International Journal of Biochemistry Research & Review

Volume 33, Issue 4, Page 1-10, 2024; Article no.IJBCRR.112857
ISSN: 2231-086X, NLM ID: 101654445

Revolutionizing Apixaban Release: Exploring Wet Granulation and Superdisintegrant Synergy for Improved Delivery Profiles

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJBCRR/2024/v33i4865

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/112857

Original Research Article

Received: 16/12/2023
Accepted: 22/02/2024
Published: 19/03/2024

ABSTRACT

The aim of the present research was to formulate and evaluate immediate release tablet of apixaban. In this research study, we are formulating apixaban by wet granulation method. Previously research has been conducted based on dry granulation and direct compression methods.

The proposed wet granulation method has several advantages in terms of feasibility and cost effectiveness. The present formulation comprises of comparative evaluation between disintegrants such as sodium starch glycolate (SSG), and croscarmellose sodium (CCS), among which CCS was found to have optimum results. Superdisintegrants, are compounds that, as their name implies, are superior to disintegrants and that facilitate or enhance the disintegration time even at low levels, usually 1-10% by weight relative to the total weight of the dosage unit. These are used to boost the potency of the solid dosage form.

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Keywords: Apixaban; formulation development by wet granulation method; CCS; HPLC method.

1. INTRODUCTION

"Apixaban is 1-(4-methoxyphenyl) -7-oxo-6- [4-(2-oxopiperidin-1 yl) phenyl]-1H, 4H, 5H, 6H, and 7H-pyrazolo [3,4-c]3-carboxamide pyridine [1]. Patients with nonvalvular atrial fibrillation should take apixaban to lower their risk of stroke and systemic embolism. Additionally, it has been used to reduce the chance of venous thrombosis" [2-5]. An examination of the literature indicates that there is just one commercially accessible formulation of apixaban, and that formulation is made by roller compactor, which is too expensive for patients on low incomes to afford. Consequently, a formulation is designed that is less expensive than the commercial formulation.

Play important role of Superdisintegrants in the formulation of apixaban tablet: Superdisintegrants have a rapid disintegration rate because of the interaction between swelling and water absorption. Superdisintegrants increase the system's wettability and dispersibility, which improves the disintegration and dissolving properties.

Synthetic Superdisintegrants: SSG and CCS are Synthetic Superdisintegrants. Both direct compression and wet granulation methods can employ croscarmellose sodium. In wet granulation, the croscarmellose sodium should be applied intra- and extra-granularly during both the wet and dry stages of the process to optimize the disintegrant's wicking and swelling properties.

Applying it to tablets made via wet granulation or direct compression is advised. In a formulation, the ideal concentration is roughly 4%, while 2% is often adequate. The suggested concentration ranges from 2 to 8%.

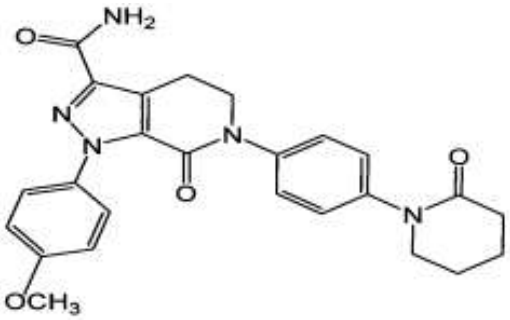

Fig. 1. Structure of apixaban

2. MATERIALS AND METHODS

Apixaban as a gift sample was obtained from Cadila research centre, Ahmedabad, lactose anhydrous, microcrystalline cellulose, crosscarmellose sodium, sodium starch glycolate, crospovidone were purchased from Aarty laboratory, sodium lauryl and magnesium stearate was purchased from peter greven [6-12].

2.1 Preparation of Apixaban Immediate Release Tablet by Wet Granulation Method

Dispensing: Carryout the dispensing of the active pharmaceutical ingredient and excipients.

Sifting: Sift Apixaban through sieve no # 30. Sift lactose, microcrystalline cellulose and croscarmellose sodium through # 30 sieve and magnesium stearate through # 60 sieve.

Dry mixing: Mix the sifted material Apixaban, MCC, lactose and CCS for 10 minute in rapid mixing granulator.

Granulation: Granulate the blend using purified water as the binder solution.

Drying: Dried the wet granules using fluidized bed dryer. Check the LOD of the granules.

Prelubrication: Sift the dries granules to the blender, add the presifted croscarmellose sodium and rotate the blender for 10 minute.

Lubrication: Add the presifted magnesium stearate above prelubricated material and blend for 3 min.

Compression: Compress the lubricated blend on B tooling compression machine.

2.2 Evaluation of Powder Blend

2.2.1 Bulk density

By adding a 25 gm. amount of tablet blend to a graduated cylinder and measuring the height, bulk density was ascertained. The following formula was used to get the bulk density.

Bulk density = Weight of the powder/Bulk volume of powder.

Table 1. Formulation of apixaban immediate release tablet

Ingredient	F1	F2	F3	F4
Apixaban	5	5	5	5
Lactose Anhydrous	86.5	86.5	86.5	86.5
MCC(102)	95	95	95	95
Sodium starch glycol ate	2	4	-	-
Crosscarmellose Sodium	-	-	2	4
SLS	1.5	1.5	1.5	1.5
Magnesium Stearate	1.0	1.0	1.0	1.0

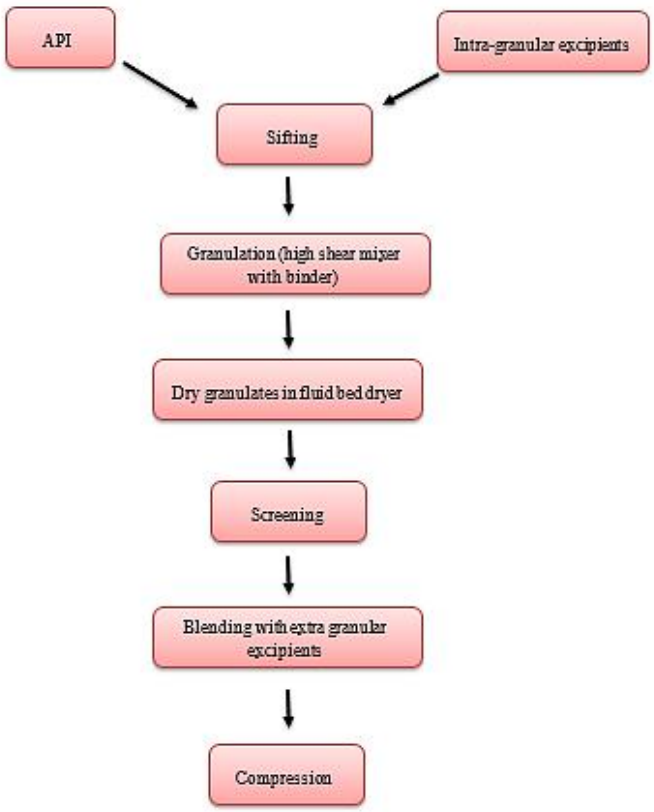

Chart 1. Flow chart representation

2.2.2 Tapped density

The ratio of tablet blend mass to tapped volume is known as the "tapped density." A graduated cylinder was filled with the tablet blend. The cylinder was then given 100 taps on a hard surface while supporting its own weight. The following formula was used to get the taped density.

Tapped density = Weight of powder taken/Tapped volume

2.2.3 Carr's Compressibility index

The powder's capacity to use bulk density and tapped density to reduce its volume under pressure is known as compressibility. The relative flow rate has an indirect bearing on it. The following formula was used to calculate Carr's compressibility index.

Compressibility index (%)= pt – po * 100 / pt

Where, pt = Tapped density gm./ml, po = Bulk density gm./ml

2.2.4 Hausner's ratio

By comparing the tapped density to the bulk density, Hausner's ratio can be used to determine the powder's flow qualities. Given the formula, Hausner's ratio was calculated.

Hausner's ratio = Tapped density / bulk density

2.2.5 Angle of repose

A fixed funnel approach was used to calculate the angle of repose (θ). The funnel's height was adjusted until the tip of the funnel just brushed the top of the granule heap. Granules were let to freely pour onto the surface through the funnel. This formula was used to determine the granular cone's diameter and determine its angle of repose.

$\tan \theta = h / r$

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

2.3 Evaluation of Apixaban Tablet

Weight variation: 20 tablets were weighed individually. Average weight was calculated and the individual tablet weight to the average was compared.

Thickness: Using vernier caliper in mm.

Hardness: Using Monsanto hardness tester.

Friability: % friability = (W1 – W2) / W1 * 100

Tablet Disintegration time: The USP device to test disintegration is six glass tubes that are 3cm long, open at the top, and held against 10# screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is positioned in 1 litre beaker of distilled water at 37± 2 ° C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker [13]

In-vitro **Dissolution study:** Dissolution testing plays an important role in the pharmaceutical industry for drug formulation development, quality control testing for batch manufacturing consistency and specification setting, and establishment of in vitro–in vivo relationships between release of drug from the dosage form and drug absorption (1, 2). USP Apparatus 1 (baskets) and 2 (paddles), the most widely used methods for dissolution tests, provide a well-stirred, medium-rich environment in which dosage form disintegration and dissolution can be evaluated

2.4 Dissolution Parameters

Medium: 0.05 M Sodium Phosphate Buffer with 0.05 % SLS, Ph 6.8

Volume: 900 ml

Apparatus: USP Type – II (Paddle)

Time: 15, 30, and 45 minutes.

Speed: 75 RPM

2.5 Chromatographic Conditions

The liquid chromatograph is equipped with a variable wavelength UV detector, an injector and a data processor.

Dissolution medium (pH. 6.8 Sodium phosphate buffer + 0.05 % SLS): Accurately weigh and transfer 68.0 g of sodium dihydrogen orthophosphate monohydrate (NaH2PO4 HO4) into 10 L of purified water. Dissolve and mix well. Adjust pH 6.8 with dilute sodium hydroxide solution. Add 5.0 g of sodium lauryl sulphate into it and mix well to dissolve.

Mobile Phase: Prepare a degassed mixture of 600 volume of water and 400 volume of acetonitrile. Add 1.0 ml of triethylamine into it and mix well.

Note: Mobile phase is stable for 3 days.

Diluent: Use dissolution medium as diluent.

Table 2. Chromatographic parameters

Column	Inertsil ODS – 3V (150 mm × 4.6 mm), 5µm
Column Temperature	40^0 C
Sample Temperature	25^0 C
Detection wavelength	280 nm
Flow Rate	1.0 Ml / minute
Injection Volume	50Ml
Retention Time	About 4 minutes for Apixaban peak
Run Time	10 Minutes

Standard stock solution: Accurately weigh and transfer 56.0 mg of Apixaban standard into 200 ml of volumetric flask, add about 140 ml of methanol and sonicate to dissolve. Dilute to volume with methanol and mix.

Standard solution (For 5 mg): Dilute 4.0 ml of this solution to 200.0 ml with diluent and mix well.

Note: Standard solution is stable for 30 hours at room temperature.

2.6 Assay

Mobile phase: Prepare a degassed mixture of 600 volume of water and 400 volume of acetonitrile. Add 1.0 ml of triethylamine into it and mix well.

Diluent:- Use mobile phase as diluent

Table 3. Assay parameters

Column	Inertsil ODS – 3V (150 mm × 4.6 mm), 5µm
Column Temperature	40^0 C
Sample Temperature	25^0 C
Detection wavelength	280 nm
Flow Rate	1.0 ml / minute
Injection Volume	10µL
Retention Time	About 4 minutes
Run Time	10 Minutes

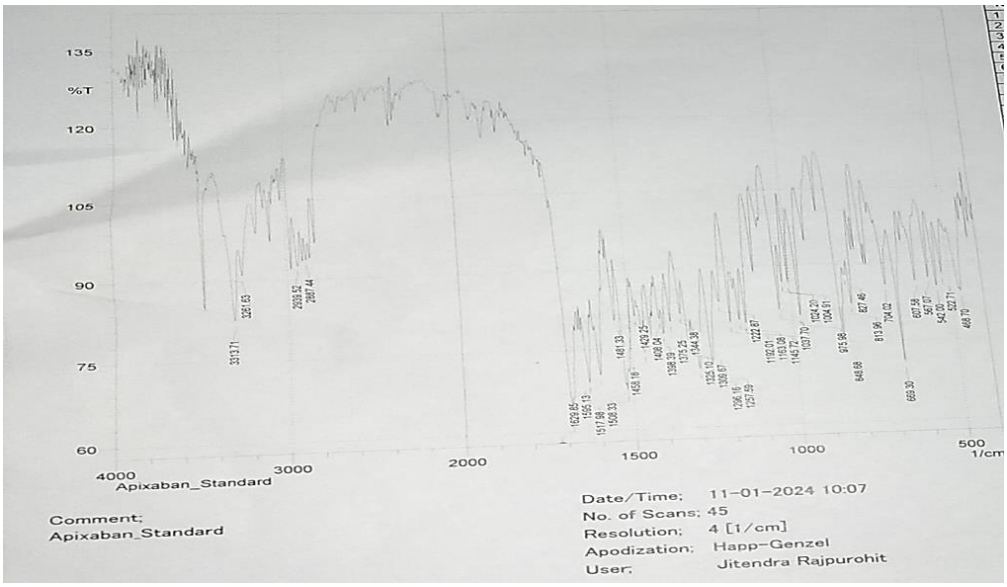

Fig. 2. IR spectrum of apixaban

3. RESULTS AND DISCUSSION

Table 4. API characterization

Sr. no	Test	Specification	Result
1	Loss on Drying(at 1050C)	Not more than 0.50 %w/w	0.17 % w/w
2	Assay:	Not less than 98.0% w/w and Not more than 102% w/w	100.22% w/w
3	Density i) Bulk ii) Tapped		0.242 g/ml 0.364 g/ml
4	Compressibility Index		33.333%
5	Hausner Ratio		1.500
6	Particle Size #	Not less than 98.0% should pass through #1250 mesh.	D (90) = NMT 10 µm

Table 5. Drug excipient compatibility studies

Sample	Ingredients	Ratio	Description
1	API	NA	White or Yellowish Powder
2	Lactose	NA	White to - off white Powder
3	Microcrystalline Cellulose	NA	White to - off white Powder
4	Croscarmellose Sodium	NA	White to - off white Powder
5	SLS	NA	White to - off white Powder
6	Magnesium Stearate	NA	White to - off white Powder
7	API + Lactose	1 : 1	White to - off white Powder
8	API + Microcrystalline Cellulose	1 : 1	White to - off white Powder
9	API + Crosscarmellose sodium	1 : 0.5	White to - off white Powder
10	API + SLS	1 : 0.5	White to - off white Powder
11	API + Magnesium stearate	1 : 0.5	White to - off white Powder

Table 6. Excipient compatibility studies: 40^{0}C /75% RH 1M close

Sr. no.	Excipient name	Condition	Pack	Result
1	API + Lactose	40^{0}C/75%RH 1M	Close	Not detected
2	API + SLS	40^{0}C/75%RH 1M	Close	Not detected
3	API + Instacoat pink	40^{0}C/75%RH 1M	Close	Not detected
4	API + Hypromellose	40^{0}C/75%RH 1M	Close	Not detected
5	API + MCC	40^{0}C/75%RH 1M	Close	Not detected
6	API + Magnesium stearate	40^{0}C/75%RH 1M	Close	Not detected
7	API + CCS	40^{0}C/75%RH 1M	Close	Not detected
8	API + SSG	40^{0}C/75%RH 1M	Close	Not detected
9	API + Crospovidone	40^{0}C/75%RH 1M	Close	Not detected

3.1 Sieve Analysis

Table 7. Particle size determination of apixaban

Sieve	Initial weight	Final weight	Weight Retained	%Retained	%Cum Retained	%Passing
20	450.62	452.25	1.63	3.25	3.25	96.75
40	356.12	359.59	3.47	6.93	16.31	83.69
60	400.53	402.92	2.39	4.77	21.09	78.91
80	397.94	401.59	3.65	7.29	28.37	71.63
100	395.24	396.96	1.72	3.43	31.81	68.19

Table 8. Evaluation parameters of tablets

Formulation Code	Thickness ± S.D. (mm) (n = 5)	Hardness ± S.D. (KP) (n = 5)	Friability (%)	Disintegration Time
F1	3.70±0.2	130-140N	0.07%	5 - 6 min
F2	3.70±0.2	130-140N	0.06%	2 – 3 min
F3	3.70±0.2	150-170N	0.01%	4- 8 min
F4	3.70±0.2	150-170N	0.02%	4:30 - 5 min

3.2 Analytical Method Validation for Dissolution of Apixaban in Apixaban Tablets by HPLC

Linearity stock solution: Accurately weigh and transfer about 55.6 mg of Apixaban standard into 200 ml of volumetric flask, add about 140 ml of methanol and sonicate to dissolve. Make volume upto the mark with methanol and mix (278µg/ml).

Linearity solution preparation: Prepare linearity solution as described in following table and inject single injections of each linearity solution onto liquid chromatograph and record chromatograms.

Table 9. *In-vitro* release profile of F4 batch of apixaban tablet pH 6.8 buffer + 0.05% SLS

Sr. No.	Time(min)	%Drug Release
1	5	78.5
2	10	95.2
3	15	100.4
4	20	103.5
5	30	104.9
6	45	105.5

Table 10. Linearity solution preparation

Linearity level	Linearity stock solution to be taken (ml)	Dilute to volume with dissolution medium and mix (ml)	Concentration of Apixaban (µg/ml)	Average area
5%	1.0	200	1.395	154702
50%	2.0	200	2.790	313891
100%	4.0	200	5.581	617917
125%	5.0	200	6.697	745367
150%	6.0	200	8.371	922723

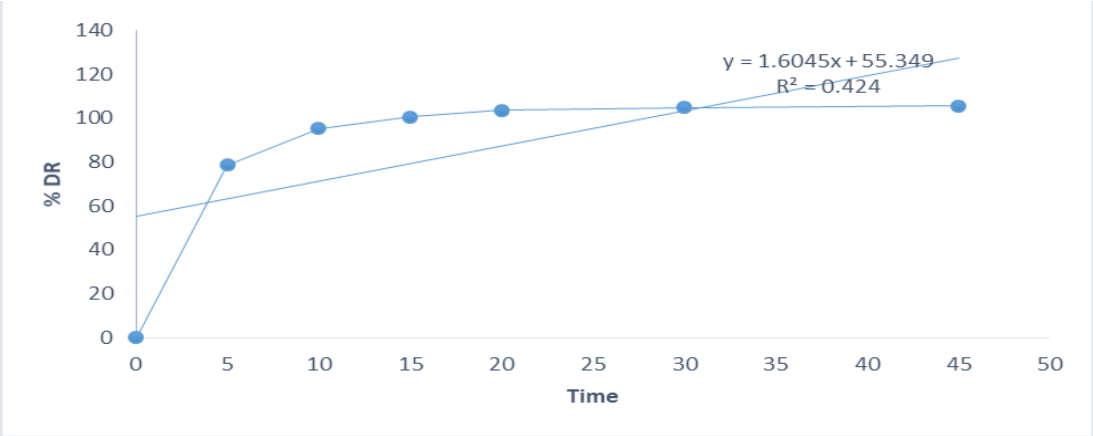

Fig. 3. *In vitro* release profile of F4 batch

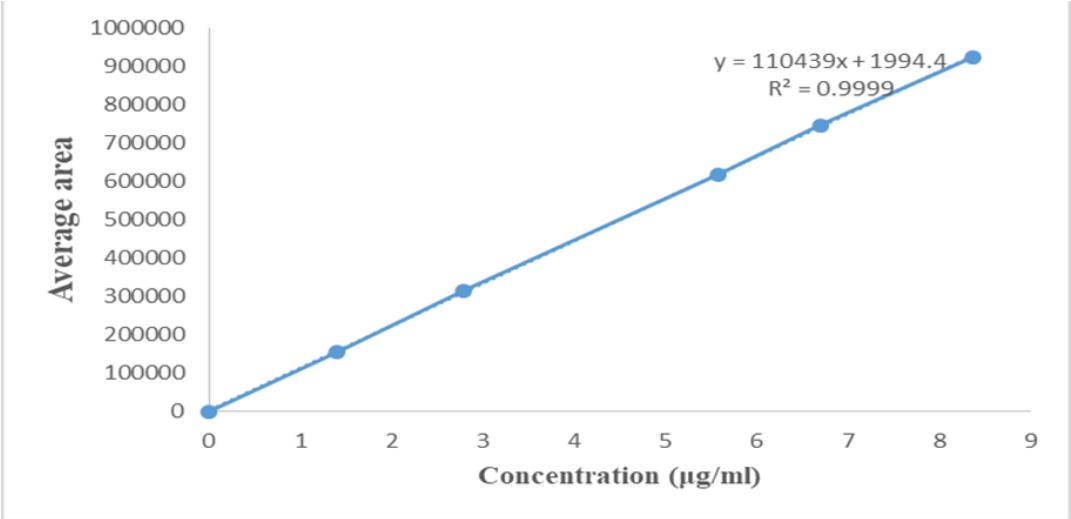

Fig. 4. Linearity of apixaban

The results are described as: Based on the literature review, the immediate release tablet was prepared and the effect of superdisintegrant and method of formulation on drug release profile was observed.

Formulation F1:

- In formulation F1 SSG used as disintegrant, Magnesium stearate is used as lubricant,
- The formulation F1 having concentrations of SSG (2.0%),
- The percentage drug release from the tablets was found to be slow
- So it was decided to increase concentrations of SSG

Formulation F2:

- In this the concentration of SSG was increased. Then these granules were compressed.
- The formulation F2 having concentration of SSG 4%.
- The formulation resulted in tablets in which the disintegration time was more and the percentage release was also found to be slow.
- So it was decided to change the disintegrant. CCS used as disintegrant instead of SSG

Formulation F3:

- In this formulation F3 CCS was used instead of SSG.
- The formulation F3 having concentration of CCS (2%).
- The formulation F3 resulted in increase of dissolution profile of Apixaban But the % release slower.
- So it was decided to increase the concentration of superdisintegrants.

Formulation F4:

- In this formulation F4 the concentration of superdisintegrants was increased than F3.
- The formulation F4 having concentration of CCS (4%).
- The formulation F4 resulted in increase of dissolution profile of Apixaban and the % release from the formulation was good.
- So it was decided that optimized concentration of CCS is 4% and F4 is the optimized formula.

3.3 Stablilty Study of Optimized Apixaban Tablet

Apixaban tablet used to treat or prevent deep venous thrombosis. The half-life of Apixaban was 12 hours.

The daily dose of Apixaban tablet was described as 5mg/ for only once daily.

Therefore an attempt is made to formulate immediate release formulation, which has disintegration time less than 15 min and the dissolution profile of the drug with very faster release [13].

In the formulation of immediate release tablet Croscarmellose sodium used as superdisintegrants, HPMC and SLS used as binder. Other excipients used are lactose, Microcrystalline Cellulose and Magnesium stearate (lubricating agent) [13].

The formulations F1, F2, F3 and F4 were prepared by wet method, formulation F1 and F2 were prepared by wet granulation method and used SSG used as superdisintegrant. The formulation resulted in tablets in which the disintegration time was more and the percentage release was also found to be slow. So it was decided to change the disintegrant. CCS used as disintegrant instead of SSG.

Formulation F3 and F4 were prepared by wet granulation method and CCS used as superdisintegrant.

The formulation F4 resulted in increase of dissolution profile of Apixaban and the % release from the formulation was good. So it was decided that optimized concentration of CCS is 4% and F4 is the optimized formula [13].

Superdisintegrants croscarmellose sodium were used to give immediate release for the tablets. The prepared immediate release tablets were evaluated for hardness, weight variation, thickness, friability, drug content uniformity, in-vitro dissolution studies. F4 formulation showed good evaluation studies and an immediate drug release [13].

Table 11. Stability study of optimized batch F4 performed for 1 month at 40 ^{0}C / 75 % RH and evaluated for various parameters

Test	Specification	Initial	1 month 40 / 75 % RH
Description	Pink colored, oval shaped tablet with plain on both sides	Complies	Complies
Assay	NLT 90 % w/w NMT 110 % w/w	99.5 %	97.2%
Dissolution	NLT 70% (Q) of the stated amount of Apixaban should dissolve in 45 minutes	Avg – 90.7% Min – 88.8% Max – 94.4%	Avg - 89.1 % Min – 85.8% Max – 90.4%

4. CONCLUSION

Batch F4 was determined to be a promising formulation appropriate for the immediate release of apixaban based on the formulation evaluation. The stability of the assay method's results indicates its simplicity, accuracy, specificity, sensitivity, and precision.

ACKNOWLEDGEMENT

Words cannot express my gratitude to my Principal Dr. Ravindra Pal Singh. I could not undertaken this journey without my guide, who generously support me in all steps. I am extremely grateful to Cadila Pharmaceuticals for their support without which it would not be possible for completion of our project. I also could not have undertaken this journey without my parent's support, which lead me toward achieving my goals.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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