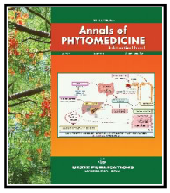
Annals of Phytomedicine 13(1): 896-906, 2024

DOI: http://dx.doi.org/10.54085/ap.2024.13.1.96

Annals of Phytomedicine: An International Journal
http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Original Article : Open Access

Formulation, evaluation and bioequivalence studies of apixaban tablet

Sadia Parveen, Ravindra Pal Singh◆ and Gulshan Rathore
Department of Pharmaceutics, NIMS Institute of Pharmacy, NIMS University, Jaipur-303121, Rajasthan, India

Article Info

Article history
Received 8 April 2024
Revised 25 May 2024
Accepted 26 May 2024
Published Online 30 June 2024

Keywords
Apixaban
Oral disintegrating film
CCS
HPLC method.

Abstract

This research showed how to prepare and assess immediate release doses of apixaban. In this research study, we are formulating apixaban by wet granulation method. Prior studies have been carried out using direct compression and dry granulation techniques.The proposed wet granulation method has several advantages in terms of feasibility and cost effectiveness. The current formulation compares the performance of disintegrants such croscarmellose sodium (CCS) and sodium starch glycolate (SSG), with the latter being proven to produce the best outcomes. Superdisintegrants are compounds that, as their name implies, are superior to disintegrants and that facilitate or enhance the dissolution time steady at minimal levels, usually 1-10% by weight virtual to the total mass of the amount item. These are used to boost the potency of the solid dosage form.

1. Introduction

For decades, administration of drugs orally has been considered the administration technique that is most commonly utilised among all methods for drug delivery from various pharmaceutical products in various pharmaceutical forms. The reason for the popularity of the convenience of administering oral medication and the conventional wisdom that states medication is well absorbed when taken orally in conjunction with food in the stomach and intestines may contribute to its popularity.This is the best and most popular way to use the drug due to its effects on the body. Moreover, oral drugs are often considered the most preferred method in the identification and creation of novel medications and pharmacological models, mostly as a result of patient acceptance, simplicity of use, and economical production techniques (Yu *et al.,* 2011; Irfan, 2016).

The process of blood changing from liquid to gel and forming blood is called coagulation, sometimes coagulation. Hemostasis, or the cessation of blood in the damaged blood vessels, will occur and then heal. Platelet activation, adhesion, and aggregation, as well as fibrin deposition and maturation, are products of the coagulation mechanism.

Anticoagulants, are medications that is used for blood clotting and make the blood last longer. Some of these occur in animals that feed on blood and help keep the bite site closed long enough for the animal to draw blood. Anticoagulants, as a group of drugs, are used in the treatment of thrombotic diseases. Many people take oral contraceptives (OACs) in tablet or pill form, and hospitals also use different types of oral contraceptives (Mehta *et al.,* 2010).

Atrial fibrillation (AFib) is an irregular and often very fast heartbeat. Irregular heartbeats are called arrhythmias. AFib can cause blood clots in the heart. During AF, the upper chamber of the heart, called the atrium, beats irregularly. They beat out of sync with the inner part of the heart, called the ventricle. For many people, AFib may have no symptoms. But atrial fibrillation can cause rapid heartbeat, shortness of breath, or dizziness (Pourmand *et al.,* 2011; Zhang, 2011).

Corresponding author: Dr. Ravindra Pal Singh
Principal, NIMS Institute of Pharmacy, NIMS University, Jaipur-303121, Rajasthan, India
E-mail: ravindraceutics@gmail.com
Tel.: +91-9982472142

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. Formulation method given in Table 1 (Varma *et al.,* 2004; Kaushal *et al.,* 2004).

2.1 Manufacturing process in detail

2.1.1 Weighing and checking

Check the weight of all the raw material as per the dispensing sheet.

2.1.2 Sifting

Co sift apixaban, lactose (Supertab 11SD), MCC and CCS through # 30 on mechanical sifter.

2.1.3 Dry mixing

Load presifted MCC and CCS. Then load pre sifted apixaban and lactose (Supertab 11 SD) and mix for 10 min slow at slow speed of impeller and chopper off position (Sekar *et al.,* 2008).

2.1.4 Binder preparation

Dissolve HPMS in purified water (37 ± 5^{0}C) under stirring until a clear solution is formed. Dissolve kolliphor sodium lauryl sulphate of purified water (35 ± 5^{0}C) under stirring until a clear solution is formed.

Table 1: Formulation of apixaban immediate release tablet

Intragranular part							
Formulation	**Quantity (mg/tablet)**						
Ingredient	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Apixaban	5.00	5.00	5.00	5.00	5.00	5.00	5.00
MCC	68.0	68.0	68.0	68.0	68.0	68.0	68.0
Lactose	100	100	100	100	100	100	100
Sodium starch glycolate	**4.00**	**8.00**	-	-	-	-	-
Crospovidone	-	-	**4.00**	**8.00**	-	-	-
Croscarmellose sodium	-	-	-	-	**4.00**	**8.00**	**8.00**
Binder solution							
Hydroxy propyl methyl cellulose	2.00	2.00	2.00	2.00	2.00	2.00	2.00
sodium lauryl sulphate	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Filtered water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Extragranular part							
SSG, CCS, Povidone	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Theoretical weight (Core tablet)			**189.00 mg**			**190.00 mg**	
Film coating							
Instacoat T2F				6.00 (mg/tablet)			
Purified water				Q.S			
Theoretical weight (Coated tablet)				**196 mg**			

Q.S = Quantity specification

2.1.5 Granulation

Add binding solution into dry mix and granulate with following parameters given in Table 2.

Table 2: Granulation method

S.No.	Process	Time	Impeller	Chopper
1	Binder addition	2 to 3 min	Slow	Fast
2	Kneading	NMT 5 min	Slow	Fast

2.1.6 Drying

Dry the granules at inlet temperature 60^0C ± 10^0C, dry the granules till the loss on drying is between 1.50 to 3.50% w/w at 105^0C in auto mode (Using halogen moisture analyzer).

2.1.7 Dry screening

Sift the dried granules through mechanical sifter equipped with # 20 sieve. Collect # 20 sieve passed and retained granules in the separate double poly bag.

2.1.8 Sifting of extra granular ingredients

Sift croscarmellose sodium through # 30 and magnesium stearate through # 60 on mechanical sifter and collect both in separate double polythene.

2.1.9 Lubrication

Add previously sifted croscarmellose sodium and mix for 10 min at 12 rpm. Add previously sifted magnesium stearate and mix for 3 min at 12 rpm.

2.1.10 Compression

Compress the lubricated blend for Apixaban tablets 5 mg using approved tooling on predefined compression parameters as mentioned below.

2.1.11 Coating

Disperse of instacoat T2F pink in specified quantity of purified water (temperature: 35 ± 5^0C) under stirring and continue the stirring for 45 min.

Filter the above suspension by using # 100 sieve. Ensure continuous mixing during coating process.

2.2 Evaluation of tablets

- Hardness test
- Weight variation test
- Friability test
- Tablet disintegration time
- *In vitro* dissolution study

2.2.1 Hardness test

The hardness of tablet is an indication about its strength. Here, the force required to break the tablet is measured. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

2.2.2 Weight variation test

The weight variation test is carried out to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average weight was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

2.2.3 Friability test

Friability is the loss in the weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to find the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets.

20 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 min. The tablets were deducted and weighed again. The percentage of weight loss was calculated again. The percentage of weight loss was calculated using the formula:

% Friability = [(W1 – W2)100]/W1

where,

W1= Weight of tablet before test

W2 = Weight of tablet after test

2.2.4 Tablet disintegration time

The USP apparatus used to test for damage is a 3 cm long glass tube with an open top and a 10# screen resting on the lower end of the basket. Place one tablet in each tube and place the basket in a 1 liter container of distilled water at 37 ± 2°C; so that the tablet will be at the bottom of the liquid, moving up and down more than 2.5 cm from the bottom of the container.

2.2.5 *In vitro* dissolution study

Immediate release tablets were subjected to in vitro drug release studies in 0.1 N HCl for 30 min to understand the ability of the formula to provide immediate drug delivery.

The drug release study was performed in an eight-level dissolution tester using a volume of dissolution medium controlled at 37 ± 10^{0}C. Keep the tablets in a cylindrical basket and spin at 100 rpm, taking 5 ml of sample without separation each time (2, 3, 5, 10, 15 and 30 min) and adding 5 ml of fresh medium to each time. Filter the sample, take 1 ml from the filter and dilute to 10 ml.

2.3 Tentative method for assay (HPLC method)

2.3.1 Reagent, solvents and standards

- Water (Milli- Q or equivalent)
- Acetonitrile (HPLC grade)
- Triethylamine (A. R grade)
- Apixaban working standard

2.3.2 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.

2.3.3 Diluent

Use mobile phase as diluent (Gupta *et al.,* 2012).

2.3.4 Standard preparation

Determine the exact weight of the Apixaban working standard by transferring 50.0 mg into a 100 ml volumetric flask. Then, add 70 ml of diluent and sonicate to dissolve. Mix after diluting with diluent to the mark. Mix thoroughly after diluting 4.0 ml of the solution with 100 ml of diluent.

2.3.5 Sample preparation

Weigh 20 tablets and calculate the average weight. Measure eight unbroken pills and transfer them to a 200 ml volumetric flask. With sporadic shaking, sonicate for 20 min after adding around 140 ml of diluent. After cooling to room temperature, dilute with diluted mixture and combine. Mix 50 ml of diluent with 5.0 ml of this solution. Filter the mixture thoroughly. 0.45 µm nylon filter, with the first 5.0 ml of the filtrate discarded (Granger *et al.,* 2011).

3. Results

The present study of apixaban immediate release tablets were developed with a view to deliver the drug immediately. The formulation development work was initiated with wet granulation method and a total of 7 formulations were made. The formulated tablets were evaluated for various precompression parameters and post compression parameters like thickness, hardness, weight variation, friability, disintegration test, drug content uniformity and *in vitro* release studies. The formulation F7 showed satisfactory physical parameters, and it was found to be stable among other formulations.

3.1 Preformulation studies

Table 3: Organoleptic properties of apixaban

S.No.	Organoleptic properties	Result
1	State	Solid
2	Color	White to off-white
3	Taste	Bitter
4	Odor	Odorless
5	Nature	Crystalline powder
6	Hygroscopicity	Hygroscopic in nature

3.2 Objectives

Preformulation studies main goal is to provide formulators with relevant data so they can create stable, bioavailable dosage forms that are scalable for mass production.

3.3 Solubility

Different solvents were used to test the apixaban solubility. The outcomes thus acquired were as follows Table 4 (Kumar *et al.,* 2016).

Table 4: Solubility of drug sample

S.No.	Media	Solubility
1	Purified water	0.04
2	0.1 N Hcl (Ph1.2)	0.04
3	Ph 4.5 acetate buffer	0.03
4	Ph 6.8 phosphate buffer	0.03
5	Ph 6.8 phosphate buffer with 0.05 % SLS	0.05
6	Ph 6.8 phosphate buffer with 0.1 % SLS	0.09

3.4 Identification of drug

3.4.1 Determination of Lambda max of apixaban

After preliminary self-testing the drug meets the prerequisites the drug's λ_{mx} of 280 nm, which matched the reported value of 280 nm, was determined by scanning the substance. An IR spectra was also consistent with apixaban reference spectrum.

3.5 Compatibility study of drug excipients given in Table 5

Table 5: Compatibility study of drug excipient

S.No.	Ingredients	Ratio	Description
1	API	NA	White or yellowish powder
2	Lactose	NA	White to - off white powder
3	Microcrystalline cellulose	NA	White color powder
4	Croscarmellose sodium	NA	White color powder
5	SLS	NA	White color powder
6	Hypromellose	NA	White to - creamy white powder
7	Magnesium stearate	NA	White color powder
8	Instacoat yellow	NA	Light yellow to yellow powder
9	Instacoat pink	NA	Pink to light red powder
10	API + Lactose	1 : 1	White powder that is off-white.
11	API + Microcrystalline Cellulose	1 : 1	White powder that is off-white.
12	API + Crosscarmellose sodium	1 : 0.5	White powder that is off-white.
13	API + SLS	1 : 0.5	White powder that is off-white.
14	API + Hypromellose	1 : 0.5	White to - creamy white powder
15	API + Magnesium stearate	1 : 0.5	White powder that is off-white.
16	API + Instacoat yellow	1 : 0.5	Light yellow to yellow powder
17	API + Instacoat pink	1 : 0.5	Pink to light red powder

Table 6: Excipient compatibility studies: Initial

S.No.	Excipient name	Condition	Pack	Result
1	API + Lactose	Initial	Close	Not detected
2	API + SLS	Initial	Close	Not detected
3	API + Instacoat pink	Initial	Close	Not detected
4	API + MCC	Initial	Close	Not detected
5	API + Magnesium stearate	Initial	Close	Not detected
6	API + CCS	Initial	Close	Not detected
7	API + Hypromellose	Initial	Close	Not detected

Table 7: Excipient compatibility studies: 40^{0}C / 75% RH 1M Close

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

3.6 Analytical method validation for dissolution of apixaban in apixaban tablets by HPLC

3.6.1 Linearity stock solution

Precisely measure and move approximately 55.6 mg of Apixaban standard into a 200 ml volumetric flask. Sonicate to dissolve. Add approximately 140 ml of methanol. Add enough methanol to fill the capacity to the mark, then stir (278 µg/ml) (Singh *et al.,* 2013; Mohamad *et al.,* 2020).

3.6.2 Linearity solution preparation

Prepare linearity solution as described and inject single injections of each linearity solution onto liquid chromatograph and record chromatograms are given in Table 8.

Table 8: Linearity curve of apixaban

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

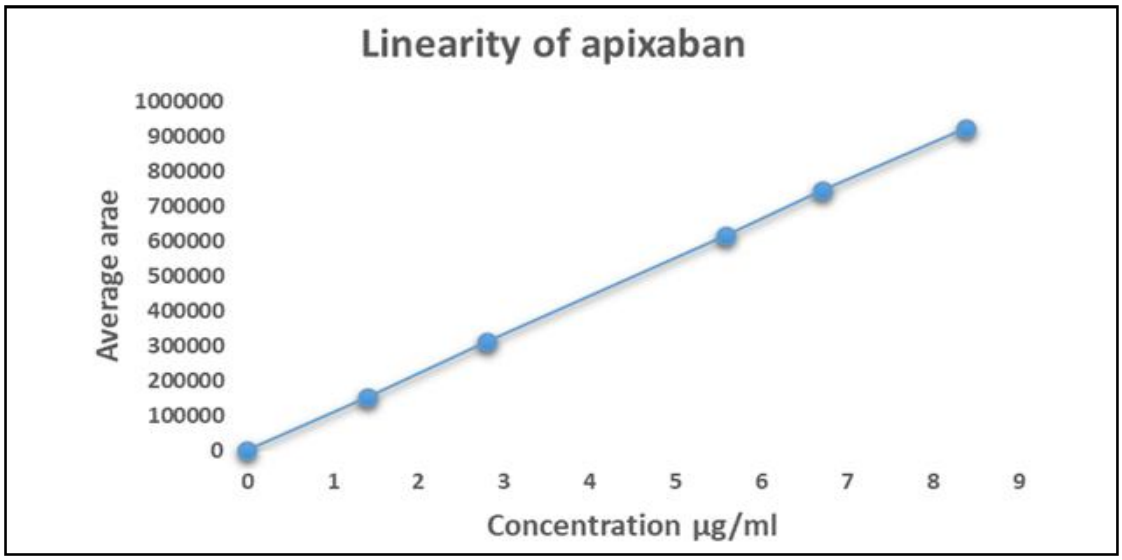


Figure 1: Linearity curve of apixaban.

3.7 Pre-compression study of preliminary trial formulations

Table 9: The flow characteristics of mixtures with various compositions

Batch	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hauser's ratio
F1	0.606	0.689	12.04	1.13
F2	0.571	0.714	12.02	1.25
F3	0.588	0.666	11.71	1.13
F4	0.606	0.714	15.12	1.17
F5	0.588	0.689	14.65	1.17
F6	0.588	0.714	17.64	1.21
F7	0.577	0.750	23.077	1.30

3.8 Post compression evaluation

Table 10: Evaluation parameters of tablets

Batch	Thickness	Hardness	Friability (%)	Disintegration time
F1	3.70 ± 0.2	130 - 140 N	0.07%	6 - 8 min
F2	3.70 ± 0.2	130 - 140 N	0.06%	2 - 3 min
F3	3.70 ± 0.2	150 - 170 N	0.01%	6 - 8 min
F4	3.70 ± 0.2	150 - 170 N	0.02%	3 - 5 min
F5	3.70 ± 0.2	150 - 160 N	0.03%	4 - 6 min
F6	3.70 ± 0.2	150 - 160 N	0.02%	4 - 6 min
F7	3.70 ± 0.2	150 - 160 N	0.02%	4:30 - 5 min

3.9 *In vitro* release profile outcomes

Table 11: *In vitro* release profile of innovator of apixaban pH 6.8 buffer + 0.05% SLS

S.No.	Time (min)	% drug release
1	5	55.7
2	10	92.9
3	15	95.5
4	20	96.6
5	30	97.8
6	45	98.7

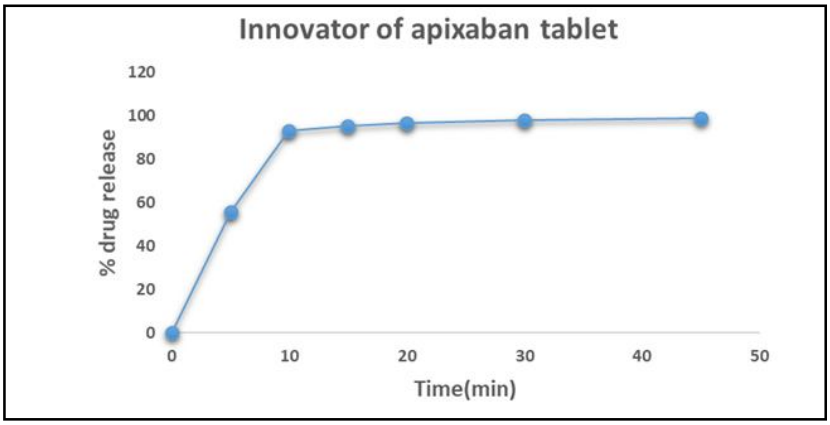


Figure 2: *In vitro* release profile of innovator of apixaban.

Table 12: *In vitro* study of F1 to F6 batch of apixaban pH 6.8 buffer + 0.05% SLS

S. No.	Time	F1	F2	F3	F4	F5	F6
1	5	35.7	45.6	55.6	58.5	55.6	60.5
2	10	49.6	56.5	67.7	65.1	64.5	63.4
3	15	64.3	68.1	75.3	77.4	73.8	74.5
4	20	70.4	74.6	78.8	81.7	79.2	80.7
5	30	78.1	83.2	82.5	85.8	88.0	90.5
6	45	83.5	88.3	86.0	88.4	89.7	93.1

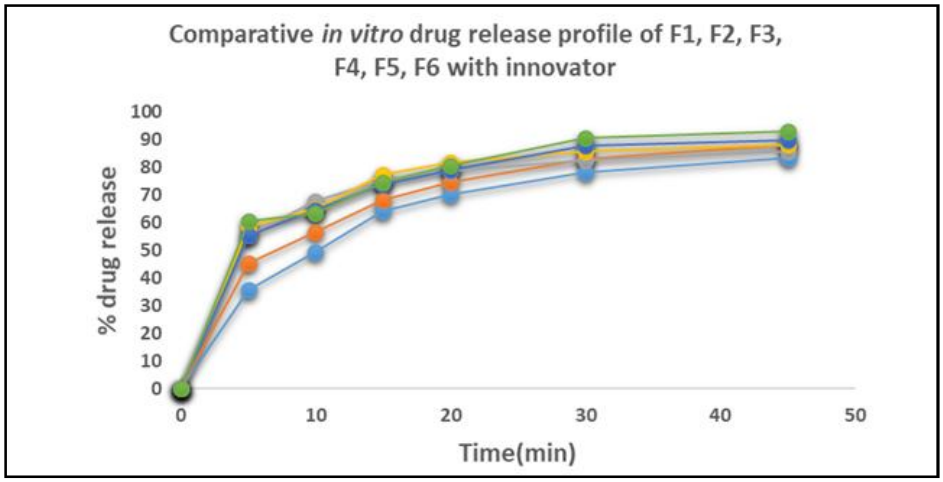


Figure 3: *In vitro* release profile of F1, F2, F3, F4, F5, F6 with innovator.

Table 13: *In vitro* release profile of F7 batch of apixaban pH 6.8 buffer + 0.05% SLS

S.No.	Time (min)	% drug release
1	5	58.7
2	10	92.9
3	15	94.5
4	20	96.6
5	30	97.6
6	45	98.5

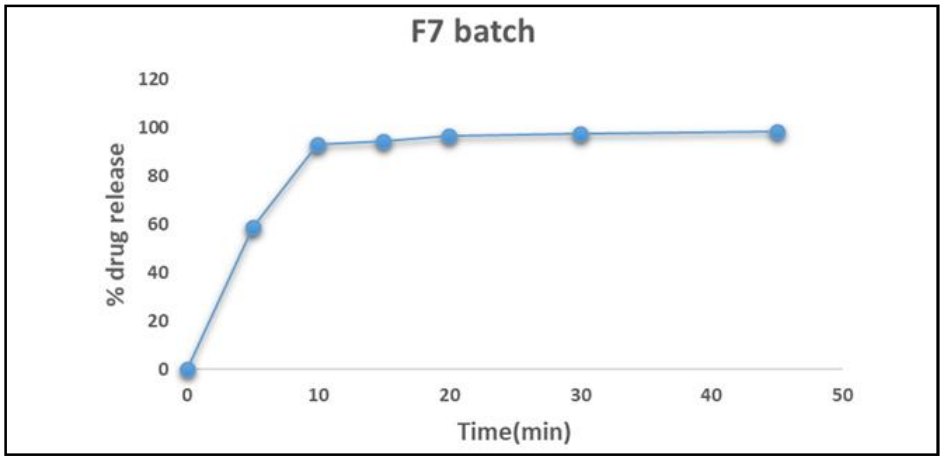


Figure 4: *In vitro* release profile of F7 batch of apixaban tablet.

Table 14: Comparison of F7 batch of apixaban tablet with innovator sample

S.No.	Time (min)	% drug release of F 7 batch	Innovator
1	5	58.7	55.7
2	10	92.9	92.9
3	15	94.5	95.5
4	20	96.6	96.6
5	30	97.6	97.8
6	45	98.5	98.7

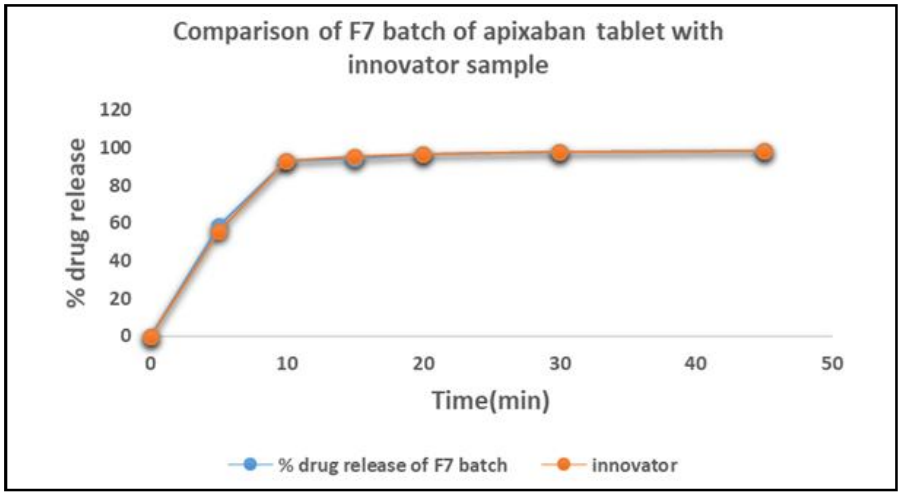


Figure 5: Comparison of F7 batch of apixaban tablet with innovator sample.

3.10 Formulation trial batches

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.

3.10.1 Formulation F1

- In formulation F1 SSG used as disintegrant, magnesium stearate is used as lubricant.
- The formulation F1 having concentrations of SSG (4.0%).
- The percentage drug release from the tablets was found to be slow when compared with the innovator sample.
- So, it was decided to increase concentrations of SSG.

3.10.2 Formulation F2

- In this formulation F2 also the same. But in this the concentration of SSG was increased.
- The formulation F2 having concentration of SSG 8.0%.
- 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 superdisintegrant.
- Hence it was decided to use crospovidone instead of SSG.

3.10.3 Formulation F3

- In this formulation F3 use crospovidone instead of SSG.
- The formulation F3 having concentration Crospovidone (4.0%)
- This formulation resulted in slightly increased dissolution than the F2. The % release of apixaban drug was very slow.
- So, it was decided to increase the super disintegrant concentration in order to enhance dissolution profile of apixaban from the formulation.

3.10.4 Formulation F4

- In this formulation F4 wet granulation was used and the concentration of the super disintegrant was increased.
- The formulation F4 having concentration of crospovidone (8.0%).
- The formulation F4 resulted in increase of apixaban % release but there is no improvement in the % release when compared with the innovator product.
- So, it was decided to change the superdisintegrant.
- Hence it was decided to use CCS instead of crospovidone.

3.10.5 Formulation F5

- In this formulation F5 use CCS instead of Crospovidone.
- The formulation F5 having concentration of CCS (4%).

- The percentage drug release from the tablets was found to be slow when compared with the innovator sample.
- So it was decided to increase the concentration of super disintegrants

3.10.6 Formulation F6

- In this formulation F6 the concentration of super disintegrants was increased than F7.
- The formulation F6 having concentration of CCS (8%).
- The formulation F6 resulted in increase of dissolution profile and the % release from the formulation was comparable with the innovator product.
- So, it was decided to take a trial to optimize F6 with similar formula as of F6. In order to optimize the formulation F6.

3.10.7 Formulation F7

- In this formulation F7 the formula is similar to F6.
- The formulation F7 having concentration of CCS (8%).
- The formulation F7 resulted in increase of dissolution profile and the % release of apixaban was comparable with the innovator product.
- So, it was decided that optimized concentration of CCS is 8% and F7 is the optimized formula.

3.11 Stability study data

The samples from the stability chambers that were enclosed in PVC blister packs underwent the subsequent examination is given in Table 14.

Table 15: stability study result

Parameter	Specifications	Initial	1st month at 40°C/ 75% RH
Description	Tablets with a plain surface on both sides, oval shape, and pink colour coated in film.	Complies	Complies
Assay	NLT 90% to NMT 110% of labelled amount.	99.7%	97.2%
Dissolution	NLT 70% (Q) of the stated amount of apixaban should dissolve in 45 min.	Avg-90.7%	Avg-89.1%
		Min-88.8%	Min-85.8%
		Max-94.4%	Max-90.4%
Moisture content	NMT 6.0%	NP	3.76%

Parameter	Initial	3 month at 40°C/ 75% RH	3 month at 30°C/ 75% RH
Description	Complies	Complies	Complies
Assay	99.7%	97.2%	97.6%
Dissolution	Avg-90.7%	Avg - 86.2%	Avg-90.6%
	Min-88.8%	Min-77.6%	Min-87.6%
	Max-94.4%	Max-90.0%	Max-93.9%
Moisture content	NP	5.49 %	5.13%

3.12 Bioequivalence study

3.12.1 Design, conduct and evaluation of bioequivalence studies of apixaban tablet 5 mg in Table 15

Table 16: Protocol synopsis

Title	An investigation of the bioequivalence of apixaban tablets 5 mg using randomised, open-label, two treatments, two periods, two sequences, single dose, balanced, two-way crossover of Cadila Pharmaceuticals Ltd., India compare with ELIQUIS (apixaban) Tablets 5mg of Bristol Myers Squibb Company under fasting conditions in mature, healthy human volunteers.
Study objectives	**Primary objective:** To determine Cadila Pharmaceuticals' apixaban Tablets, 5 mg, bioequivalency Ltd, India compare with ELIQUIS (apixaban) tablets 5 mg of Bristol-Meyers company. **Secondary objective:** The assessment of safety parameters, such as adverse events and clinical laboratory testing.
Sample size	The study will involve the enrollment of forty (forty) human subjects who are healthy adults between the ages of 18 and 45.

Check-in and stay	Subjects will be housed in the clinical facility of the clinical. At least eleven hours prior to medication delivery and up to twenty-four hours following drug administration, the pharmacology and pharmacokinetic unit.
Investigational product	
Test product (T)	Apixaban tablets 5 mg of Cadila Pharmaceuticals Ltd., India.
Reference product (R)	ELIQUIS (Apixaban) tablets 5 mg of Bristol-Myers Squibb Company
Administration	In the subject's setting posture, 240 millilitres of drinking water and a single oral dose of either the test product or the reference product will be given, at ambient room temperature in each period as per the randomized schedule.
Sample collection processing and separation	23 blood samples, each containing 95.0 ml, will be taken during each time. At least one hour before the medication is administered, a pre-dose blood sample will be taken. 0.00 h and then at 00.50, 01.00, 01.50, 02.00, 02.50, 02.75, 03.00, 03.25, 03.50, 03.75, 04.00, 04.25, 04.50, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 24.00, 36.00 and 48.00 h post-dose.
Washout period	There will be a minimum of seven-day washout interval in between each time period Ghourichay *et al.,* 2021.

3.12.2 Apixaban 5 mg fasting study

Parameters	gmT	gmR	Ratio	Power	Intra-cv	90% CI lowerbound	90% CI upperbound	Bioequivalence
LnCmax	210	220	95.34	99.97	11.16	89.36	101.72	YES
LnAUC,	1982	2092	94.75	99.99	9.83	89.5	100.32	YES
LnAUCinf	2008	2122	94.64	100	9.68	89.47	100.11	YES

4. Discussion

Apixaban tablet used to treat or prevent deep venous thrombosis. The half-life of Apixaban was 12 h. The recommended daily dosage for an Apixaban tablet was 5 mg, to be taken only once a day.

The formulations F1 to F7 batch were prepared by wet method, and SSG used as superdisintegrant in F1 and F2 batch. The resulting tablets with the formulation had a longer disintegration period and a slower percentage release. Thus, it was determined to switch out the disintegrant. As a disintegrant, crospovidone is utilised rather than SSG. Formulation F3 and F4 crospovidone used as superdisintegrant. The solubility profile of Apixaban increased with formulation F4, and the formulation's percentage release was satisfactory. However, it did not correspond with the innovator per cent medicine release. The dissolving profile increased as a result of the formulation F5, but comparison with the innovator sample revealed that the tablets' medication release percentage was lower. The decision was made to raise the CCS of Apixaban concentrations. CCS 8% and super disintegrants were the concentration in formulation F6. The innovator product's percentage release and the formulation F6's higher dissolving profile of Apixaban were both observed. To optimise F6 using a formula comparable to F6, a trial was therefore decided upon.

The super disintegrants in formulation F7 had a CCS concentration of 8%. Here, drug release of Apixaban was comparable with innovator on the basis of *in vitro* drug release profile.

The results of the isolation show the formation of the most successful research was F7, which showed a medication release pattern that was similar to the innovator drug release profile. Since F7's medication content was determined to be superior to that of other formulations, it was chosen as the optimal formulation.

5. Conclusion

Batch F7 was determined to be a promising formulation appropriate for the immediate release of apixaban based on the formulation evaluation. The results of dissolution studies indicated that formulation F7 is the most successful of the study, exhibited drug release pattern close to innovator drug release profile. The drug content of F7 was found to be better than other formulation, so that it was selected as optimized formulation. The designed immediate release film coated tablets of formulation F7 release 92.9% of apixaban in 10 min and 98.58% at 45 min. The developed immediate release film coated tablet formulation was quite stable with regard to drug content, physical properties and dissolution rate. Hence, it can be concluded that once daily immediate release film coated tablet of apixaban 5 mg having satisfactory drug release profile which may provide an increased therapeutic efficacy. The stability of the assay method's results indicates its simplicity, accuracy, specificity, sensitivity, and precision.

Acknowledgements

Words cannot express my gratitude to my Principal, Dr. Ravindra Pal Singh. I could not undertake 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.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Aulton, M.E. (2002). The Science of dosage form design; Churchill living stone; 2nd edition, pp:414-418.

Cooper, J. and Gun, C. (1986). Powder flow and compaction. Inc Carter SJ, Eds. Tutorial Pharmacy. New Delhi, hidix CBS Publishers and Distributors, pp:211-233.

Chen, Y. and Yao, J. (2016). Improving the solubility and bioavailability of apixaban *via* apixaban-oxalic acid cocrystal. Cryst. Growth Des, pp:2923-2930.

Do drill, P. and Gosa, M.M. (2015). Pediatric dysphagia: Physiology, assessment, and management. Ann. Nutr. Metab., **66**(S5):24-31.

Dilfuza, J.; Kannepalli, A.; Mohina, F.; Khurshid. S.; Dilbar, K.; Zafarjon Jabbarov and R. Z. Sayyed (2020). Isolation and characterization of endophytic bacteria from ginger (*Zingiber officinale*). Ann. Phytomed., **9**(1): 116-121.

Erdem, G; Esme, M. and Dogu, B.B. (2022). Systematic review and meta-analysis of randomized controlled trials on safety and effectiveness of oral anticoagulants for atrial fibrillation in older people, Ir. J. Med. Sci., **191**(6):2517-2523.

Frost, C.; Wang, J. and Nepal, S. (2013). Apixaban, an oral, direct factor X a inhibitor: Single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. Br. J. Clin. Pharmacol., pp:476-487.

Ghourichay, M.P. and Kiaie, S.H. (2021). Formulation and quality control of orally disintegrating tablets (ODTs): Recent advances and perspectives. Bio. Med. Res., pp:611-641.

Granger, C.B. and Alexander, J.H. (2011). Apixaban versus warfarin in patients with atrial fibrillation. N. Engl. J. Med., **365**(11):981-992.

Hoffmann, E.M.; Breitenbach, A. and Breitkreutz, J. (2011). Advances in orodispersible films for drug delivery. Expet Opin. Drug Deliv., pp:299-316.

Irfan. M.; Rabel, S. and Bukhtar Q (2016). Orally disintegrating films: A modern expansion in drug delivery system. Saudi Pharmaceut. J., **24**(5):537-546.

Jacob, S.; Nair A.B.; Boddu, S.H.S. and Gorain B. (2021). An updated overview of the emerging role of patch and film-based buccal delivery systems. Pharmaceutics, **13**(8):1206.

Karagianni, A.; Kachrimanis, K. and Nikolakakis, I. (2018). Co-amorphous solid dispersions for solubility and absorption improvement of drugs: Composition, preparation, characterization and formulations for oral delivery. Pharmaceutics, pp:10-98.

Lachman, L. and Lieberman, H.A. (1987). The theory and practice of Industrial pharmacy. Varghese Publishing House Bombay, pp:171-293

Lalitha, V.; Shila, G.; Amsa, P.; Prabha, T.; Saravana R. and Madhavan R. (2022). The indispensable role of herbs and other treatment strategies against gallstones. Ann. Phytomed, pp:52-64.

Martin, A. (2001). In: Martin A, ed. Physical Pharmacy. Baltimores, MD: Lippincott Williams and Wilkins, pp:423-454.

Mehta, K. and Garala K, Basu. (2010). An emerging trend in oral drug delivery technology: Rapid disintegrating tablets. J. Pharm. Sci. Tech., pp:318-329.

Patni, S.D.; Gondkar, S.; Darekar, A.; Sharma, Y. and Saudagar, R. (2013). Comparative evaluation of natural and synthetic superdisintegrants for fast dissolving tablet. J. Drug Deliv. Ther., pp:22-30.

Patil, C. and Das, S. (2011). Effect of various superdisintegrants on the drug release profile and disintegration time of Lamotrigine orally disintegrating tablets. Afr. J. Pharm. Pharmacol., pp:76-82

Pourmand, M. R.; Azar, M. S. and Aghavalijamaat, M. (2011). Development of validated UV spectrophotometric method for *in vitro* analysis of sumatriptan in pharmaceutical preparations in comparison with HPLC. Pharm. Chem. J., **44**(10):585-589.

Rohini, R.; Shimmula, Vishnu, P.; Atla, Srinivas, N.; Haarika, B. and Shanthi, PC. (2023). Formulation and evaluation of esomeprazole magnesium trihydrate controlled release floating tablets. Ann. Phytomed., **12**(2):963-971.

Sekar, V. and Chellan, VR. (2008). Immediate release tablets of telmisartan using superdisintegrant-formulation, evaluation and stability studies. Chem. Pharm. Bul., **56**(4):575-577.

Tripathi, K.D. (2008). Essentials of Medical Pharmacology. 6th ed. New Delhi: Jaypee Prakashan.

Varma, M. V. and Kaushal, A. M. (2004). Rapid and selective UV spectrophotometric and RP-HPLC methods for dissolution studies of oxybutynin immediate release and controlled-release formulations. J. Pharm. Biomed. Anal., **36**(3):669-674.

Vyas, S.P. and Roop, K. Khar. (2002). Controlled drug delivery concept and Advances, 1st Edition, pp:54-71.

Zhan, Y.; Joza, J.; Rawahi, M. and Barbosa, R.S. (2018). Assessment and management of the left atrial appendage thrombus in patients with non valvular atrial fibrillation. Can. J. Cardiol., pp:252-261.

Zhang, D.; He, K. and Herbst, J.J. (2013). Characterization of efflux transporters involved in distribution and disposition of apixaban. Drug. Metab. Dispos., pp:41-83.

Citation **Sadia Parveen, Ravindra Pal Singh and Gulshan Rathore (2024). Formulation, evaluation and bioequivalence studies of apixaban tablet. Ann. Phytomed., 13(1):896-906. http://dx.doi.org/10.54085/ap.2024.13.1.96.**