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Formulation and Evaluation of Immediate-Release Tablets of Edoxaban Tosylate

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ABSTRACT

The immediate-release dosage form breaks down quickly and gets dissolved to release the medicaments. Immediate-release drug delivery is suitable for drugs having long biological half-life, high bioavailability, lower clearance, and lower elimination half-life. The basic design of the system consists of a rapid-release core. The core tablets were prepared using rapid Mixer Granulation and Fluidized bed Granulation Technique. The Mixture was blended further with the addition of Crospovidone and Magnesium Stearate. Nine (F1-F9) formulations of the core were prepared using NF Pharma and HPC-L Nippon Soda as binders in different proportions (2, 3 & 4 %w/w) to study the effect of variable concentrations of these on the characteristics of the formulation. The core blend was evaluated for Flow properties, Hardness, Thickness, Friability, and *in-vitro* drug release. The drug (Edoxaban) is compatible with all excipients. All the parameters were in the optimum range. Among the Nine formulations F8 containing HPC Nippon Soda (2%) as a binder showed a better drug release of 100% over 60 minutes was selected. 400mg of resultant powder blend was manually compressed at a pressure of 100 tablets, with 10.60mm punch and die to obtain the core tablet. Among these, F8 was optimize based percent of drug release (99% of drug release in 60 minutes).

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INTRODUCTION

The definition of immediate delivery for drugs is a strategy in which galenic controls do not overtly or intentionally slow down the pace at which medications arrive or, maybe, are assimilated from the body. Immediate delivery dosage structures disintegrate quickly to distribute the medication. In the present situation, prompt delivery of a suitable chemically acceptable diluent or transporter may be administered [1]. Quick delivery drug conveyance is appropriate for pharmaceuticals with lengthy natural half-lives, high bioavailability, lesser freedom, and lower disposal half-lives. In any event, the unpleasant solvency of the medication and the need for the quick activity of drugs to cure undesired blemish or illness are the primary requirements for sure-fire discharge measurements structure. Edoxaban Tosylate, an anticoagulant medication, inhibits coagulation component Xa^1 when taken orally (activated factor X). It is used to treat pulmonary embolism and deep vein thrombosis. It is an anticoagulant, a platelet aggregation inhibitor, and a coagulation aspect Xa inhibitor [2].

MATERIALS AND METHODS

Edoxaban tosylate gift sample from S D Fine Chemicals Ltd, Mumbai, Microcrystalline cellulose, Prege-

latinized starch, Crospovidone, HPC-L Nipponsoda, Hydroxypropyl cellulose LF, Magnesium stearate, is from Ranbaxy fine Chemical Ltd, New Delhi, India.

Methodology

Preformulation Studies

Pre-Compression Parameters

Bulk Density

Bulk density is a given powder mass's ratio and bulk volume. It is determined by transferring an accurately weighed powder sample to the graduated cylinder. The ratio of the Weight of the model to the book it occupied was calculated [3, 4].

$$Bulk\ density = Mass\ of\ the\ blend\ /Bulk\ volume\ of\ the\ blend$$

Tapped Density

The device was programmed for 500, 750, and 1250 taps. The tapped density was determined by dividing the Mass of the blend by the tapped volume. It was created by pouring a known amount of the mix into a graduated cylinder and setting it on the device.

$$Tapped\ density = Mass\ of\ the\ blend\ /Tapped\ volume$$

Angle of Repose

The Angle of repose by passing the Mixture through a funnel fixed to a burette stand at a particular height (4 cm). The Height and radius of the pile were measured [Table 1]. The Angle of repose of the blend was calculated using the formula:

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where,

h = Height of the pile;

r = Radius of the pile

Compressibility Index

It is measured by tapped density apparatus for 500, 750, and 1250 taps, for which the difference should be less than 2%. Based on the apparent bulk density and tapped density, the percentage compressibility [Table 2] of the blend was determined using the following formula:

$$\%\ Compressibility = (Tapped\ density - Bulk\ Density\ /Tapped\ volume) \times 100$$

Hausner's Ratio

The proportion between the powders' tapped density and bulk density is known as Hausner's ratio. It indicates the flow properties of the powder [Table 3].

$$Hausner's\ ratio = Tapped\ density\ /\ Bulk\ density$$

Drug-Excipient Compatibility Studies

To perform drug excipient similarity research, the medication is mixed with various excipients to varying degrees and placed in a vial. An elastic plug is then affixed to the vial and securely fastened. Glass containers were used for the studies under Sped conditions (40° C 2° C/75% RH 5% RH) for roughly a month to reach capacity [Table 4]. After capacity, the sample was compared and controlled between 2 and 8 degrees Celsius, and the true liquefaction, hardness, and staining were seen [5].

HPLC Method

Preparation of Solutions

pH 3.5 Buffer Preparation (Mobile phase A)

Pour 0.96 grams of 1-pentane sulphonic acid into 1 liter of water, thoroughly mix, and then raise pH to 3.5 by adding a diluted phosphoric acid solution. Next, pass the solution through a PVDF membrane filter (0.45 m) [6, 7].

Mobile Phase-B

100% Acetonitrile.

Diluent

Acetonitrile and water combined at a 50:50 ratio.

Standard Preparation

Prepare a Standard Stock Solution Containing 0.2mg/mL of Edoxaban

Weigh accurately and transfer 27mg of Edoxaban standard into a 100 mL volumetric flask. Add 50mL of diluent. Sonicate to dissolve and mix thoroughly and dilute to the desired volume.

Prepare a Standard Solution Containing 0.001mg/mL of Edoxaban

Further pipette out 5mL of standard solution into 100mLvolumetric flask, mix thoroughly and dilute to the desired volume. From this solution, pipette out 1ml and transfer into a 10ml flask, mix thoroughly, and cut to the desired volume.

Preparation of Placebo

Add 35 mL of diluent, accurately weigh and put a placebo into a 50 mL volumetric flask equivalent to 25 mg of Edoxaban, and Sonicate for 15 minutes with intermittent shaking. Cool the flask to room temperature after removing the solution from the sonicator, then add diluent to make the capacity 50mL. The sample should be centrifuged at 4000 RPM for 10 minutes. Fill an HPLC vial with the supernatant liquid and inject it.

Table 1: Angle of Repose

Angle of Repose (Degrees)	Flow Property
25-30	Excellent
31-35	Good
36-40	Fair
41-45	Possible
46-55	Poor
56-65	Very poor
>66	Very very poor

Table 2: Car's Index

Compressibility Index (%)	Flow Property
<10%	Excellent
11-15	Good
16-20	Fair
21-25	Possible
26-31	Poor
32-37	Very poor
>38	Very very poor

Table 3: Hausner's Ratio

Flow Properties	Hausner's Ratio
Excellent	1.0-1.11
Good	1.12-1.18
Fair	1.19-1.25
Possible	1.26-1.34
Poor	1.35-1.45
Very poor	1.46-1.59
Very very poor	>1.60

Table 4: Drug and Excipient Ratios

Name of the Material	The Ratio of Active to Excipients
Edoxaban tosylate	50mg
Microcrystalline cellulose	1:1
Pregelatinized Starch	1:3
Crospovidone	1:1
Hydroxy Propyl Cellulose	1:1
Magnesium stearate	1:0.5
Iron oxide Yellow	1:0.5
All excipients	NA

Table 5: Operating Procedure

Parameters	Specifications
Column details & Description	Zorbax eclipse XDB-C18 250×4.6 mm, 5μm
Flow rate	0.6mL /min
Wavelength	260nm
Colum temperature	40°C
Injection Volume	10μL
Run Time	70 minutes
Mode of Elution	Gradient

Table 6: Gradient Table

Time in Minutes	Mobile Phase-A in %	Mobile Phase-B in %
0	80	20
5	80	20
10	70	30
30	50	50
60	50	50
61	80	20
70	80	20

Table 7: Inject the Sample as per the Sequence Below

Sample ID	No. of Injections
Blank	1
Placebo	1
Standard	6
Sample(s)	1
Blank	1
Bracketing standard (after every 6 sample injections)	1

Table 8: System Suitability Criteria

Parameter	Criteria
Retention Time	About 34.0 mins
%RSD for six replicate injections of Edoxaban in standard	NMT 10.0
Column Efficiency of Edoxaban standard	NMT 2000 theroretical plates
Tailing factor of edoxaban in standard	NMT 2.0

Table 9: Impurity Name with RRT

S. No	Impurity Name	RRT
1	MITICA	0.22
2	ADCCPO	0.92
3	TCPAODCC	2.10
4	DCBCPO	2.25

Table 10: Composition of Edoxaban Tosylate Tablets

S.no	Ingredients	Rapid Mixer Granulator			Fluidized Bed Granulator					
		F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
	Intragranular									
1	Edoxaban tosylate	80.82	80.82	80.82	80.82	80.82	80.82	80.82	80.82	80.82
2	Microcrystalline cellulose	198.68	202.68	194.68	198.68	202.68	194.68	198.68	202.68	194.68
3	Pregelatinized starch	84	84	84	84	84	84	84	84	84
4	Crospovidone	11.5	11.5	11.5	11.5	11.5	11.5	11.5	11.5	11.5
	Binder solution									
5	HPC-L Nippon Soda	12	8	16	12	8	16	-	-	-
6	Hydroxypropyl cellulose LF (Klucel LF)	-	-	-	-	-	-	12	8	16
7	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Extra granular									
8	Crospovidone	7	7	7	7	7	7	7	7	7
	Lubrication									
9	Magnesium stearate	6	6	6	6	6	6	6	6	6
	Core tablet weight	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**
10	Opadry yellow	16	16	16	16	16	16	16	16	16
11	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Coated tablet weight	**416**	**416**	**416**	**416**	**416**	**416**	**416**	**416**	**416**

Sample Preparation

Accurately weigh a sample equivalent to 25mg of Edoxaban into 50mL of volumetric flask and add 35mL of diluent and Sonicate for 15 minutes with intermediate shaking. Centrifuge the sample for 10 minutes at 4000 RPM. Transfer the supernatant liquid into an HPLC vial and inject it into HPLC. Remove the solution from the sonicator, cool the flask to room temperature, and make up the volume of 50mL with diluent.

Operating Procedure

Equilibrate the instrument with the following chromatographic parameters [Table 5, Table 6, Table 7, Table 8 and Table 9].

The Formulation Composition of Edoxaban Tosylate Immediate-Release Tablets

Formulation of immediate-release edoxaban tosylate 60mg tablets was carried out by fluidized bed granulation technique [8] [Table 10].

The Manufacturing Procedure of Immediate-Release Edoxaban Tosylate Tablets

Dispensing

Edoxaban tosylate monohydrate, microcrystalline

Table 11: In-Process Parameters of FBP

Parameter	In-Process Parameters During Fluid Bed Granulation Time (Clock)					
	14.00	14.15	14.30	15.00	15.15	15.30
Blower Speed	25	30	38	50	40	25
Blower CFM	38	42	56	67	54	40
Inlet Temperature (^{0}C)	60	65	70	70	50	50
Bed Temperature (^{0}C)	35	34	35	35	40	51
Product Temperature (^{0}C)	35	34	34	35	39	50
Exhaust Temperature (^{0}C)	33	33	32	33	36	46
Bag Shaking Interval (Min.)	5	5	5	5	5	5
Bag Shaking Strokes (No)	3	3	3	3	3	3
Pump Speed (RPM)	5	10	12	20	0	0
Main Air Pressure (BAR)	5.2	5.3	5.3	5.2	5.3	5.2
Atomization Air Pressure (BAR)	0.96	0.96	0.96	0.96	0	0

Table 12: Compression Punch Parameters

Punch Parameters	
Punch diameter	10.60mm
Punch Shape	Round shape
Upper punch	Embossed with'ED60'
Lower punch	Embossed with '888.'

Table 13: Coating Parameters

Parameter	Set	Actual
Inlet Temperature(^{0}C)	58	56-63
Product Temperature(^{0}C)	45	40-44
Exhaust Temperature(^{0}C)	45	40-44
Inlet Blower	600	575
Exhaust Blower	550	515
Pan RPM	2-7	1-6
Spray RPM	1-3	1-3
Atomization Air pressure	0.25	0.25
Fan Air	0.2	0.2

Table 14: Operating Procedure

Parameters	Specifications
Column details & Description	Zorbax eclipse XDB-C18 250$\times$4.6 mm, 5μm
Flow rate	1.2mL /min
Wavelength	260nm
Colum temperature	40°C
Injection Volume	10μL
Run Time	10 minutes
Mode of Elution	Isocratic

Table 15: Inject the Sample as per the Sequence Below

Sample ID	No. of Injections
Blank for baseline check	1
Check Standard (Standard-1)	1
Standard-2	5
Sample(s)	2
Bracketing standard (after every 6 sample injections)	1

Table 16: System Suitability

Parameter	Criteria
Retention Time	About 3.5 mins
%RSD for five replicate injections of standard-2	NMT-2.0
Column Efficiency of Edoxaban standard -2	NMT 2000
Tailing factor of edoxaban in standard-2	NMT 2.0
Similarity factor between standard-1 and standard-2	0.98-1.02

Table 17: Flow Properties of Edoxaban (API)

Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Angle of Repose
0.2214 g/cc	0.3073 g/cc	27.9411%	1.3877	Not passed from the funnel

cellulose 101, Pregelatinized starch Crospovidone and binder are weighed in required quantities [9].

Sifting

Sift edoxaban tosylate, microcrystalline cellulose 101, pregelatinized starch, and Crospovidone through the #30 sieve.

Binder Preparation

Take the required quantity of purified water in a beaker, add the binder while stirring, and keep going until the binder completely dissolves.

Wet Granulation by Rapid Mixer Granulator (F1-F3)

Sifted Edoxaban Tosylate, Microcrystalline Cellulose, Pregelatinized starch, and Crospovidone loaded to the RMG bowl and dry mix it for 10min at speed with impeller slow (100 RPM) and Chopper OFF. Add binder solution within 2 min at speed with impeller slow (100 RPM) and chopper OFF. Continue Kneading for 30sec at a rate of impeller fast (200 RPM) and chopper fast (2000 RPM)

Drying

Transfer wet Mass from RMG bowl to Fluidized Bed Dryer and dry it for 30 min at 60°C until required LOD achieves.

Fluid Bed Granulation: (Top Spray Granulation)

Sifted Edoxaban Tosylate, Microcrystalline Cellulose, Pregelatinized starch, and Crospovidone loaded to the FBP bowl and mixed for 3min at 25% of blower speed followed by binder solution spraying and drying as indicated parameters in the Table 11.

Drying - 25 Min

LOD: 5.70% w/w at 105^0C

Milling /Sizing

The dried granules are passed through a cone mill fitted with a 0.5mm screen, and these milled granules are passed through a # 20 sieve.

Blending

Dispense Crospovidone and magnesium stearate as per the Weight of dried granules.

Pre-lubrication

Add #40 sifted extra granular Crospovidone and sized granules to the Octagonal Blender and blend for 05 min. At 08 rpm.

Lubrication

Magnesium Stearate #60 sifting is added to the blender, and the process takes 05 minutes at a speed of 8 rpm [Table 12].

Coating Dispersion Preparation

Opadry yellow dispersed in purified water under continuous stirring for 45 min.

Table 18: Edoxaban Tosylate - Excipients Compatibility Study Results at Initial

Condition	API	API + MCC 101	API + Prege-la-tinized starch	API + HPC-L	API + Mag-nesium stearate	API + Opadry yellow	API + Crospovi done	API + HPC(Nip-pon soda)	API + Mix-ture of excip-ients
Unknown @0.58	ND	ND	ND	ND	ND	ND	0.01	ND	0.01
Unknown @0.92	ND	ND	0.01	ND	ND	ND	ND	ND	ND
ADCCPO@0.92	0.01	0.01	0.03	0.01	0.01	0.01	0.01	ND	0.01
DCBCPO@2.18	0.02	2.19	ND	0.02	0.02	0.02	0.02	0.02	0.02
TCPAODCC @2.03	ND	ND	ND	ND	ND	ND	ND	ND	ND
Unknown @0.94	ND	0.01	ND	ND	ND	ND	ND	ND	ND
Unknown @0.98	0.03	0.03	ND	0.03	0.03	0.03	0.05	0.03	0.05
Unknown @1.05	0.02	0.06	0.02	0.04	0.06	0.05	0.02	0.04	0.02
Unknown @1.07	0.03	0.04	0.03	0.03	0.04	0.04	0.05	0.03	0.03
Unknown @1.08	ND	ND	ND	ND	ND	ND	ND	ND	ND
Unknown @1.12	ND	ND	ND	ND	ND	ND	0.01	ND	ND
Unknown @1.19	ND	ND	ND	ND	0.01	ND	0.01	ND	0.01
Unknown @1.21	0.02	0.02	0.02	0.02	0.02	0.02	0.04	0.02	0.02
Unknown @1.24	ND	ND	ND	ND	ND	ND	ND	ND	ND
Unknown @1.25	ND	ND	ND	ND	ND	ND	0.01	ND	0.01
Unknown @1.40	ND	ND	ND	ND	ND	ND	0.01	ND	ND
Unknown @1.42	0.08	0.08	0.08	0.08	0.08	0.07	0.05	0.08	0.07
Unknown @1.84	ND	ND	ND	ND	ND	ND	ND	ND	ND
Unknown @1.52	ND	ND	ND	ND	ND	ND	ND	ND	ND
Unknown @2.40	ND	ND	ND	ND	ND	ND	ND	ND	ND
Unknown @2.47	ND	ND	ND	ND	ND	ND	ND	ND	ND
Unknown @3.07	0.04	0.04	0.05	0.04	0.04	0.04	0.04	0.05	0.04
Total impuri-ties	0.25	0.31	0.26	0.27	0.31	0.28	0.33	0.27	0.29

Table 19: Edoxaban Tosylate - Excipients Compatibility Study Results at 40°C/75%RH, Four Weeks Open

Condition Impurities	API	API + MCC 101	API + Pregelatinized starch	API + HPC-L	API + Magnesium stearate	API + Opadry yellow	API + Crospovidone	API + HPC(Nippon soda)	API + Mixture of excipients
Unknown @0.24	ND	ND	ND	0.01	ND	ND	ND	ND	ND
Unknown @0.58	ND	ND	ND	0.01	ND	0.01	ND	ND	0.01
Unknown @0.92	ND	ND	ND	ND	ND	0.01	ND	ND	ND
ADCCPO @0.92	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
DCBCPO @2.18	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	ND
TCPAODCC @2.03	ND	ND	ND	ND	0.03	0.01	ND	ND	ND
Unknown @0.94	ND	ND	ND	0.01	ND	0.01	0.01	0.01	ND
Unknown @0.98	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.06
Unknown @1.05	0.05	0.05	0.02	0.06	0.06	0.05	0.06	0.05	0.02
Unknown @1.07	0.04	0.04	0.03	0.04	0.04	0.04	0.04	0.04	0.04
Unknown @1.12	ND	ND	ND	ND	ND	0.01	ND	ND	ND
Unknown @1.19	ND	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.02
Unknown @1.21	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Unknown @1.24	ND	ND	ND	ND	ND	ND	ND	ND	ND
Unknown @1.25	ND	0.01	0.01	ND	ND	ND	0	0.01	0.01
Unknown @1.40	ND	ND	ND	ND	ND	ND	ND	ND	0.01
Unknown @1.42	0.08	0.08	0.08	0.09	0.08	0.08	0.08	0.08	0.11
Unknown @1.84	ND	0.02	ND	ND	0.03	0.03	ND	0.02	ND
Unknown @3.07	0.06	0.05	0.07	0.06	0.07	ND	0.07	0.07	0.07
Total impurities	0.31	0.34	0.3	0.37	0.4	0.34	0.35	0.37	0.4

Table 20: Pre-Compression Specifications for Batches of Edoxaban Tosylate

Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose
F1	0.447±0.006	0.593±0.006	24.62±1.65	1.32±0.88	26.43±0.681
F2	0.468±0.002	0.604±0.003	22.51±1.46	1.29±0.51	25.35±0.450
F3	0.472±0.003	0.528±0.007	10.6±1.54	1.11±0.64	27.31±0.486
F4	0.463±0.004	0.556±0.003	16.72±1.34	1.20±0.33	24.86±0.271
F5	0.456±0.002	0.574±0.002	20.05±1.66	1.24±0.26	23.12±0.450
F6	0.461±0.005	0.587±0.005	21.46±1.27	1.27±0.61	26.72±0.632
F7	0.484±0.002	0.547±0.006	11.51±1.89	1.13±0.87	24.44±0.187
F8	0.472±0.003	0.528±0.007	10.6±1.54	1.11±0.64	23.37±0.121
F9	0.478±0.007	0.563±0.004	15.01±1.76	1.17±0.54	24.65± 0.28

Table 21: Post-Compression Parameters of Edoxaban Tosylate Tablets

Batch	Hardness (kg/cm^2)	Thickness (mm)	Weight Variation (%)	Friability (%)	Disintegration Time (Min)	Assay (%)
F1	7.1±0.13	4.75±0.15	398±0.7	0.70±0.04	3.05	97.74
F2	6.3±0.22	4.70±0.20	400±0.6	0.55±0.13	2.50	98.01
F3	7±0.14	4.65±0.17	402±0.4	0.62±0.34	2.58	102.29
F4	6.6±0.21	4.69 ±0.15	399±0.5	0.54±0.27	3.10	97.70
F5	7±0.30	4.75±0.12	398±0.2	0.42±0.19	3.00	98.49
F6	7.2±0.11	4.68±0.15	405±0.3	0.57±0.14	2.30	98.97
F7	7.5±0.13	4.67±0.06	397±0.5	0.55±0.13	3.05	97.49
F8	6.8±0.24	4.67±0.07	401±0.6	0.62±0.14	2.50	98.09
F9	6.5±0.32	4.65±0.07	398±0.6	0.52±0.14	2.00	97.85

Table 22: Cumulative Percentage of Drug Release

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	Innovator
0	0	0	0	0	0	0	0	0	0	0
5	27	42	45	52	56	49	41	58	44	59
10	48	54	69	79	82	67	73	81	76	83
15	60	61	73	81	87	69	81	86	82	87
30	76	75	82	89	90	78	86	92	89	93
45	82	81	91	91	93	82	93	95	93	96
60	88	85	93	93	95	89	97	99	95	101

Coating

Core tablets are loaded in a coating pan and pre-warmed for 10 minutes at 37°C. The coating solution started on pre-warmed tablets up to weight build-up of 4%weight by using the following parameters [Table 13]. After completion of coating, tablets are dry at 35°C-40°C temperature for 15 minutes [10].

Evaluation of Edoxaban Tosylate Tablets

Post-Compression Parameters

The tablets were examined for in-progress and finished item quality control tests, including appearance, aspects (width and thickness), weight variety, hardness, friability, assay, and drug content [11–13].

Appearance

The tablet should be free of cracks, problems, pinholes, and other issues. The tablet's color and cleanliness should be consistent over its entire surface. The pills' outside should have a smooth surface.

Thickness

For the 20 pre-gauged tablets of each group utilizing a computerized Vernier scale, the standard in mm

Table 23: Stability Data of Optimized Formula

Test	Edoxaban Tablets 60mg Tentative Specification	Initial	40°C/75%RH 1M	2M	3M	6M
Description	Yellow color, round shape, biconvex and plain on both sides	Yellow color, round shape, biconvex and straight on both sides				
Assay by HPLC	95-105%	101.6	99.4	100.2	101.3	102.2
MTHTPCA@0.22	NMT 0.5%	0.01	0.08	0.08	0.03	0.02
ADCCPO@0.92	NMT 0.5%	0.02	0.02	0.01	0.01	0.01
DCBCPO@2.24	NMT 0.5%	0.08	0.03	0.03	0.03	0.03
TCPAODCC@2.29	NMT 0.5%	ND	ND	ND	ND	ND
Maximum Unknown	NMT 0.2%	0.07	0.08	0.08	0.08	0.08
Total impurities	NMT 2%	0.47	0.55	0.40	0.40	0.40
Dissolution 60	Media: pH 6.0 Phosphate Buffer, Volume - 900 mL, Speed - 50 RPM, Apparatus - Type II (Paddle)					
	Not less than 80% in 30 minutes	99%	97%	98%	96%	98%

is still up in the air. The tablet thickness should not exceed the average by more than 5%.

Weight Variation

Twenty pills were chosen randomly from a group and independently weighed. On the off chance that no medicine contrasts by more than one, the tablets meet the USP details, while perhaps not all tablets are outside as far as is practicable.

Hardness Test

Hardness (polar pounding strength) is a force that can be used to break a tablet. A tablet's solidity can be inferred by how hard it is. The tablet should withstand mechanical pressure while being handled and transported. With different tablet brands and different types, the degree of hardness varies. Ten tablets were tested for hardness, and the average hardness was established. The unit is KP or kg/cm^2.

Friability Test

As a result of the surface's evacuation of microscopic particles, friability is the absence of the Weight of the tablet in the holder or bundle. This is a test for in-process quality control. It is done to ensure that tablets can endure shocks during handling, care, transit, and shipment. The Roche Friabilator was used to gauge how friable the pills were. It is turning at a speed of 25 rpm. The tablets are subject to rolling in the friabilator due to a sudden drop inside the friabilator's office. The tablets are taken from the stabilator after 4 minutes, and the undamaged tablets are once more weighed together. 1.0% is the allowable friability cap.

The percentage friability was measured by using the following formula:

$$\% F = \{1 - (W / Wo)\} x 100$$

Where,

%F = friability in percentage;

Wo = Initial Weight of tablet;

W = Weight of tablets after the revolution.

Disintegration Time

The tablet's time to separate into smaller particles is known as the degradation time. The disintegration test apparatus includes a bushel rack along with six glass containers that are each 7.75 cm long and 2.15 mm in diameter and whose lowest portion has a filter with a #10 cross-section. 28–32 times per second, the bin is raised and lowered in a 900 ml container preserved at 37 °C. Each tablet is placed in each of the cylinders, and the deteriorating season was defined as the time it took for all of the tablet pieces to travel through the lattice (# 10).

Dissolution Studies

Method

The dissolution test was completed in USP Device

Type II (paddle) with pH 6.0 phosphate support as the disintegration medium. The examples were drawn at 5, 10, 15, 20 30, min. New medium volumes were supplanted with the removed book to keep up with the sink conditions.

Dissolution Parameters

Dissolution Apparatus: USP Apparatus Type II (Paddle)

Dissolution Medium: pH 6.0 Phosphate buffer

Volume: 900 ml

Temperature : $37 \pm 2^{\circ}$ C

RPM: 50

Sampling Intervals (min): 5, 10, 15, 20, 30, and 45 min

Assay of Edoxaban Tosylate Tablets by HPLC

Preparation of Solutions

pH 3.5 Buffer Preparation

Pour 0.96 grams of 1-pentane sulphonic acid into 1 liter of water, thoroughly mix, and then raise pH to 3.5 by adding a diluted phosphoric acid solution. Next, pass the solution through a PVDF membrane filter (0.45 m).

Mobile Phase Preparation

Acetonitrile in a 70:30% v/v mix as a buffer.

Diluent

50/50 acetonitrile and water should be combined.

Preparation of Standard

Transfer 81 mg of standard edoxaban tosylate precisely weighed into a 50 ml volumetric flask. Add 35mL of the diluent, sonicate it to dissolve it, then add the remaining diluent and thoroughly combine. Pipette 5 mL of the standard stock solution into a 100 mL volumetric flask, add diluent to fill the flask to volume and then mix thoroughly.

Sample Preparation

Weigh the tablet, carefully transfer it to the designated volumetric flask, and then pour 70% diluent into it. Thirty minutes of intermediate shaking while sonicating. Take the flask out and let it cool to room temperature. Then combine the diluent to make up the remaining volume. The solution should be centrifuged at 4000 RPM for 10 minutes [Table 14, Table 15 and Table 16].

$$\% \ Assay = \frac{Average\ Sample\ Area}{Average\ S\tan dard{-}2\ Area} \times \frac{Ws}{50} \times \frac{5}{100} \times \frac{250}{No.of\ tablets\ taken} \times \frac{100}{5} \times \frac{1}{L} \times \frac{P}{100} \times \frac{548.056}{738.3} \times 100$$

Where,

P = %Potency of Edoxaban Tosylate Standard;

L = Label the amount of Edoxaban Tosylate in mg;

Ws = Weight of the standard-2 taken

Stability Study

Evaluating how temperature and humidity affect a drug's stability is critical. It facilitates data generation for forecasting the product's shelf life and suggested storage settings [14]. Following ICH recommendations, optimized instant-release tablets and their final tablet formulation were subjected to accelerated stability testing for a month in a stability chamber at 40 2°C and 75 5% RH. The samples were put into vials, sealed with aluminum caps, and plugged with Bromo butyl rubber.

RESULTS AND DISCUSSION

Preformulation Studies

The flow properties of edoxaban (API) is shown in Table 17.

Excipients Compatibility Study

The edoxaban and excipients were compatible for four weeks because the impurities were below acceptable levels [Table 18].

Excipients Compatibility Study Results at 40°C/75%RH

Because the contaminants were found below permitted levels, the edoxaban and excipients were first declared compatible for four weeks [Table 19].

Characterization of Tablets

The values for Hausner's ratio fall in the range of 1.17 to 1.32. The result concluded that the powder blends had good flow properties, which can be used for tablet manufacture. Bulk densities and tapped densities of various formulations were in the range of 0.456 to 0.478 (gm/cc) and 0.528 to 0.604 (gm/cc), respectively [Table 20]. The Angle of repose was found in the range of 23^0 to 27^0.

Pre-Compression Specifications

Hardness Test

The tablets' hardness is between 6.0 and 8.0 kg/cm^2, notwithstanding their rapid deterioration. The reduced standard deviation values showed that the numerous details' hardness was consistent with the precise method and had a good balance of hardness and mechanical strength [Table 21].

Friability Test

The study's findings show that every formulation falls well below the acceptable range (1%). The values were located inside the boundaries. Tablets have strong mechanical properties as a result [Table 21].

Weight Variation Test

All the tablets passed the weight variation test since the weight variation% ranged from 397.5% to 401.6%, within the pharmacopoeial limitations [Table 21].

Thickness

The thickness was measured for three tablets from each batch [Table 21]. The outcome revealed that the tablet's average thickness ranges from 4.65 mm to 4.75 mm.

Disintegration Time

All the cores of various formulations quickly dissolved between 2 min to 3 min 10 sec.

Assay

The assay of different formulations was within 97-102%.

The In-Vitro Drug Release Pattern

A table displaying the findings of the dissolving profiles for each formulation was F8 had a very short in vitro disintegration time [Table 22]. 99% of the medication is released according to F8 within 60 minutes of interaction with the dissolving medium [Figure 1].

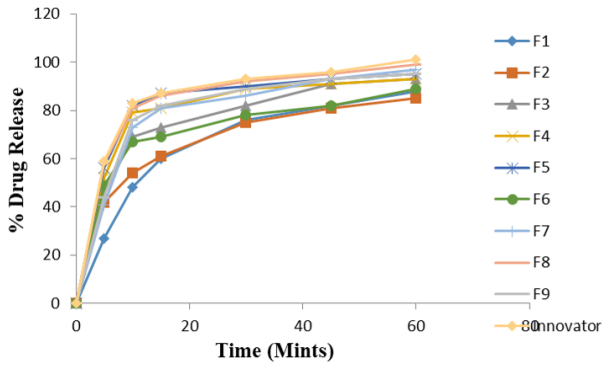

Figure 1: *In Vitro* Dissolution Studies For F1-F9 and Innovator

Stability Data

The stability test findings revealed that throughout the first, second, and third months of accelerated condition storage, the release rate of Edoxaban tablets stored at a temperature of 40°C and relative humidity of 75% remained unaltered [Table 23].

CONCLUSION

HPLC studies showed that there was no interaction between drugs and excipients. Core tablets obtained were evaluated for pre-compression and post-compression parameters, all parameters shown within limits. Nine different formulations (F1-F9) of Edoxaban immediate release tablets were prepared using Rapid Mixer Granulation and Fluidized bed granulation method and by changing drug: binder rations. In this in-vitro drug release study, formulation F8 showed 99% drug release within 60 minutes. The formulation F8 dissolution profile was found comparable to the Reference product. The optimized formula was subjected to stability studies and was found to be stable.

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Conflict of Interest

The authors declare that this study has no conflict of interest.

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