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FORMULATION AND EVALUATION OF DABIGATRAN ETEXILATE MESYLATE CAPSULES

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ABSTRACT

Dabigatran etexilate mesylate is a drug used as anti-coagulant in deep vein thrombosis. Dabigatran etexilate mesylate has less solubility inorder to increase the solubility of Dabigatran etexilate mesylate was formulated as pellets by taking tartaric acid pellets as a core pellets (tartaric acid pellets create acid environment which initiates drug to dissolve). The present study was under taken to design the formulation and evaluation of the Dabigatran etexilate mesylate immediate release pellets by fluid bed technology. The present invention of Dabigatran etexilate mesylate capsules provides pellets in capsules and its compositions containing Dabigatran etexilate mesylate and excipients. Drug and excipient studies were done at 40 ± 2°C and 75 ± 5% RH for 30 days with Drug : Excipient ratio 1:1 for different excipients by FT-IR Spectroscopy and no characteristic change was observed. Various formulations were formulated with different polymers like hydroxyl propyl cellulose, povidone k30 and Formulations were analyzed for different parameters like UV absorption studies, Drug content estimation, In-vitro drug release profile and Formulation F6 was optimized based on comparative In-vitro dissolution profiles and by statistical evaluation (similarity and dissimilarity) with that of innovator product PRADAXA.For optimized Formulation F6 accelerated stability studies were done for three months at 40°C & 75% RH no significant change with respect to physical appearance, disintegration time, assay and dissolution.

KEY WORDS: *Dabigatran Etexilate Mesylate, Immediate Release Pellets, Fluid Bed Technology, Povidone K30, Hydroxy Propyl Cellulose*

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

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selected for present investigation as a model drug.[1,2,3,4,5]

Preformulation Studies

Preformulation involves the application of biopharmaceutical principles and physicochemical parameters of drug substance were characterized with the goal of designing optimum drug delivery system. It is important part in drug development process. The information relating to drug development acquired during this phase is used for making critical decisions in further stages of development. Characterization of drug is very important step at preformulation phase of product development followed by studying the properties of excipients and their compatibility.

Drug-Excipients compatibility Studies

FT-IR studies: In this study, potassium bromide disc method was employed. IR studies of pure drug and physical mixtures of drugs and excipients were done. The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was then compressed into transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer (Schimadzu FT IR – 8700) using sample holder and spectrum was recorded.

Stability studies: The drug and excipient compatibility study was done at accelerated conditions for short period of time (40 ± 2˚C / 75 ± 5 % RH) with periodic observation and physical evaluation. Samples of dabigatran etexilate mesylate and individual excipients were intimately mixed in equal parts (1:1) ratio by weight and filled in glass vials. Samples were physically observed at the end of 15days and 30days. Result were shown in Table. No.7.4.

Standard Calibration Curve

Identification of Identification of λ_{max} of Dabigatran Etexilate Mesylate by Uv-Spectroscopy:

Ultraviolet Absorption:

Wavelength Range: 200–400 nm

Standard Solution: 0.1 mg/mL of USP Dabigatran Etexilate Mesylate in methanol. Use sonication to dissolve.

Sample Solution: Transfer the contents of capsules, equivalent to 100 mg of Dabigatran Etexilate Mesylate, to a 100mL volumetric flask, add about 75 mL of methanol and sonicate for about 5 min with intermittent shaking. Cool, dilute with methanol to volume, further dilute with methanol to obtain a solution containing 0.1 mg/mL of Dabigatran Etexilate Mesylate, and pass through a nylon filter of 0.45µm pore size.

Acceptance Criteria: Meet the requirements: The retention time of the major peak of the Sample solution corresponds to that of the standard solution, as obtained in the assay.

Preparation of 0.01 N HCl (pH 2.0) Buffer:

About 0.085 ml of hydrochloric acid was dissolved in 100ml purified water. Later it was made up to volume with water in 1000ml volumetric flask.

Preparation of standard stock solution:

50 mg of pure Dabigatran etexilate mesylate was accurately weighed and transferred to 50ml of volumetric flask containing 0.01N HCL.

Procedure for plotting calibration curve of pure drug:

From the standard stock solution 0.5ml ,1ml ,1.5ml, 2ml, 2.5ml dilutions were made in 10ml volumetric flask and volume was made up to the mark with 0.01N HCl (pH 2.0) buffer to obtain concentration in range of 5-25 µg/ml. The spectra were recorded, absorbance were measured at 224nm and calibration curve was plotted.

Manufacturing Procedure for Dabigatran Etexilate Mesylate Immediate Release Pellets by Fluid Bed Technology:

Preparation of Seal Coating Solution:

Step 1: Take required quantity of isopropyl alcohol and acetone in beaker to it add accurately weighed povidone K-30 under continuous stirring.

Step 2: To the solution from step 1 add accurately weighed quantity of polyethylene glycol under continuous stirring and stirring was continued to 30minuutes.

Preparation of Drug Loading Solution:

Step 1: Take required quantity of isopropyl alcohol and acetone in beaker to it add accurately weighed povidone K-30 under continuous stirring.

Step 2: To the solution from step 1 add accurately weighed quantity of polyethylene glycol under continuous stirring.

Step 3: To the solution from step 2 add accurately weighed quantity of Dabigatran Etexilate Mesylate under continuous stirring and stirring was continued to 30minuutes.

Step 4: Solution from step 3 was passed through ASTM # 40 sieve.

Seal Coating Manufacturing Process for Dabigatran Etexilate Mesylate IR Pellets by Fluid Bed Technology:

Step 1: Tartaric acid pellets were loaded in fluid bed chamber

Step 2: Seal coating solution was sprayed under controlled process parameters

Step 3: Check the weight of the pellets after attained required weight gain drying was done for 15minutes

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Table 1. FORMULATION TABLE FOR DABIGATRAN ETEXILATE MESYLATE IR PELLETS (F1-F7):

Formulation Code	F1 (mg/cap)	F2 (mg/cap)	F3 (mg/cap)	F4 (mg/cap)	F5 (mg/cap)	F6 (mg/cap)	F7 (mg/cap)
Seal Coating							
Tartaric acid Pellets 500	203.629	0	0	0	0	0	152.63
Tartaric acid Pellets 700	0	203.629	203.629	152.63	152.63	152.63	0
Povidone K-30	9.697	9.697	0	7.268	0	7.268	7.268
HPC	0	0	9.697	0	7.268	0	0
PEG 400	0.485	0.485	0.485	0.363	0.363	0.363	0.363
IPA	67.631	67.631	67.631	50.69	50.69	50.69	50.69
Acetone	67.631	67.631	67.631	50.69	50.69	50.69	50.69
Drug Loading							
Seal Coated pellets	213.811	213.811	213.811	160.261	160.261	160.261	160.261
Dabigatran etexilate mesylate	172.95	172.95	172.95	172.95	172.95	172.95	172.95
Povidone K-30	30	30	0	30	0	30	30
HPC	0	0	30	0	30	0	0
PEG-400	1.5	1.5	1.5	1.5	1.5	1.5	1.5
IPA	408.9	408.9	408.9	499.1	499.1	499.1	499.1
Acetone	408.9	408.9	408.9	499.1	499.1	499.1	499.1
ProtectiveCoating							
Opadry white	10.289	10.289	10.289	10.289	10.289	0	0
Lubrication							
SLS	0	0	0	0	0	8.289	8.289
Talc	0	0	0	0	0	2	2

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Table 2. No Seal Coating Manufacturing Process Parameters of Dabigatran Etexilate Mesylate Immediate Release Pellets by Fluid Bed Technology

Time (mins)	Inlet temperature (°C)	Product temperature (°C)	Outlet temperature (°C)	Atomization air (bar)	Blower drive speed (%)	Air flow (cfm)	Spray pump speed (rpm)	Inlet RH (%)
05	60	43	40	1.0	55	46	2	14
30	60	39	39	1.0	55	43	9	12
60	60	47	41	1.0	58	45	12	10
120	60	48	43	1.0	59	47	12	10
180	60	42	40	1.0	57	46	9	10

Table. No-3 Drug Loading Manufacturing Process Parameters of Dabigatran Etexilate Mesylate Immediate Release Pellets by Fluid Bed Technology

Time (mins)	Inlet temperature (°C)	Product temperature (°C)	Outlet temperature (°C)	Atomization air (bar)	Blower drive speed (%)	Air flow (cfm)	Spray pump speed (rpm)	Inlet RH (%)
05	60	43	40	1.0	55	46	2	14
30	60	39	39	1.0	55	43	6	12
60	60	47	41	1.0	58	45	9	10
120	60	48	43	1.0	59	47	15	10
180	60	42	40	1.0	57	46	12	10

Step 1: Seal coated pellets were loaded in fluid bed chamber
Step 2: Drug loading solution was sprayed under controlled process parameters
Step 3: Check the weight of the pellets after attained required weight gain drying was done for 15minutes
Lubrication: Drug loaded pellets were lubricated with accurately weighed required quantities of sodium lauryl sulphate and talc.
Capsule Filling: Required quantity of lubricated pellets were filled in capsule size '1' cellulose capsules.
Weight of empty size '1' cellulose capsule = 75mg
Fill weight for each capsule = 375mg
Target weight of the capsule = 450mg

Evaluation Parameters

Disintegration Test:[50]

Six capsules were taken randomly from each batch and placed in USP disintegration apparatus baskets, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37°C and observed over the time described in the individual monograph. To fully satisfy the test the capsules disintegrate completely into a soft mass having no palpably firm pellets. Results were shown in Table. No-7.9.

Particle size:[50]

Particle size analysis is a technical procedure which determines size range or mean size of particles in the powder. A typical sieve analysis involves the nested column of sieves with wire mesh cloth. The individual sieve weight is noted. A representative weighed sample is poured into the top sieve which has the largest screen openings. Each lower sieve in the column has smaller openings than the one above. At the base is a round pan, called the receiver. The column is typically placed in a mechanical shaker. The shaker shakes the column, usually for some fixed amount of time. After the shaking is complete the material on each sieve is weighed. The weight of the sample of each sieve is then divided by the total weight to give a percentage retained on each sieve. The size of the average particle on each sieve is then analyzed to get a cut-off point or specific size range, which is then captured on a screen. Results were shown in Table. No-7.7.

Assay Procedure

Preparation of mobile phase: Methanol and water were mixed in the ratio of 70:30 and filtered through 0.45µm membrane filter and degassed in a sonicator for 10 minutes.

Preparation of Standard solution

The stock solutions of Dabigatran etexilate mesylate (1000µg/ml) was prepared by dissolving appropriate amount of analyte in diluent. Working standard solution was prepared by mixing above stock

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solution of Dabigatran with final concentration of 20µg/ml, respectively.

Preparation of Test Solution:

Sample solution of a concentration of 20µg/ml of Dabigatran Etexilate Mesylate was prepared by using diluents from stock solution (1000µg/ml).

Water content by KF:

The Water Determination Test (Karl Fischer Method) is designed to determine water content in substances, utilizing the quantitative reaction of water with iodine and Sulphur dioxide in the presence of a lower alcohol such as methanol and an organic base such as pyridine.

Take 20ml of methanol for water determination in the dried titration vessel, and titrate with water determination TS. Weigh accurately a suitable quantity of the sample containing 10－50 mg of water, transfer the sample quickly into the titration vessel, add an excessive and definite volume of water determination TS, stir for 30 min, protecting from atmospheric moisture, and then titrate the solution with Water Methanol Standard Solution under vigorous stirring. Results were shown in Table. No-7.8.

Formula

$$F = \frac{\text{Weight of water taken in g x 1000}}{\text{Volume of KF reagent consumed in mL}}$$

Acceptance criteria: Not more than 4.0% (w/w)

Dissolution:

The dissolution studies of the prepared capsules were carried using Electro lab apparatus I (basket). Dissolution was performed in 900 ml 0.01 N HCl (pH 2.0) Buffer in at 37 ±0.5°C at 100 rpm. An auto sampler, coupled to the dissolution apparatus was programmed to withdraw and replace 10 ml of the dissolution media at 10, 20, 30 and 45minutes

Independent Model Method (Data Analysis)

Similarity Factor (f2):

As the name specifies, it stresses on the comparison of closeness of two comparative formulations. Generally similarity factor in the range of 50-100 is acceptable according to US FDA. It can be computated using the formula

$$f2 = 50 \times \log \{[1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

Where, n is the number of dissolution sample times, R_t and T_t are the individual or mean percent dissolved at each time point, t, for the reference and test dissolution profiles, respectively.

The similarity factor should be between 0 and 100. It is 100 when two comparative groups of reference and test are identical and approaches 0 as the dissimilarity increases.

Difference Factor (f1):

Difference factor focuses on the difference in percent dissolved between reference and test at various time intervals. It can be mathematically computed by using

$$f1 = \{[\Sigma_{t=1}^{n} |R_t - T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100$$

Therefore the factors directly compare the difference between percent drug dissolved per unit time for a test and a reference product.

Similarity factor of 50-100 ensures sameness of two products

Difference factor of 0-15 ensures minor difference between two products.

Prior to in vivo study, comparison of in vitro dissolution profiles using similarity and difference factors may be the promising surrogate.

Stability Studies:[51][52]

Table. No-4 Storage Conditions in Stability Studies

Study	Storage condition	Minimum time period covered by data at submission
Accelerated	40ºC ± 2 ºC/ 75% RH ± 5% RH	30, 60 and 90 days

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RESULTS

Preformulation Studies: Evaluation of Drug Characterization of Dabigatran Etexilate Mesylate

Table. No- 5.Evaluation of Drug Characterization Dabigatran Etexilate Mesylate

S. No	Test	Specifications	Result
1	Description	Yellow white to yellow powder	Yellow white
2	**Organoleptic Properties** Color Odour	 Yellow white Odourless	 Yellow white Odourless
3	**Physical characteristics** Solubility Loss on drying(LOD) Water content by KF Related substances(RS) ✓ Individual impurity ✓ Total impurity	 Freely soluble in methanol and slightly soluble in ethanol and isopropanol Not more than 1.0%w/w Not more than 1.0%w/w Not more than 0.15 Not more than 0.15	 Complies 0.17%w/w 0.28 0.14 0.13
4	Identification by HPLC	The retention time of major peak in the chromatogram of the sample preparation shall correspond to standard preparation	Complies
5	Heavy metals	Not more than 10ppm	7ppm
6	Assay	NLT 98.0%w/w & NMT 102%w/w	99.25%w/w

Evaluation of Micromeritic properties of Dabigatran Etexilate Mesylate (API)

Table. No- 6. Micromeritic Properties of Dabigatran Etexilate Mesylate (API)

S. No	Parameters	Average ± S.D
1.	Angle of repose	50º ± 1
2.	Bulk density (BD)	0.77 ± 0.05 g/ml
3.	Tapped density (TD)	1.04 ± 0.72 g/ml
4.	Hausner's ratio (HR)	1.35±0.023
5.	Result	Very poor flow

Marketed Product Characterization

The marketed sample studied on the bases of physical characterization, its drug release pattern in the dissolution, was replicated in our formulation. The main criterion is to replicate the dissolution profile of the marketed sample so that there will be a proper correlation between ours and marketed product.

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Table. No- 7. Marketed Product Characterization and Physical Evaluation:

Formulation Parameters	
Name of the Product	PRADAXA 150mg
Distributed By	Boehringer Ingelheim Pharmaceuticals
Dosage Form	Capsules
Route of Administration	Oral
Label Claim	150mg
Shelf Life	3years

Drug & Excipient Compatibility Studies of Dabigatran Etexilate Mesylate IR Pellets

It was determined as as per procedure given in experimental session. The following table illustrates results.

Table No-8. Drug & Excipient Compatibility Studies of Dabigatran Etexilate Mesylate IR Pellets:

S. No	API &EXCIPIENTS	Ratios	40^{0}C/75%RH	40^{0}C/75%RH	
			15 days	30 days	Conclusion
1	Dabigatran Etexilate Mesylate +	1:1	NC	NC	Compatible
2	Dabigatran Etexilate Mesylate + Tartaric Acid Pellets	1:1	NC	NC	Compatible
3	Dabigatran Etexilate Mesylate + Polyvinylpyrrolidone (Povidone K-30)	1:1	NC	NC	Compatible
4	Dabigatran Etexilate Mesylate + Hydroxy Propyl Cellulose	1:1	NC	NC	Compatible
5	Dabigatran Etexilate Mesylate + Polyethylene Glycol 400	1:1	NC	NC	Compatible
6	Dabigatran Etexilate Mesylate + Sodium Lauryl Sulphate	1:1	NC	NC	Compatible
7	Dabigatran Etexilate Mesylate + Talc	1:1	NC	NC	Compatible
8	Dabigatran Etexilate Mesylate + Opadry white	1:1	NC	NC	Compatible

NC- No change

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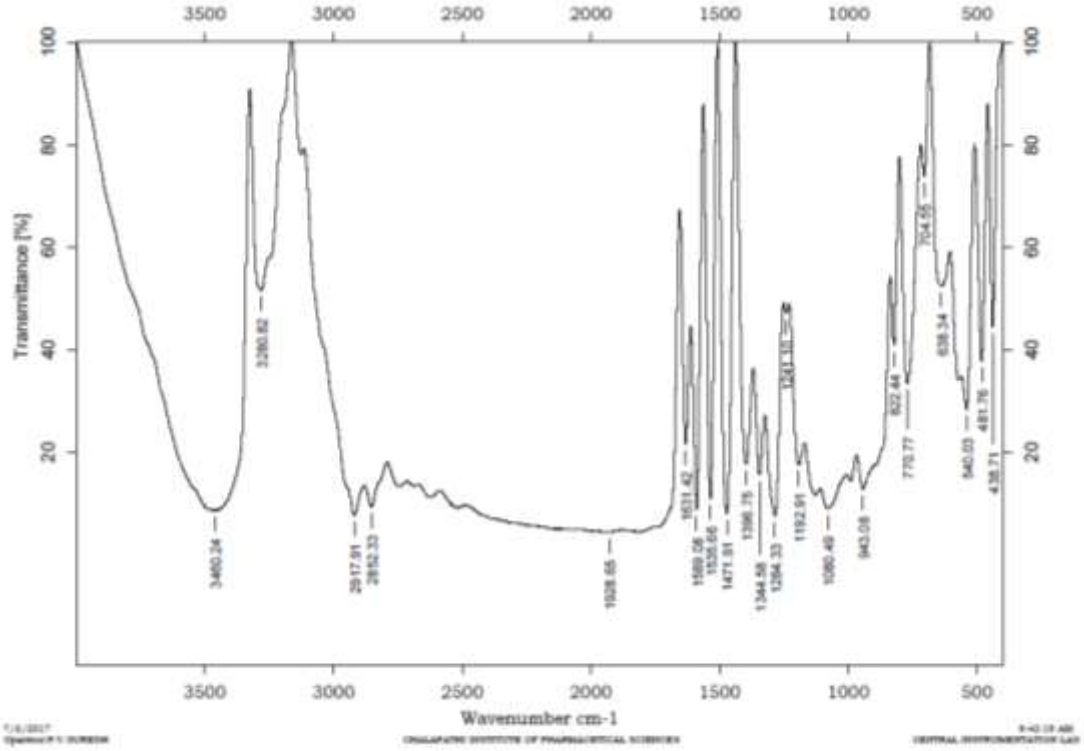
Fig. no-1 FT-IR Spectrum of Physical Mixture

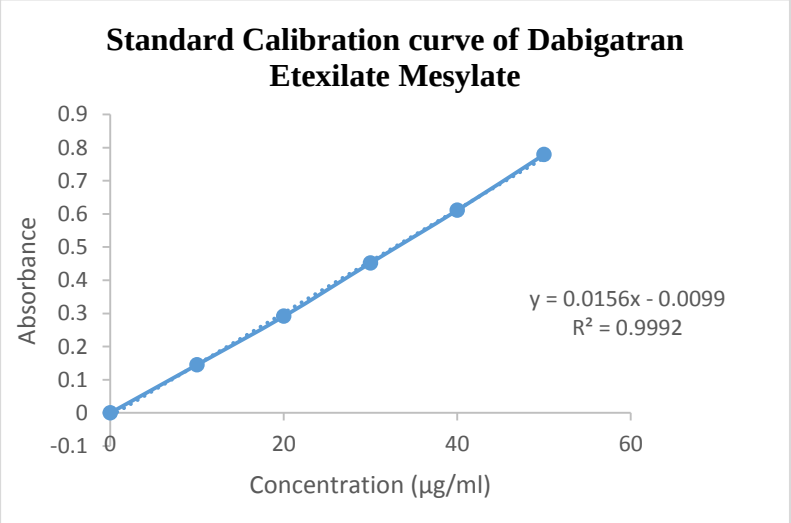


Inference: FT-IR SPECTRUM of Dabigatran etexilate mesylate pure drug and combination with excipients were concordant. So, polymers were found to be compatible with the drug.

Identification of λ max of Dabigatran Etexilate Mesylate: The λmax of Dabigatran Etexilate Mesylate by UV-spectroscopy was found to be 220nm.

Standard Calibration curve of Dabigatran Etexilate Mesylate pH 2.0 0.01N HCL Buffer: The absorbance was measured in a UV visible spectrophotometer at 224nm against pH 2.0 0.01N HCL Buffer as a blank. The absorbance's so obtained was tabulated as in table (7.6) and calibration curve was plotted and shown in figure (7.1)

Fig. No-2. Standard Calibration curve of Dabigatran Etexilate Mesylate



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Evaluation of Micromeritic Properties of Dabigatran Etexilate Mesylate IR Pellets

The Dabigatran Etexilate Mesylate IR Pellets of different formulation (F1-F7) were evaluated for bulk density (BD), tapped density (TD), Hauser's ratio and angle of repose. The results of these evaluations are as follows: -

Bulk Density and Tapped Density: Bulk and tapped densities are used for the measurement of Compressibility index. The BD and TBD ranged from 0.716±0.023 to 0.843±0.062 g/ml and 0.782±0.056 to 1.112±0.010 g/ml respectively.

Hauser's Ratio: Hauser ratio ranged from 1.03±0.15 to 1.46±0.01. The result indicates the good flowing properties of the pellets

Angle of Repose: Angle of repose ranged from 29 º± 3 to 48º ± 2. The results of optimized formulation was found to be 29 º± 3 and hence pellets was found to have good flow ability.

Table. No-9. Micromeritic Properties of Dabigatran Etexilate Mesylate IR Pellets (F1-F7)

Sl.no	Formulation Code	Bulk density ± SD (g/ml)	Tapped density ± SD (g/ml)	Hausner's ratio ± SD	Angle of Repose θ± SD (º)
1	F1	0.793±0.051	0.924±0.003	1.17±0.05	34±2
2	F2	0.752±0.002	0.853±0.010	1.13±0.01	32±3
3	F3	0.768±0.023	0.848±0.036	1.10±0.19	30±4
4	F4	0.719±0.009	0.805±0.015	1.12±0.05	31±1
5	F5	0.765±0.052	0.834±0.023	1.09±0.10	27±3
6	F6	0.821±0.062	0.847±0.009	1.03±0.12	28±3
7	F7	0.816±0.078	0.924±0.069	1.13±0.15	31±2

Particle size distribution of Dabigatran Etexilate Mesylate IR Pellets for Optimized Formulation (F6):

Particle size distribution for Dabigatran Etexilate Mesylate IR pellets optimized formulation (F6) was done. Cumulative percentage retained on ASTM sieve (#) number 14 and 25 were found to be 0 and 97.67% respectively.

Table. No-10. Particle size distribution of Dabigatran Etexilate Mesylate IR Pellets for Optimized Formulation (F6)

S. No	# Sieve No	Initial Weight of # sieve (g)	Final weight (g)	Blend Weight (g)	% Retained	Cumulative % Retained
1	14	340.5	340.5	0	0	0
2	25	299.8	312.7	12.9	43	97.67
3	B Plate	376.4	377.3	0.9	3	100.00

Results of Assay and Water Content by Karl Fisher Method for Dabigatran Etexilate Mesylate IR Pellets Formulations (F1-F7):

Assay (%): Assay was done for formulations F1-F7. The results were found to be ranged from 97.36±0.265% to 101.5±0.058% respectively. From formulation F1 to F7 assay was found to be within limits (Not less than 95% and not more than 105%).

Water Content by KF (%): Water Content by KF (%) was done for formulations F1-F7. The results were found to be ranged from 1.0±0.023% to 2.6±0.123% respectively.

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Table. No- 11. Results of Assay and Water Content by Karl Fisher Method for Dabigatran Etexilate Mesylate IR Pellets Formulations (F1-F7)

S. No	Formulation Code	Assay (%)	Water by KF (%w/w)
1.	F1	99.78±0.012	1.0±0.023
2.	F2	100.0±0.095	1.9±0.075
3.	F3	98.65±0.235	2.4±0.029
4.	F4	101.5±0.058	3.0±0.024
5.	F5	97.36±0.265	1.6±0.056
6.	F6	100.1±0.084	1.8±0.245
7.	F7	99.87±0.045	2.6±0.123

Evaluation of Parameters of Dabigatran Etexilate Mesylate IR Capsules (F1-F7):

The prepared capsules were evaluated for various physical parameters namely– Weight variation, lock length and disintegration.

Weight Variation Test: The average weights of capsules for all formulations are present in Table. No-7.1.10 All the formulations (F1-F12) passed weight variation test as per the Pharmacopoeial limit of 5%.

Lock Length: The lock lengths of capsules were ranged from 18.73 ± 0.21to 19.31 ± 0.011mm (Table. No-7.1.10). Capsules mean lock lengths were uniform in all formulations.

Disintegration Time: The disintegration time of capsules from all formulations (F3-F12) were ranged from 6.12 ± 0.754 to 8.12 ± 0.478 mins.

Table. No-12. Evaluation of Parameters of Dabigatran Etexilate Mesylate IR Capsules (F1-F7)

S.No	Formulations	Average Weight (mg) (±SD)	Lock Length (mm)	Disintegration Time (min)
1	F-1	455 ± 1.28	18.98 ± 0.12	6.23 ± 0.012
2	F-2	446 ± 1.15	18.96 ± 0.26	6.42 ± 0.452
3	F-3	468 ± 1.32	18.89 ± 0.18	6.12 ± 0.754
4	F-4	443 ± 1.56	18.73 ± 0.21	7.11 ± 0.561
5	F-5	454 ± 1.45	18.95 ± 0.15	7.42 ± 0.651
6	F-6	453 ± 1.36	19.01 ± 0.11	6.55 ± 0.014
7	F-7	438 ± 2.98	18.91 ± 0.24	8.12 ± 0.478
8	Innovator	445 ± 1.28	19.31 ± 0.11	7.13 ± 0.029

Table. No-13. Comparative *In-vitro* Dissolution profiles of Dabigatran Etexilate Mesylate IR Pellets (F1-F7)

Time (min)	Cumulative % Drug Release						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
10	65	40	50	68	70	75	78
20	75	73	71	85	79	91	94
30	96	100	95	98	96	99	96
45	101	101	95	99	98	100	99

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Fig. No-4.Comparative *In-vitro* Dissolution Profile of Dabigatran Etexilate Mesylate IR Capsules (F1-F7)

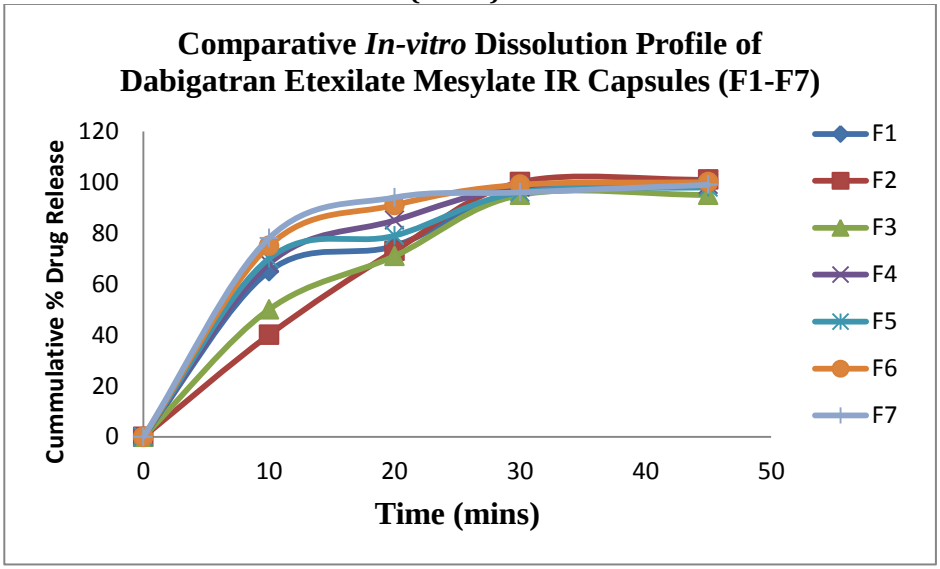

Table. No-14. Comparative *In-vitro* Dissolution profiles of optimized batch(F-6) with innovator:

Time(min)	Cumulative % Drug Release	
	Innovator	F6
0	0	**0**
10	81	75
20	92	91
30	100	99
45	100	100

Fig. No-5. Comparative In-vitro Dissolution Profile of Innovator & Optimised Formulation of Dabigatran Etexilate Mesylate IR Capsules (F6)

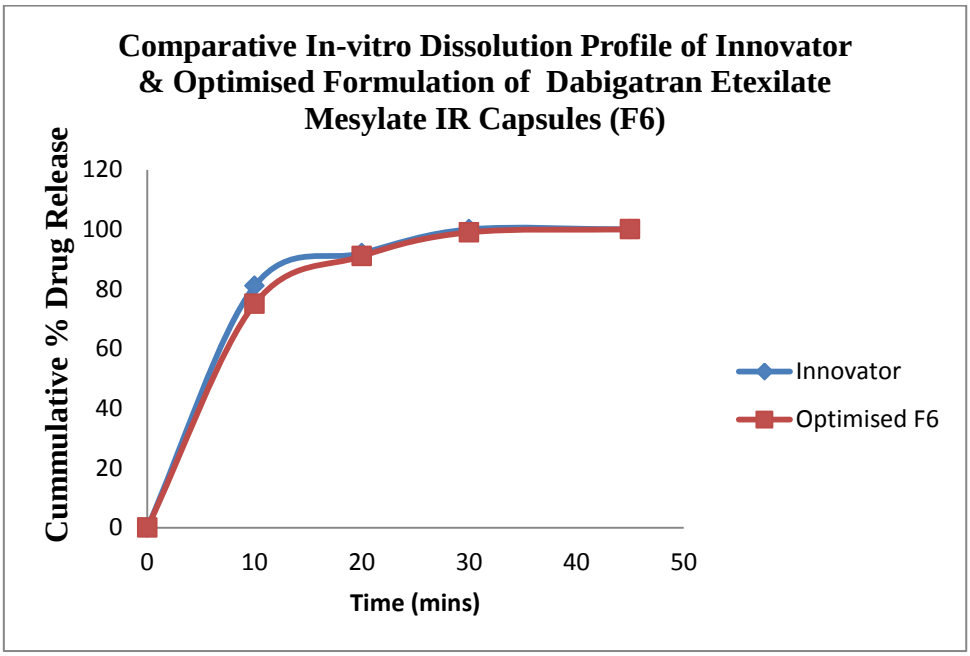

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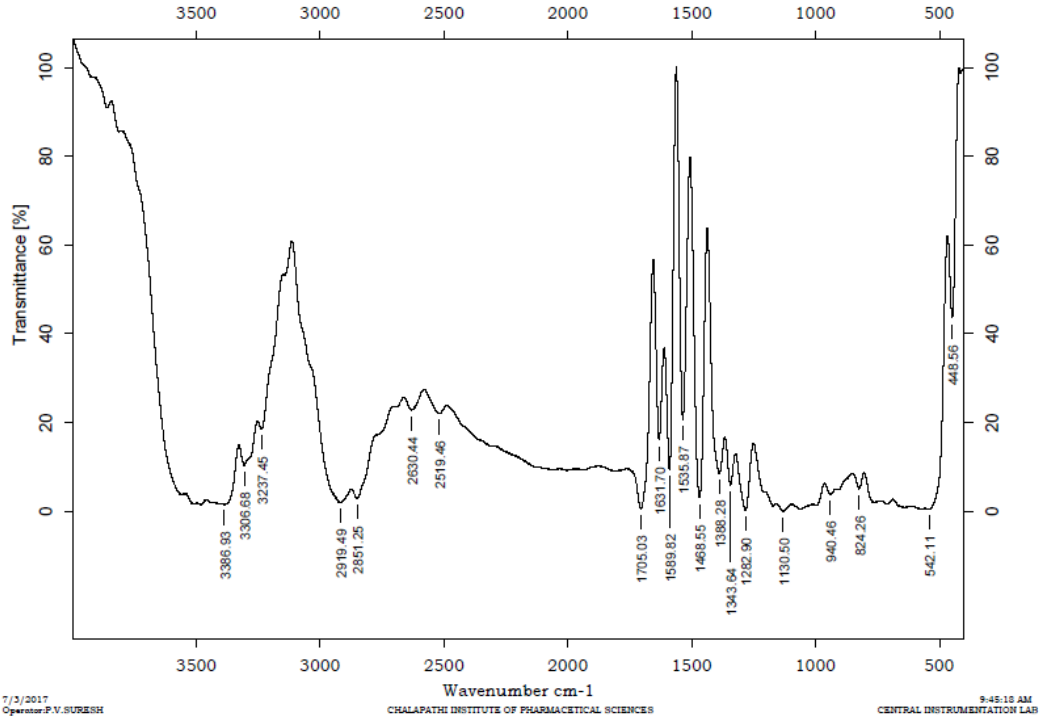
Figure 6.FT-IR SPECTUM OF OPTIMISED FORMULATION



Statistical Evaluation between F6 and Marketed Product

The relevance of difference in the *in-vitro* dissolution profile of optimized formulation (F6) with that of marketed formulation was evaluated statistically.

Table. No-15. Statistical Evaluation of Optimized Formulation F6 and Marketed Product: Similarity and Difference Factors

Time	Innovator (R)	F-6 (T)	D=(Rt-Tt)	$(Rt-Tt)^2$	$\frac{1}{\sqrt{1+\frac{Sum(R-T)^2}{n}}}$
0	0	**0**	0	0	
10	81	75	6	36	
20	92	91	0	0	**0.34099717**
30	100	99	1	1	
45	100	100	1	1	

Table. No-16. Similarity and Difference Factors of Optimized Formulation F6 and Marketed Product

Parameter	Time point (5)	Limit
f1 Value	2.14	0-15
f2 Value	76.64	50-100

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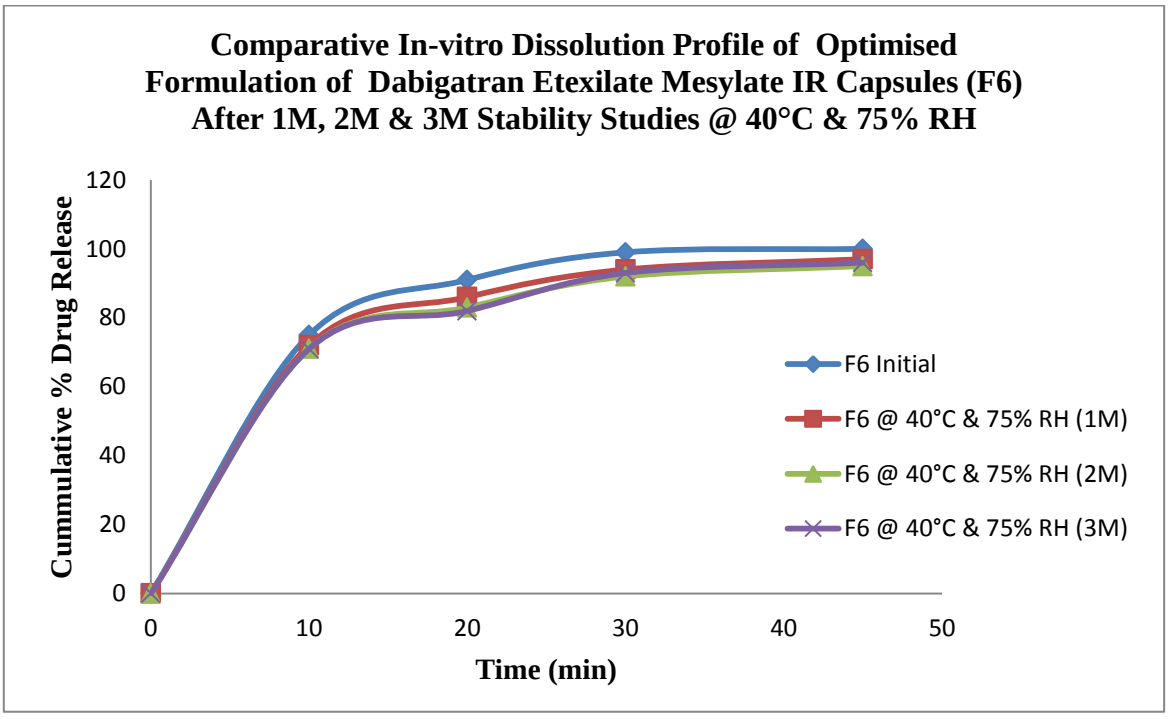
Table. No-17. Stability Studies of Optimized Formulation F-6

S.No	Formulation Code	Stability Conditions			
		Assay @ Initial	Assay (%) @ 40°C & 75% RH		
		0 Day	1 month	2month	3month
1	F-6	100.1	99.4	98.8	98.0

Table. No-18. *In-vitro* Dissolution Profiles Data of Dabigatran etexilate mesylate IR Capsules Optimized formulation (F6) after 1M, 2M & 3M Stability Studies @ 40°C & 75% RH

Time (min)	Cumulative % Drug Release			
	F6 Initial	1st month	2nd month	3rd month
0	**0**	0	0	0
10	75	72	71	71
20	91	86	83	82
30	99	94	92	93
45	100	97	95	96

Fig. No-7. Comparative *In-Vitro* Dissolution Profile of Optimized Formulation of Dabigatran Etexilate Mesylate IR Capsules (F6) After 1M, 2M & 3M Stability Studies @ 40°C & 75% RH



DISCUSSION

In formulation **F1** Tartaric acid pellets of 500 micron size were taken, Povidone was used as binder and lubrication wasn't done.The pellets were small in size, due to this there poor flow and sticking of pellets was observed.In formulation F2 Tartaric acid pellets of 700 micon size was taken, Povidone as binder and no lubrication was done**.**The pellets were observed to be brittle. Hence binder was changed.In formulation F3, Hydroxy propyl cellulose was taken as binder.The pellets were found to be brittle. Hence trial has to be taken by reducing the concentrations of povidone K30 and PEG 400.In formulation F4, Tartaric acid pellets of 700microns were taken. Povidone K30 and PEG 400 concentrations were reduced by 2%. Pellets were good and no sticking was observed. But flow of pellets need to be increased. Trail with another binder was done.In formulation F5, Tartaric acid pellets of 700microns were taken. Hydroxy propyl cellulose and PEG 400 concentrations were reduced by 2%.Flow of pellets need to be increased. Hence lubrication of pellets was

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done.In formulation F6, Povidone K30 as binder and lubrication was done with SLS and Talc.Flow of pellets was good. A trail with HPC was taken by the addition of SLS and Talc.In formulation F7, HPC as binder and SLS and Talc was taken for lubrication.Flow of pellets was good.

Evaluation tests of capsules were done for all the formulations. Average weight for formulations (F1- F7) was in the range from 438± 2.98 to 468 ± 1.32. Lock length for formulations F1- F7 was in the range from 18.73 ± 0.21 to 19.01 ± 0.11. Disintegration time for formulations F1- F7 was in the range from 6.12± 0.754 to 8.12± 0.478. *In-vitro* dissolution studies were performed for formulations F1- F7. The % drug release for formulations F1- F7 was in between 95-101%. Similarity and difference factor were done for all formulations. The F6 formulation showed similarity value 76.64 close to the innovator. Stability studies were done for optimized formulation for 3 months at 40ºC & 75% RH. *In-vitro* dissolution was performed after 3 months. The % drug release was inbetween 95-100%.

The current investigation was predominantly founded on the "Detailing and Evaluation of Dabigatran Etexilate Mesylate Immediate Release Pellets 150mg" (Anti-coagulant) by liquid bed innovation. Different definitions of Dabigatran etexilate prompt delivery pellets were set up by utilizing diverse extent and mix of excipients. The aftereffects of the examination demonstrated that there was no physical change in drug excipient powder combinations. Pellets were readied and micromeritic reads were done for those, for example, point of rest, mass thickness, tapped thickness and Hauser's proportion for definitions (F1 – F7) were assessed and results were accounted for in Table. No-7.1.7. From the outcomes got by HPLC, the alignment bend was developed having relapse estimation of 0.999. Test estimations of the details were seen in the scope of 98 to 102%. Similarity examines were performed and it was seen that all the fixings utilized were viable with the medication. Definition (F6) was detailed by including Povidone K-30. The outcomes indicated 100% medication discharge was found in 45 min. In this way, detailing (F6) was taken as advanced plan. Quickened steadiness reads were performed for improved cluster (F6). Measure and Dissolution reads were performed for the upgraded detailing (F6) at 40°C and 75% RH for 1M and 2M. All the boundaries were discovered to be agreeable disintegration considers were performed and it was discovered that definition F6 have demonstrated best outcomes and equivalent with the trend-setter.

CONCLUSION

From the above experimental results it can be concluded that immediate release capsules of Dabigatran etexilate *can be prepared by using* different proportion & combination of excipients and we selected F6 as best formulation based on dissolution profile and physical characteristics. Formulation (F6) showed cumulative drug release in 45 min and showed good flow properties when compared to other formulations. Finally I conclude the optimized batch (F-6) having similar drug release with the innovator similarity factor (f2) was found to be within limits 76.64 and Accelerated stability studies were performed. Assay and Dissolution studies for the optimized formulation (F6) at 40°C & 75% RH for 1M and 2M were found to be 99.4,98.8 & drug release was 97, 95% at 45 mins respectively.

REFERENCES

1. *Bhandari Neeraj*, Kumar Abhishek, A Review On Immediate Release Drug Delivery System International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS), 2014; 4(1):78-87.*
2. *Lachman.L, Lieberman.A, Kinig.J.L, The Theory and Practice of Industrial Pharmacy, 4th edition, Varghese Publishing House, Bombay, 1991:317.*
3. *Survase S, Kumar N., Immediate release drug delivery: Current scenario, Current Research & Information on Pharmaceutical Science, 2007; 8:1-8.*
4. *N. Harrison, R. Gordon, MB Fawzi, RU Nesbitt, Evaluation of a high-speed pelletization process and equipment, Drug Delivery, International Journal, 1985;11:1523-1541.*
5. *Ravi Teja Pusapati*, T. Venkateswara Rao, Fluidized bed processing: A review Indian Journal of Research in Pharmacy and Biotechnology, 2014 ISSN: 2321-5674(Print) ISSN: 2320 – 3471.*
6. *V. R. Sirisha K.* , Sri , K. Suresh , G. Kamalakar Reddy , N. Devanna A Review Of Pellets And Pelletization Process - A Multiparticulate Drug Delivery System, International Journal Of Pharmaceutical Sciences and Research 2013 Sr no 12, Page no.2145-2158.*
7. *Saibaba, S.V.; Kumar, M.S.; Ramu, B. Pharmaceutical impurities and their characterization. European J Pharm Med Res 2016, 3(5), 190-196.*
8. *Wurster D. E., This journal, 1959; 8:48.*
9. *Umang, Pharmatech Pvt. Ltd., Umang offers road to Pelletisation through spherodization, Express Pharma Pulse, 2000.*
10. *Umprayn K., Chitropas P., Amarekajorn S., Influence of process variables on physical properties of the pellets using an extruder and spheronizer, Drug Delivery Ind. Pharm., 1999;25: 45-61.*

SJIF Impact Factor: 7.001| ISI I.F.Value:1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 5 | Issue: 12 | December 2020 - Peer Reviewed Journal

11. *S Gopalakrishnan, A Chenthilnathan. Formulation and In Vitro evaluation of Aceclofenac oral floating tablets. Research J. Pharm. and Tech. 4(4): April 2011; Page 642-645.*
12. *Bandameedi R, Pandiyan PS. Formulation and evaluation of gastro retentive floating bioadhesive tablets of hydrochlorothiazide. Asian J Pharm Clin Res 2017;10:150-5.*
13. *Addanki Gopikrishna, B. Ramu, G. Srikanth, Dr. Bigala Rajkamal (2016). Formulation of isoniazide sustained release formulation by using carbopol 934 P P. Int J App Pharm Sci Res. 1(2):60- 69. Doi: 10.21477/ijapsr.v1i2.10177.*
14. *N Granger (1980) "Pharmaceutical compositions" U.S. Patent 4 198 391, R.P. Scherer Ltd.*
15. *MS Patel, FSS Morton, & H Seager (1989) "Advances in softgel formulation technology" Manuf Chem, July 26–28.*
16. *Leon Lachman, Herbert A. Lieberman, Kanig. JL, editors. The Theory and Practice of Industrial Pharmacy Third Indian ed. Bombay: Varghese Publishing House; 1987:293-94.*
17. *Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, Third Edition, Vol 72, Marcell Dekker, Inc. NewYork, 1995: 575-609.*
18. *warbrick J, Boylan JC. Encyclopedia of pharmaceutical Technology. 1st Edition.1980,3, 281-86. G. Remington, The Science and Practice of pharmacy, 20th ed, Vol.I, 2003, 903- 913.*
19. *Schellong, Sebastian M. Dabigatran for the treatment of venous thromboembolism, Expert Review of Hematology (2015), 8(4), 413-425.*
20. *Hirano, Teruyuki, Bunshi No Kekkanbyo Evidence and action mechanism of novel anticoagulation, (2013), 12(4), 356-361.*