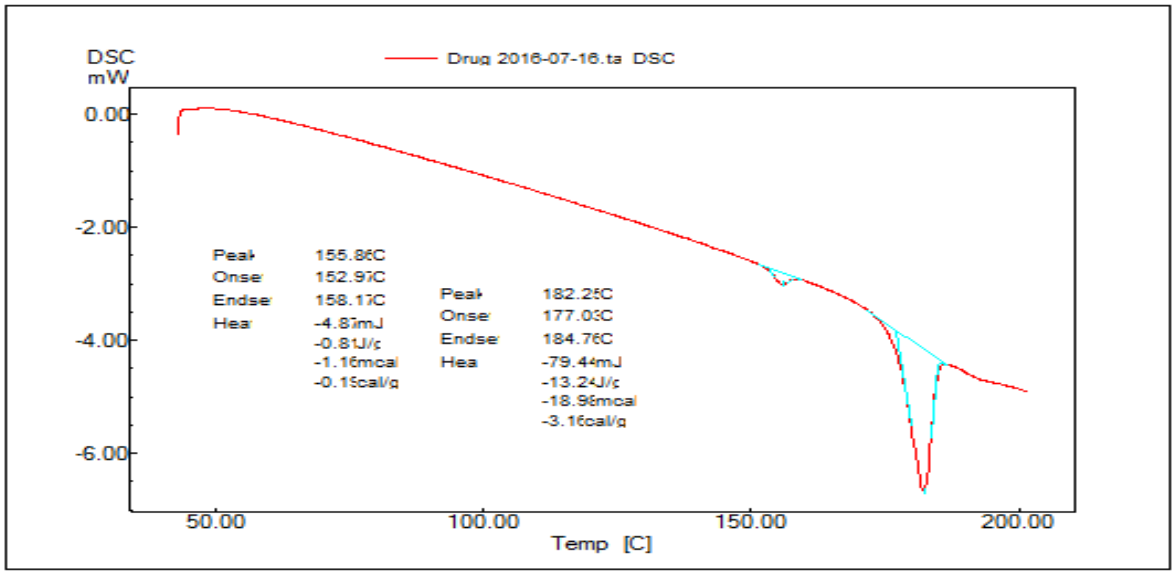

Fig. 6: DSC graph of pure drug

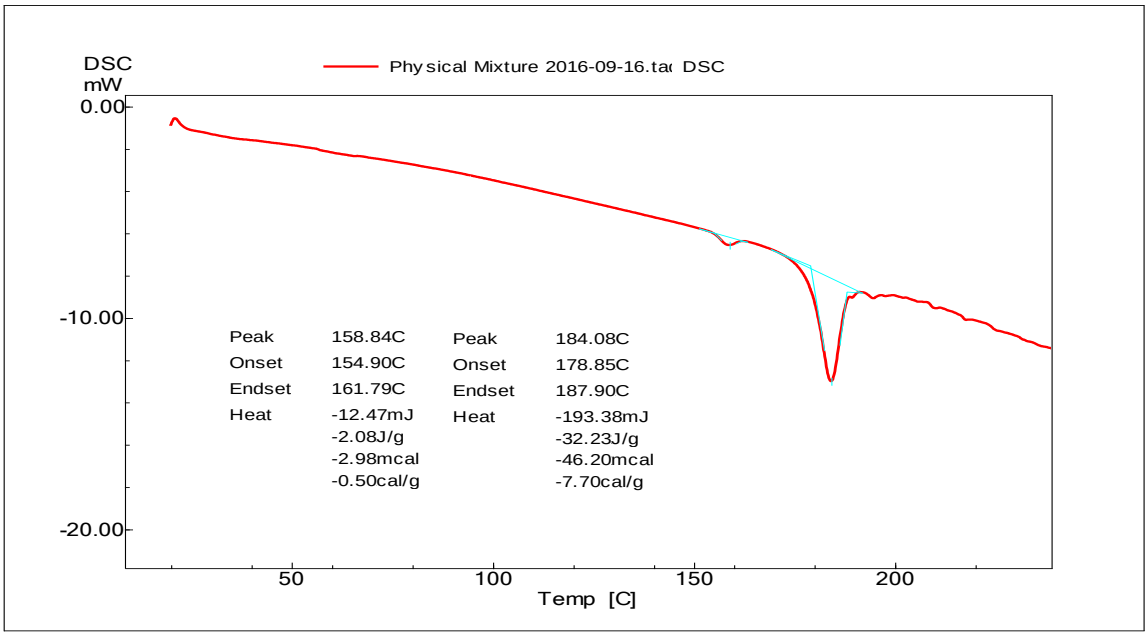

Fig. 7 : DSC graph of LSP

Table 5: Stability study of optimized formulation (LSP)

Parameters	0 (Initial)	1st week	2nd week	1month
Appearance	No change	No change	No change	No change
Drug content (%)	99.25±0.35	99.01±1.20	98.85±1.2	98.68±1.76
Hardness (Kg/cm^2)	2.5±0.12	2.5±0.27	2.5±0.58	2.5±0.29
Disintegration time (mins)	3.10±0.24	3.10±0.57	3.10±0.25	3.10±.027

DSC of the pure drug (figure 6) showed a sharp peak at 180ºC. DSC of LSP (figure 7) showed peak characteristic of the drug with no additional peaks. So, it can be concluded that the drug and carrier showed no interaction.

Stability study

Accelerated stability studies were performed at 40ºC±2ºC/75%±2% RH for a period of one month for optimised formulation LSP and the results are tabulated in table 5.

The optimized LSP formulation was subjected to various quality control parameters like appearance, drug content, hardness and disintegration time at respective time intervals. The results were similar to the initial data indicating the formulation was stable.

CONCLUSION:

The present study was to improve the dissolution rate of dabigatran etexilate mesylate utilizing the approach of liquisolid compacts technology using various carriers. It was envisaged that this technique would improve the solubility of dabigatran etexilate mesylate, since it is poorly soluble drug (BCS class II). Various non-volatile solvents (PEG 600, PEG 400, Castor oil, Span 80, Tween 80, Glycerine, Transcutol, Olive oil, Liquid Paraffin, Sesame oil) were used and maximum solubility was observed in combination of span80 and castor oil (400.96ug/ml). Various carrier materials like Maize starch, MCC, Avicel pH101, Avicel pH102 were preliminary studied for holding capacity of nonvolatile solvent and maximum holding capacity has been selected for each carrier material (0.72, 0.75, 0.77, 0.87 and 1.75) respectively. Aerosil 200 as the coating material was added in a ratios (R) of 5, 10, 15, 20 and 25. The Liquisolid tablets were evaluated for weight variation, friability, drug content, hardness, thickness and content uniformity. All the parameters were within the specification limits. LSP formulation containing Prosolv SMCC 50 showed higher dissolution profiles (99 % in 30 min) than pure drug (11.15 %). The optimized formulation of dabigatran etexilate mesylate was characterized by X-ray diffraction, FTIR, and DSC

studies. No interaction was observed. XRD data revealed that the formulation showed reduced crystallinity when compared to pure drug. Stability studies indicate the formulations were stable. In conclusion it can be stated that the objective of the study was achieved in improving the solubility of the dabigatran etexilate mesylate using liquisolid compact technology.

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