

## “Reimagining Apixaban Delivery with Microsphere Tablets.”

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### ABSTRACT

Thrombophilia is a condition where blood clots form easily. It often needs long-term treatment with blood medicines. Apixaban is a medicine that stops blood clots from forming. It is commonly used to treat blood clot disorders. However, taking Apixaban in the way can be hard for patients. They have to take it which can be annoying. This study is about making Apixaban tablets that release the medicine slowly. This way the medicine works better. Patients have to take it less often. The Apixaban tablets are made with spheres that contain the medicine. These spheres are made using a method with materials like hydroxypropyl methylcellulose and sodium alginate. The spheres were tested for their size, surface and how well they hold the medicine. The best spheres were then made into tablets. Tested for their hardness, how well they hold together and if the medicine is evenly spread. The results showed that the medicine is released slowly from the tablets. This makes the tablets work better and patients have to take them often. This new way of making Apixaban tablets seems promising for treating blood clot disorders. The Apixaban tablets can help patients take their medicine easily. Apixaban is a medicine, for stopping blood clots. Apixaban works well when it is released slowly in the body

**Keywords:** Apixaban, Microspheres, Ionic gelation technique, Thrombophilia, Controlled release, Sodium alginate, Tablet formulation

**How to cite this article:** Ghavate SA, Shinde JV, Bhosale A. “Reimagining Apixaban Delivery with Microsphere Tablets.” *Int J Drug Deliv Technol.* 2026;16(63s):359-364. DOI: 10.25258/ijddt.16.63s.38

**Source of support:** Nil.

**Conflict of interest:** None

### INTRODUCTION

Thrombophilia is a condition where the blood forms clots easily. This often means that people, with Thrombophilia need to take medicine to prevent blood clots for a time. Apixaban is a medicine that helps prevent blood clots. It is used to treat conditions where blood cloture a problem. The usual way of taking Apixaban is to take it times a day. This can be hard for people to remember to do. So, we tried to make a kind of tablet that would release Apixaban slowly over time. This way people would not have to take it often. We made tiny balls called microspheres that had Apixaban inside them. We used a technique to make these microspheres. The microspheres were made with a material called hydroxypropyl methylcellulose. We looked at the microspheres to see how big they were and what they looked like. We also checked to see how well they worked. Then we made tablets using the microspheres and other ingredients. We tested the tablets to make sure they were quality. We checked things like how hard they were and if they broke easily.

We also did a test to see how the Apixaban was released from the tablets. We used a machine to do this test. The results showed that the tablets released Apixaban over time. This is what we wanted to happen. The Apixaban was released because of the way the microspheres worked.

(9)

### MATERIALS AND METHODS

Apixaban API was procured from SM Pharma. HPMC K 15 and Calcium Chloride were obtained by Research lab fine chem industry Mumbai were, Sodium Alginate was purchased from Sentalab Industries for the preparation of microspheres.

Talc, magnesium stearate was obtained by Research lab fine chem industry Mumbai for the preparation of tablets.

#### Solubility Study:

Excess drug was added slowly to 10 ml of buffer solutions in a conical flask. I used a spatula to add

it while stirring. This went on until I got a mixture of solid and liquid. The solution with solid was then closed tightly and stirred at 150 rpm on the room temperature for a day. After that I filtered the solution with solid using a filter. Next, I made dilutions and checked them using a UV spectrophotometer. I did this at the required nanometer range, for the drug. The drug was checked in buffer solutions. The drug was analyzed properly.<sup>(2)</sup>

**PREPARATION OF CALIBRATION CURVE**

Accurately weigh 10 mg of Apixaban and dissolve in methanol to prepare a stock solution (1000µg/mL).

Dilute the stock solution with suitable medium to obtain concentrations (e.g., 2–20µg/mL).

Measure absorbance at  $\lambda_{max} \approx 278$  nm using a UV spectrophotometer. Plot concentration vs absorbance to obtain the calibration curve.<sup>(2) (9)</sup>

**FORMULATION DESIGN**

Batches	Type	Drug	HPMC	Sodium Alginate	Calcium Chloride	Distilled water
F1	Blank	0	50	100	5	100
F2	Blank	0	100	500	5	100
F3	Blank	0	200	750	10	100
F4	Blank	0	500	1000	15	100
F5	Loaded	10	100	500	5	100
F6	Loaded	10	200	750	10	100
F7	Loaded	10	500	1000	15	100

**Table no. 1 formulation design for Apixaban microsphere using different ratio of polymer**

“The first batch (F1) failed to form microspheres, likely due to insufficient polymer concentration or improper cross-linking conditions during the formulation procedure.”**Procedure:**

**Method used: Ionic Gelation Technique:**

Microspheres of Apixaban were prepared by ionotropic gelation method using Drug & Sodium alginate, and Polymers HPMC K15M, and calcium chloride.

Step 1: Add the weighed quantity of Sodium alginate and dissolved in 25ml of distilled water.

Step 2: Next to this, weighed quantity of drug and polymers were added to sodium alginate solution with stirring at about 800 rpm.

Step 3: The mixture was extruded dropwise through a 22G syringe needle into drop wise to 100 ml of calcium chloride (1%) solution under continuous stirring. Stirring was continued for 60 minutes. The obtained microspheres were filtered and washed with purified water and then dried for 12 hours at 70°C. Preparation of microspheres was optimized based on entrapment efficiency and release data.<sup>(12)</sup>

**Preparation of Microsphere-Loaded Tablets**

Ingredients	F1	F2
Microsphere containing drug equivalent	50 mg*	50 mg*
MCC	125mg	120mg
Talc	15mg	15mg
Magnesium Stearate	5mg	5mg
Starch	5mg	10mg
Total weight of Tablet	200mg	200mg

**Table no. 2 formulation design for Tablets Method: Dry Granulation Procedure:**

1. First, we need to sieve the microspheres and the other things that are added to it. We do this by passing the microspheres and excipients through a sieve that has tiny holes the size of the holes is, between 40 and 60.
2. Next we have to mix the microspheres with some powder called MCC and a disintegrant. We need to make sure that the microspheres and these powders are mixed together well so that they are uniform.
3. Then we add some magnesium stearate and a glidant to the mix. We have to blend these so that everything is combined properly.
4. Finally, we use a machine called a tablet press to compress the mixture into tablets the tablet press is used to make the microspheres and the other things into the shape of a tablet.<sup>(11)</sup>

**RESULTS AND DISCUSSION:**

**Solubility studies:**

Sr. No	Solvent	Saturation Solubility	Inference
1.	Water	1.0	Sparingly Soluble

2.	Methanol	1.50	Highly Soluble
3.	Ethanol	1.20	Freely Soluble
4.	Phosphate buffer 6.8	0.12	Moderate Solubility

Table No.3 Solubility

studies

UV Spectrum of Apixaban: (In methanol)

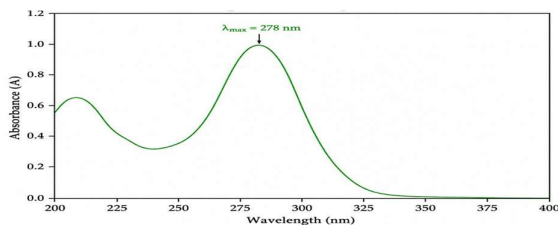


Fig No 2: UV Spectrum of Apixaban at 278 nm

**Discussion:** The Apixaban analysis using a light test showed a big peak at 278 nm when we used the right liquid. This peak is from the way the molecules, in Apixaban are arranged. It helped us measure how much of the drug was present. The graph we got was clear. Always looked the same which means the Apixaban sample we used was pure and the method we used was good enough to use again in other studies. We used this method to learn more about Apixaban.

Standard Calibration Curve:

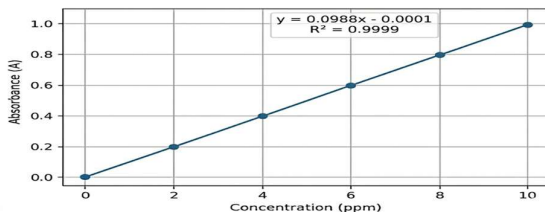


Fig No: 3 Standard

Calibration Curve

**Discussion:** The calibration curve of apixaban was made by using the amounts of apixaban at 278 nm. We saw that the amount of apixaban and how much it was absorbed were connected in a line. This follows the rules of Beer-Lambert’s law. The connection is very strong, with a correlation coefficient of about 0.999. This means the method of measuring apixaban is good and can be trusted to give the results for the amount of apixaban in a sample.

IR Spectra of Apixaban:

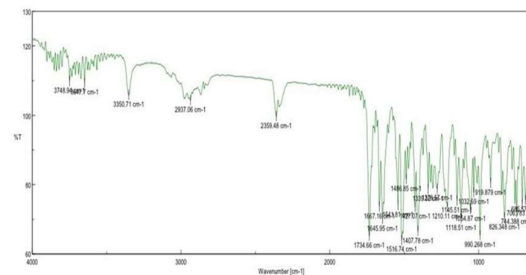


Fig No 4: IR Spectra of

Apixaban

**Discussion:** The IR spectrum of apixaban has some peaks that match its different parts. There is a peak at around 3300 cm<sup>-1</sup> and that shows N–H stretching. The peaks at 1650 cm<sup>-1</sup> are from C=O stretching of amide groups. Apixaban also has peaks at around 1600 cm<sup>-1</sup>, which's from aromatic C=C stretching, between 1200–1300 cm<sup>-1</sup> show C–N stretching and that proves apixabans core structure is there. The IR spectrum of apixaban shows these peaks. They help identify apixaban.

Flow Properties of Microsphere:

Parameter	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of Repose	Hausner’s Ratio
F2	0.48 ±0.02	0.60±0.01	27.12±0.45	1.25±0.03
F3	0.50 ±0.01	0.61±0.02	26.45±0.38	1.22±0.04
F4	0.52 ±0.03	0.64±0.01	28.30±0.52	1.23±0.02
F5	0.54 ±0.02	0.66±0.02	29.10±0.60	1.22±0.03
F6	0.56 ±0.01	0.68±0.01	27.85±0.41	1.21±0.02
F7	0.65±0.04	0.69±0.02	28.20±0.41	1.20±0.02

Table No.4 Flow Properties of

Microsphere

**Discussion:** Formulations F1–F6 show good flow properties with angle of repose below 30° and Hausner’s ratio around 1.20–1.25. Bulk and tapped density increase gradually, indicating better packing.

Evaluation of Microspheres:

Parameter	Particle size (µm)	Percentage Yield (%)	Entrapment Efficiency (%)	Drug Content (%)	Zeta Potential (mV)	Swelling Index
F2	180 ± 8	68.2 ± 2	-	-	- 12.5 ± 1.1	82.2 ± 2.3

F3	260 ± 10	73.6 ± 2.3	-	-	-	98.6 ±2.8
F4	360 ± 12	77.8 ± 2.5	-	-	-	115. 2±3. 2
F5	220 ± 10	74.5 ± 2.2	70.4 ± 2.1	78. 4 ± 1.2	-	92.7 ±2.6
F6	310 ± 11	86.8 ± 2.8	84.6 ± 2.5	91. 6 ± 1.0	-	118. 5±3. 4
F7	420 ± 15	80.3 ± 2.6	79.2 ± 2.3	86. 8 ± 1.4	-	138. 6±3. 8

Table

**No.5 Evaluation of Microspheres Discussion:**

Particle size and percentage yield increased from F1 to F6 indicating improved microsphere formation. Drug-loaded batches (F4–F6) showed good entrapment efficiency and high drug content. This suggests effective incorporation of drug and better formulation performance in later batches.

**In Vitro Drug Release Study:**

Time	F5	F6	F7
1	12.5 ± 1.0	14.2 ± 1.1	10.8 ± 0.9
2	22.8 ± 1.2	26.8 ± 1.3	20.4 ± 1.1
4	40.6 ± 1.5	45.6 ± 1.5	36.2 ± 1.4
6	58.2 ± 1.7	61.3 ± 1.7	52.8 ± 1.6
8	72.4 ± 1.6	74.8 ± 1.6	66.5 ± 1.5
10	82.7 ± 1.4	85.6 ± 1.4	78.2 ± 1.3
12	88.9 ± 1.3	92.4 ± 1.3	85.6 ± 1.2

Table No.6 Dissolution

**Study**

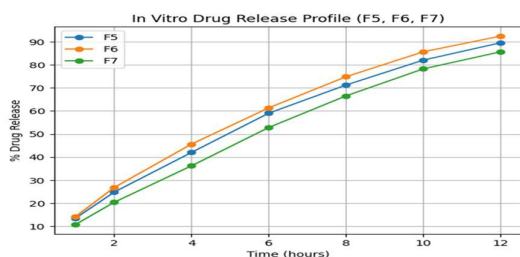


Fig. No 5 In Vitro drug

release from microsphere

Medium used: Phosphate buffer pH 6.8

**Discussion:** At first Apixaban was released a little at a time. This showed that it did not release much

all, at once. Then it kept releasing more Apixaban. This steady release happened because Apixaban moved out of the polymer mix. For the spheres Apixaban release lasted 12 hours. This showed that the Apixaban release was controlled. When the tiny spheres were pressed into tablets, the best formulation, F6 released Apixaban over a time. It released all of the Apixaban about 92% in 24 hours. This means it can be taken once a day and still work well. The way Apixaban was released may be because of two things the polymer getting bigger and soaking up liquid and Apixaban moving out of the polymer mix. This mix of things helped Apixaban release happen steadily. The Apixaban release was. Steady. The Apixaban release happened over a time.

**Evaluation of Tablets:**

Formulation	F1	F2
Thickness (mm)	3.8± 0.05	3.9±0.04
Diameter (mm)	8.0±0.03	8.0±0.02
Hardness (kg/s)	4.8±0.12	5.6±0.10
Weight Variation (mg)	199±3	200±2
Friability (%)	0.82±0.04	0.48±0.03

Table No.7 Evaluation of

**Tablets**

**F2 shows better characteristics for a controlled-release microsphere-loaded tablet due to:**

- higher hardness,
  - lower friability,
  - and better weight uniformity,
- indicating improved mechanical strength and tablet stability.

**In vitro Dissolution Study (Tablet)**

Time (hrs.)	% Drug Release
1	12.5
2	21.8
4	40.6
6	57.8

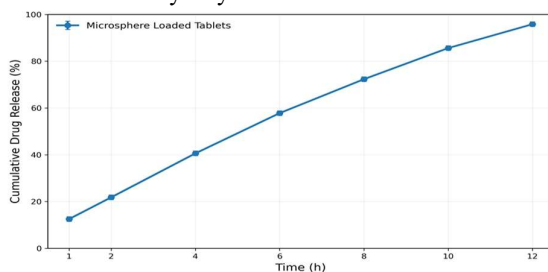
8	72.3
10	85.6
12	95.8

**Table No.8 In-vitro Dissolution**

**Study (Tablet)**

**Discussion:**

The microsphere loaded tablets released the drug in a steady way over 12 hours. At first 12.5 percent of the drug was released after 1 hour. By the end of 12 hours the microsphere loaded tablets had released 95.8 percent of the drug. This shows that the microsphere loaded tablets can deliver the drug over a period of time. The microsphere loaded tablets did not release the drug, at once which is what we want for controlled release therapy. The microsphere system is a way to give people the drug they need in a slow and steady way.



**Fig No.6 In Vitro drug**

**release from tablet**

**Conclusion:**

This study was done to make and test apixaban loaded microspheres that are in controlled release tablets. These tablets were made using a method called ionic gelation technique. The microspheres that were made had properties like the right size and the amount of apixaban in them. They also worked well when they were made into tablets. The tablets had the hardness and were not too thick or too thin. They were also the weight. One of the batches of tablets was better than the others. Had the best properties. This batch was chosen to do tests to see how the apixaban is released from the tablets. The loaded microspheres, in this batch were very good and the tablets made from them were very good too. The apixaban loaded microspheres were used to make the controlled release tablets.

The study on how the tablet breaks down showed that the special tablet with balls inside it can give a steady and controlled release of the drug for up to 12 hours. This tablet can help keep the amount of drug in the blood at a level. It can also reduce the ups and downs that happen with tablets. The tablet can be taken often and that makes it easier for patients to take their

medicine. The way we made the tiny balls was simple and did not use any solvents. This is good for drugs like apixaban that're sensitive. The tablet with the balls is a good way to make the drug work better and safer for people with blood clot problems. The microsphere loaded tablet is an idea for helping people with blood clots. The microsphere loaded tablet can make the drug work better. Be safer for people, with thromboembolic disorders.

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