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HYDROPHILIC CARRIER BASED AMALGAMATION TO IMPROVE THE *IN-VIVO* PERFORMANCE: DABIGATRAN AS A MODEL DRUG

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ABSTRACT

Context: The present study aimed to investigate the processability of API-Hydrophilic carrier composite into Multiple unit pellet system (MUPS) formulation and therefore to reveal the benefits of the composite formation in *IN-VIVO* performance. **Objective**: Coated pellets, consisting of active layer embedded on acidic base pellets, were manufactured by wurster process in fluid bed coating. Release profile as well as *IN-VIVO* performance of the formulation with reference product was compared. **Method:** Simple and economical spray drying method was developed for the formulation of Dabigatran etexilate mesylate solid dispersion (SD). Initial characterization of pure drug, physical mixtures, reference product and solid dispersions were carried out by *in vitro* dissolution, dissolution efficiency, permeation study, wetting study, solubility study, FT-IR, differential scanning calorimetry (DSC) and *IN-VIVO* bioavailability study. **Result and Discussion:** DSC study showed that Dabigatran etexilate mesylate was present in its amorphous form. FT-IR study showed there is no incompatibility between any polymeric systems with drug components. Improvement in the solubility and dissolution rate was observed for all samples. During ageing study, almost no decrease of *in vitro* drug dissolution was observed as compare with freshly prepared solid dispersions. Solid dispersions showed more than 75% Dabigatran etexilate mesylate release after 45 min during dissolution test. Significant difference between reference product and present formulation was observed in *IN-VIVO* study as shows more than threefold increase in bioavailability in Rabbit plasma. **Conclusion:** The result showed

that the wurster process of a liquid feed with hydrophilic carrier based dispersion is an attractive and promising alternative to obtain enhanced solubility and bioavailability. Thus, present study demonstrated the high potential of wurster process technique for obtaining stable solid dispersions of poorly water-soluble drugs using various solubilizing polymers.

KEYWORDS: Multiple unit pellet system, Bioavailability, Dissolution rate, Wurster technique, Hydrophilic polymers, Differential scanning calorimetry (DSC), FT-IR.

INTRODUCTION

Dabigatran etexilate is a pro-drug of dabigatran, a representative of a new therapeutic class of direct thrombin inhibitors. Thrombin is a serine protease produced by the proteolitic cleavage of prothrombin. It is a final mediator in the formation of fibrin in the coagulation cascade and a potential platelet activator. As a specific and reversible inhibitor of thrombin, dabigatran has a potential to improve the management of thromboembolic disorders. The structure of dabigatran molecule was designed to improve the in vivo potency of binding with thrombin.[1,2,3]

The chemical name (IUPAC) of dabigatran etexilate mesylate is ethyl N-{[2-({[4-((E)- amino {[(hexyloxy) carbonyl] imino} methyl) phenyl] amino} methyl)-1-methyl-1H- benzimidazol-5-yl] carbonyl}-N-pyridin-2-yl-ß-alaninate methanesulfonate corresponding to the molecular formula C35H45N7O8S. The CAS number of dabigatran etexilate mesylate is 593282-20-3. The molecular mass is 723.86 for the salt and 627.75 for the free base.[1,2,3]

Dabigatran etexilate mesylate is a yellow-white or yellow non-hygroscopic crystalline powder. The apparent partition coefficient of the neutral form (free base) is log P = 3.8, and the dissociation constants are pKa1 = 4.0 ± 0.1 (benzimidazol moiety) pKa2 = 6.7 ± 0.1 (carbamaic acid hexyl ester moiety). Solubility is strongly pH dependent with increased solubility at acidic pH. A saturated solution of the drug substance in pure water was found to have a solubility of 1.8 mg/ml. Because of the low solubility of dabigatran etexilate mesylate in water (pH 3 to pH 7.5) and the high intrinsic passive permeability, dabigatran etexilate mesylate is considered to be a Class II drug substance according to the Biopharmaceutical Classification System and selected for present investigation as a model drug.[1,2,3,4,5]

Dabigatran etexilate mesylate (BIBR1048MS) is a double pro-drug with low solubility at pH ≥ 3. Dabigatran etexilate base is quickly absorbed (tmax 1 hour in fasted state) and converted by esterase-catalyzed hydrolysis to the active moiety dabigatran (BIBR953ZW).

Therefore, various formulation approaches have been followed to improve the dissolution rate as well as the bioavailability of Dabigatran etexilate mesylate.

Solid dispersion was selected for evaluation as an alternative drug delivery system to enable a higher drug loading per unit dose. SD of Dabigatran etexilate mesylate has been focused on water-soluble carrier only. Solubilisation of poorly soluble drug such as Dabigatran etexilate mesylate within the GIT is considered a crucial step in the oral absorption process. The selection of suitable carriers has extensively been reviewed. The use of water-soluble carriers such as Kolliphor and Gelucire class carriers with solubilising properties have been studied as tools to enhance the solubility of poorly water soluble drugs.

A method that could produce solid dispersion of drug in a dosage form in one step would be valuable for making solid dispersion. Fluidized-bed is capable of spraying solution onto the granular surface of excipients or sugar spheres to produce granules ready for tableting or drug-coated pellets for encapsulation in one step. [7] In this study, Dabigatran was selected as a model drug with poor water-solubility to examine the possibility of employing fluidized-bed system to prepare solid dispersion in a pellet form.

The spray-drying technique is extensively used in the pharmaceutical industry to produce dispersions, micro particles, as an alternative to emulsification methods. This technique transforms the liquid feed into a dry powder in one step and is feasible for the scaling-up of the microencapsulation, continuous particle processing operations and can be applied to a wide variety of materials. Spray drying can be also used to enhance the solubility and improve particulate design. Through proper formulation and selection of excipients, the SD technology is applicable to compounds with a broad range of physiochemical properties.[8,9,10)]

Solvent evaporation method by spray drying technique was chosen as the appropriate method to develop the SD. The primary objective of this study was to optimize SD formulation using attainable manufacturing process as well as pharmaceutically acceptable excipients. The second goal was to adsorb dispersion on base pellets using wurster process, characterize the formulated solid dispersion (SD) for solubility/bioavailability enhancement.[7,8,9,10,11,12,13]

MATERIALS AND METHODS

Materials

Dabigatran etexilate mesylate was gifted from Alembic Research Center, Gujarat, INDIA. Gelucire 50/13 (Stearoyl Macrogoglycerides EP, solid pastilles) and Gelucire 44/14 (Lauroyl Macrogoglycerides EP, semi-solid) were generous gift from Gattefosse, Mumbai, INDIA. Kolliphor P 188 and Kolliphor P 407 were obtaining from BASF Corporation, Mumbai, INDIA. All other chemicals and solvents were of analytical grade.

Methods

Phase Solubility Study

Phase Solubility study was conducted as per the method reported by M. Cirri et.al.[14] Drug and carrier as per the specified drug: carrier ratio were weighed accurately and added to pure drug with water in screw capped bottles. All the bottles were shaken in incubator shaker at 24°C and 37°C for 24 h. The container with drug and water was used as control. After 24 h the solutions were filtered using (0.4 nm) filter paper and the filtrates were diluted. The absorbances were measured in spectra at 325 nm. From the absorbance the solubility of the drug were calculated in various carrier based system.

Preparation of Physical Mixtures

Physical mixtures containing the base pellets, drug, carriers and other excipients were prepared in the same proportions used for SD preparation in order to allow comparison between them. The ingredients were slowly mixed with a spoon in a glass flask. These physical mixtures were tested for their physical properties and Drug solubility.

Preliminary trials for selection of Hydrophilic polymer

In this study, Hydrophilic polymers were used to formulate solid dispersion. Different grade of Gelucire and Kolliphor and combination of same were evaluated for the preparation of solid dispersion. Different Drug: polymer ratio was selected based on phase solubility data and saturated solubility study data.

Preparation of feed dispersion for seal coating and drug layering

After several trials, it was found that ethanol was able to adequately dissolve both API as well as hydrophilic polymer and easy to feed into wurster process. Add polymers slowly in this solvent and continue stir for 30 minutes or till clear solution is obtained. Add Talc (ultramicronized) to above solution with continuous stirring for at least 15 minutes or till

homogeneous dispersion is obtained. Drug dispersion system prepared using above prepared dispersion and add drug slowly till dispersion become homogenous.

Wurster Process

The wurster process was performed in a laboratory-scale fluid bed coater (Model: Lab scale, Cronimech FBD, Mumbai, INDIA) equipped with a wurster assembly. Load the citric acid pellets (50# retain) into the FBC with the Wurster Column. Adjust the Inlet Air Damper sufficiently to fluidize the Pellets and start the atomization air. Commence spraying of seal coating dispersion as product temperature reaches around 30°- 40°C with continuous stirring and maintain process parameters at optimum range. Follow same procedure for the Drug layering process.

Optimum batch was finalized to capsule filling in size 00 capsules and characterized for further study.

Characterization of SD

Saturation Solubility

Saturation solubility studies were conducted as per the method reported by J.Hecq et.al.[15] To evaluate the increase in solubility of Dabigatran etexilate mesylate after spray drying (with hydrophilic carriers) or only by the presence of excipients (physical mixtures), saturation solubility measurements were conducted. The known excess (approximately 50 mg) of Dabigatran etexilate mesylate, equivalent quantity of pellets and physical mixtures was added to 10 ml of dissolution media. Samples were rotated at 20 rpm in a water bath (37 °C) for 48 hours. The samples were then filtered, suitably diluted and analyzed by UV spectrophotometer at 325 nm.

Drug Content

Pellets equivalent to 75 mg of Dabigatran were weighed accurately and dissolved in a suitable quantity of methanol. The solutions were filtered through a membrane filter (0.45 mm). The drug content was determined at 325 nm by UV spectrophotometer (Shimadzu 1800) after suitable dilution.

Determination of Percent Yield

The percent yield of Dabigatran etexilate mesylate pellets was determined by using the following formula:

Percent yield= (Weight of prepared pellets/weight of drug + carriers)* 100

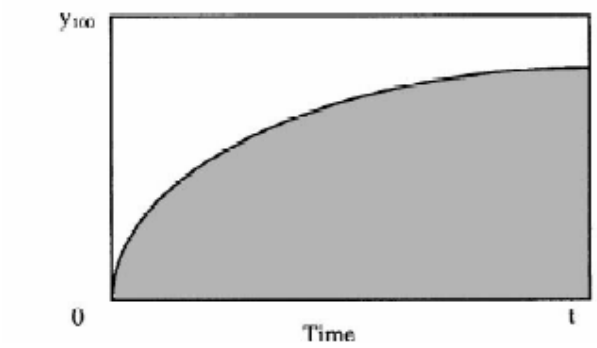
***In vitro* Drug Release Study**

Dissolution is a critical parameter for Dabigatran etexilate mesylate, as it is a poor water-soluble drug. Dissolution studies were carried out for all the developed formulations. Dissolution of marketed Dabigatran etexilate mesylate formulation was also carried out for comparison. Dissolution test was performed using USP apparatus type I (Basket) for 100 min. Samples of Dabigatran pellets equivalent to 75 mg of the drug in Capsules were added to the dissolution medium (900 ml of 0.01 N Hydrochloric acid, pH 2.0 at a temperature of 37 °C ±0.5 °C), which was stirred at 100 rpm. At suitable time intervals (10, 20, 30 and 45 min), 10 ml samples were filtered through 0.45 µ filter and analysed at λ max of 325 nm using UV visible spectrophotometer. Equal volume of fresh medium prewarmed at the same temperature was added in to the dissolution medium after each sampling to maintain its constant volume throughout the test. Each test was performed in triplicate and calculated mean values of cumulative drug release were used while plotting the release curves.

Dissolution efficiency (%)

Dissolution efficiency (DE) represents the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100 % dissolution in the same time.

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\%$$



Where y is the drug percent dissolved at time t.

Differential scanning calorimetry

Modulated DSC analysis was conducted using a Shimadzu Instruments Model TA- 60 (Japan) equipped with a refrigerated cooling system. Samples were weighed to 5 ± 0.5 mg in aluminum crimped pans. Samples were heated at a rate of 10 °C/min from 30 to 300 °C with modulation temperature amplitude of 0.5 ºC and a modulation period of 40 seconds for all

studies. Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 40 ml/min. The thermogram for pure Dabigatran and various polymer based spray dried dispersions of Dabigatran were obtained.

FT-IR study

Drug-excipients interactions play a vital role in the release of drug from formulation. The pure Dabigatran etexilate mesylate and its mixture with polymer and drying aids were mixed with IR grade KBr and were scanned over a range of 400-4000 cm^{-1} using FTIR instrument (FTIR-1700, Shimadzu, Kyoto, Japan).

***IN VIVO* study**

Performed Open label, Balanced, Randomized, Two-Treatment, Two-sequence, Two-Period, Single dose, Crossover design, Oral Bioavailability study of Two different formulation of Dabigatran (Test Vs. reference) in normal healthy Albino rabbits subject in group of 6 under fasting condition. After administration of a dose of Dabigatran, about 1ml of blood sample was collected through marginal ear vein up to 24hr.

Study protocol

The protocol for in vivo pharmacokinetic study of Dabigatran was approved, under protocol no. **IP/PCOL/FAC/20/36**, by the Institutional Animal Ethics Committee (IAEC), Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India. This study was carried out to predict the comparative in vivo drug release behaviour of Dabigatran pellets (optimized batch) and reference product. 12 Albino rabbits, having weight between 2.0 to 2.5 Kg, were taken for the study. Rabbits were randomly divided in two groups- one group for suspension of reference product and another group for suspension of test product. Animals were kept under fasting condition overnight with free access of water. Suspension (in water) of both Dabigatran pellets (optimized batch) and reference product were orally administered to the animals in dose equivalent to 70 mg/kg body weight of Dabigatran. After oral administration of both the suspensions to the respective groups of animals, 1.0 ml of blood sample were collected from the marginal ear vein at 0, 0.25, 0.5, 0.75, 1, 1.25, 2, 3, 6, 12 and 24 h time intervals.

Assay method

The drug from the plasma samples are extracted by optimizing a method for extraction. 500µl rabbit plasma is taken in a screw-capped plastic tube and 2.5 ml of Methanol is added in

plasma sample and vortexes for 1 min to extract Dabigatran. Blood samples were centrifuged at 10,000 rpm for 10 min at 4 °C in refrigerated centrifuge (BL-150R, Biolab, Mumbai, India) to separate the plasma from other blood components. Plasma samples were stored at −20 °C until further HPLC analysis for the drug content. The developed method for the determination of drug is optimized for chromatographic conditions. All solutions were filtered through a 0.45 µm filter before injection into the column. The flow rate was set at 0.8 mL/min with a mobile phase of (Methanol: Water) (70: 30 v/v). The mobile phase was filtered under vacuum through a 0.45 µm modified hydrophilic PTFE membrane and degassed ultrasonically for 30 min prior to use. The column temperature was maintained at 30 °C. Peak areas (in volts) were used as the measured analytical response, with detection at 325 nm.

RESULTS

Phase solubility study

Phase solubility study of Dabigatran etexilate mesylate was conducted as per the method reported by M. Cirri et.al. Table: 1 gives the phase solubility data. The solubility of Dabigatran etexilate mesylate was found to be increasing constantly on increasing the concentration of the carrier when physically mixed with the drug. The negative ΔG values of the formulations indicate the spontaneity of the process at low temperature. The thermodynamic Parameters results proved the solubilisation effect of the carrier on the drug.

Table 1: Phase solubility data of Dabigatran etexilate mesylate physical mixture.

Polymeric System	Slope	Intercept	Ka	Log Ka	ΔG Kj/mol
Kolliphor P 188	0.828	2.271	2.120	0.326	-0.443
Kolliphor P 407	0.935	2.357	6.102	0.786	-1.067
Gelucire 44/14	0.910	3.440	2.939	0.468	-0.636
Gelucire 50/13	0.850	3.440	1.647	0.217	-0.295

Characterization of Solid Dispersions

Saturated solubility study, Drug content and Percent yield

Aiming to characterize the SD obtained with highest solubility and acceptable yield, several physical-chemical analyzed were carried out, like solubility, practical yield and drug content. All parameters for various polymeric systems were described in table 2. The solubility of Dabigatran etexilate mesylate was determined in 0.01 N Hydrochloric acid at 37 °C (table 2). In general, the presence of polymers increased the solubility of Dabigatran etexilate mesylate.

In every polymeric system polymer concentration increases solubility comparatively increased in a small scale.

Table 2: Selection parameters for formulations (Solubility, % yield).

Sr no.	Batch no.	Polymer	Drug-polymer ratio	Saturated Solubility (mg/ml)	% yield
1	Pure drug	-	-	2.30	-
2	G50/3	Gelucire 50/13	1:3	8.40	85 %
3	P188/3	Kolliphor P188	1:3	7.90	86 %
4	P407/3	Kolliphor P407	1:3	7.70	86 %
5	G44/3	Gelucire 44/14	1:3	8.20	91 %
6	P188:P407/2:1	Drug: Kolliphor P188: Kolliphor P407	1: (2:1)	8.10	85 %
7	P188:P407/1:2	Drug: Kolliphor P188: Kolliphor P407	1: (1:2)	7.80	90 %
8	P188:P407/1.5:1.5	Drug: Kolliphor P188: Kolliphor P407	1:(1.5:1.5)	7.60	92 %
9	-	RLD	-	3.40	-
10	P188/1	Drug: Kolliphor P188	1:1	4.4	85 %
11	P188/2	Drug: Kolliphor P188	1:2	5.9	82 %

***In vitro* dissolution study**

Table 3 shows the release data and profile of Dabigatran etexilate mesylate SD. The interpretation of the data and the profile showed that the cumulative percentage release (CPR) from Dabigatran etexilate mesylate SD were higher than pure drug. The CPR from the batches was also found to be increased on increasing the concentration of the carrier incorporated in formulations.

% CPR, Mean Dissolution Time and %DE considered as characteristics parameters for obtained formulations. Results obtained from the batches prepared from various polymers are summarized in Table 3 and plotted in figure 1. As we increased the ratio of polymer compare to drug it increased the *in vitro* dissolution of Dabigatran etexilate mesylate in comparison with pure drug and market product. From the above data, ratio of 1:2:1 (Drug: Kolliphor P 188: Kolliphor P 407) in solid dispersion selected for optimization.

Dissolution efficiency

In vitro drug release data obtained from various batches summarized in table 3 describe that dissolution efficiency of SD was much higher compare to pure drug and marketed formulation. All data were summarized in table 3.

Table 3: Comparison of *in vitro* drug release, MDT & %DE @ 30 min from different formulations.

Sr No.	Time (Min)	Cumulative Percentage Release (CPR)*						
		Batch No						
		P188/3	P407/3	G50/3	G44/3	P188:P407/2:1	P188:P407/1:2	Reference
1	0	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
2	10	7.333 (13.995)	8.200 (36.585)	3.400 (31.126)	5.533 (48.840)	8.833 (16.804)	4.600 (11.503)	5.267 (17.124)
3	20	71.967 (4.822)	69.800 (7.316)	40.200 (13.495)	43.133 (11.180)	78.767 (3.715)	58.267 (3.438)	59.567 (4.872)
4	30	87.800 (4.030)	85.257 (3.617)	68.533 (3.984)	70.300 (2.725)	96.067 (1.968)	80.867 (1.491)	86.833 (1.393)
5	45	96.267 (2.018)	96.867 (4.172)	91.633 (2.770)	93.400 (2.702)	99.333 (3.022)	92.367 (4.604)	94.333 (2.124)
Mean Disso. Time		0.29 hr	0.30 hr	0.37 hr	0.38 hr	0.28 hr	0.33 hr	0.32 hr
%DE at 30 min		60.80	58.67	49.86	50.18	64.47	58.37	61.37

***** Value in parenthesis expressed as RSD

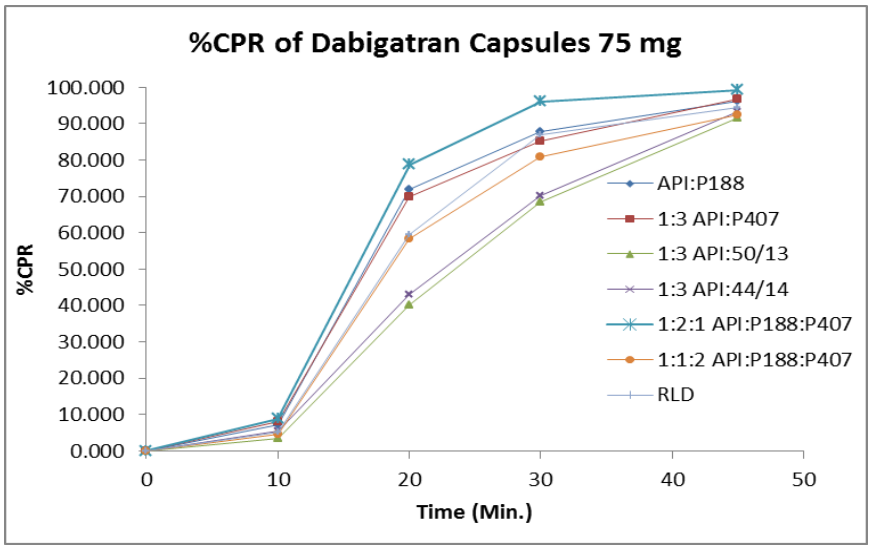


Figure 1: Comparison of *in vitro* drug release of different formulations.

Wetting study

The funnel method of Dabigatran etexilate mesylate and selected batches were investigated as per the method reported by M .C. Gohel et.al.[16] and Sunil Kumar et.al.[17] respectively and findings are shown in Table 4. The wetting time of the pure drug was found higher indicating poor wettability of the drug. The wetting time of samples was found to be very less compare to pure drug. This behaviour may be attributed to increased wettability by the action of hydrophilic carrier used in the formulation.

Permeation study[18]

The data for Cellulose nitrate membrane was given in the Table 4. It was observed that the amount of drug permeated from selected batches in both membranes was found to be higher than pure drug. The results can be considered as the evident for increase in release rate of Dabigatran etexilate mesylate from Solid dispersion embedded pellet formulation.

Table 4: Permeability and Wettability data from different drug-polymer combination.

Batch	Drug: polymer ratio	Permeability (mg/ml/hr)		Wettability	
		Cellulose acetate membrane		Funnel method (min)	
		SD	PM	SD	PM
Pure drug	-	0.016		60	
	1:2:1	0.030	0.004	35	58
	1:1:2	0.026	0.003	42	54
	1:1.5:1.5	0.028	0.003	34	52

DSC study

DSC analysis demonstrated that Dabigatran etexilate mesylate was rendered entirely amorphous in these formulations as indicated by the absence of the melting endotherm peak, which is seen with the Dabigatran etexilate mesylate pure drug. In the binary mixture of drug and polymer suppression of endothermic peak was seen.

FT-IR study

The FTIR spectra of Dabigatran etexilate mesylate showed characteristic peaks of Dabigatran etexilate mesylate in formulation.

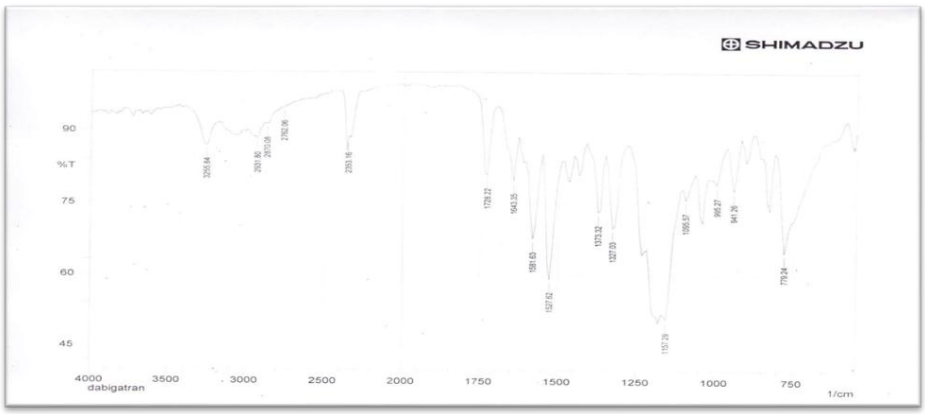


Figure 2: FT-IR Spectra of Dabigatran.

***IN VIVO* study**

The collected plasma samples were analyzed using laboratory developed validated HPLC method. Pharmacokinetic parameters describe in table no 5 reveals more than 3 fold increase in the Cmax of test formulation in comparison of reference formulation. From the above

discussion it is clear that improvement in solubility and dissolution rate of Dabigatran from solid dispersion has been reflected in increase in Cmax and AUC in comparison to reference formulation. The study revealed improvement in the bioavailability of Dabigatran from solid dispersions.

The comparative plasma concentration time profile of optimized batch and reference product in rabbits were plotted and are shown in Fig. 3,while pharmacokinetic parameters were calculated using PK Solver. PK Solver is a freely available add-in program in Microsoft Excel for pharmacokinetic and pharmacodynamics data analysis. A marked increase of more than threefold in peak plasma concentration (C) was observed after administration of Dabigatran pellets (2.028 µg/ml ± 2.15 µg/ml) as compared to Reference product (0.602 ± 0.83 µg/ml). Peak plasma concentration was achieved with in (T) 90 min in both cases. A marked increment (more than threefold) in bioavailability of Dabigatran was observed after oral administration of Dabigatran pellets, with an increase in AUC max (11.478 µg h/ml vs. 3.787 µg h/ml) as compared to Reference product. The increase in bioavailability could be due to an increase in saturation solubility and dissolution velocity of the Dabigatran pellets.

Table 5: Pharmacokinetic parameters of Test vs Reference.

Parameters	Test	Reference
Dose	70 mg/kg	70mg/kg
Cmax	2.028 ± 2.15 µg/ml	0.602 ± 0.83 µg/ml
Tmax	1.5 hr	1.5 hr
AUC_{0-t}	11.478 µg*hr/ml	3.787 µg*hr/ml
$AUC_{0-\infty}$	11.478 µg*hr/ml	3.787 µg*hr/ml
$AUC_{t-\infty}$	0.000 µg*hr/ml	0.000 µg*hr/ml
Kel	0.211	0.175
$T_{1/2}$	3.289 hr	3.949 hr

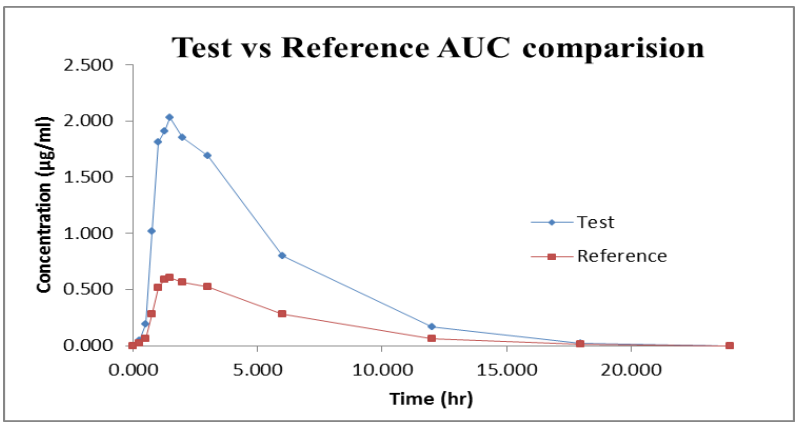


Figure 3: AUC comparison Test vs Reference.

CONCLUSION

In this study, Dabigatran solid dispersions were successfully prepared by wurster process using Hydrophilic polymers. Drug: Kolliphor P188: Kolliphor P 407 in 1:2:1 ratio exhibited better solubility & Bioavailability of Dabigatran as compared to other polymeric system. Formulation was successfully optimized and was further characterized for in vitro drug release as well as in vivo bioavailability study. Results of DSC and FTIR are showing compatible drug-polymer system after process which resulted in increase in the solubility as well as in vitro dissolution. Significant enhancement in bioavailability of Dabigatran was observed after oral administration of Dabigatran pellets as compared to Reference product. The results show that the spray-drying process for producing a solid dispersion of Dabigatran etexilate mesylate starting from liquid feeds to pellets is an attractive and promising alternative to increase drug solubility, together with adequate pharmacotechnical properties. It can also be concluded that the best condition to obtain SD containing Dabigatran etexilate mesylate, the best solubility/bioavailability was the one performed with 1:2:1 (Dabigatran etexilate mesylate: Kolliphor P 188: Kolliphor P 407) combination. Thus, the results obtained in the study are in support for the application of Hydrophilic carrier system in wurster process in the preparation of Dabigatran solid dispersion.

Declaration of interest: The authors report no conflicts of interest.

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