A Review on Design and Development of Rivaroxaban Tablet and Comparative Dissolution Profiling

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ABSTRACT

The aim of present study is design and development of Rivaroxaban table and comparative dissolution profile in other development formulation. Dissolution testing is an in vitro technique of great importance in formulation and development of pharmaceutical dosage forms. The main objective of the present study is to conduct the comparative dissolution studies of various brands of same dosage forms and treatment of obtained dissolution data by using Graphical technique whether all the formulations used were equivalent. Rivaroxaban 10 mg tablet (In-House product) and Rivaroxaban Tablets 10 mg (Xarex 10) (Market sample) from different manufacturers were used in the study, and dissolution testing in different dissolution media 0.1 N HCl solution, phosphate buffer of pH 4.5 and phosphate buffer of pH 6.8 was conducted for 6 tablets from each brand for 60 min. by using dissolution testing apparatus USP type-II., 50rpm, 37±0.5 temperature and used 900 ml media. Samples were withdrawn at 5, 15, 30, 45 and 60 minutes and 50. time interval and analyzed for drug content by using UV spectrophotometer technique and used UV detector 250 nm. Percent drug release at each time interval was calculated for tablets and the data obtained were treated with Graphical technique.

KEY WORDS: Rivaroxaban tablet, Xarex tablet (Market product), Dissolution profile comparison. comparative studies of in-vitro dissolution, Dissolution apparatus USP type-II, UV spectrophotometer technique.

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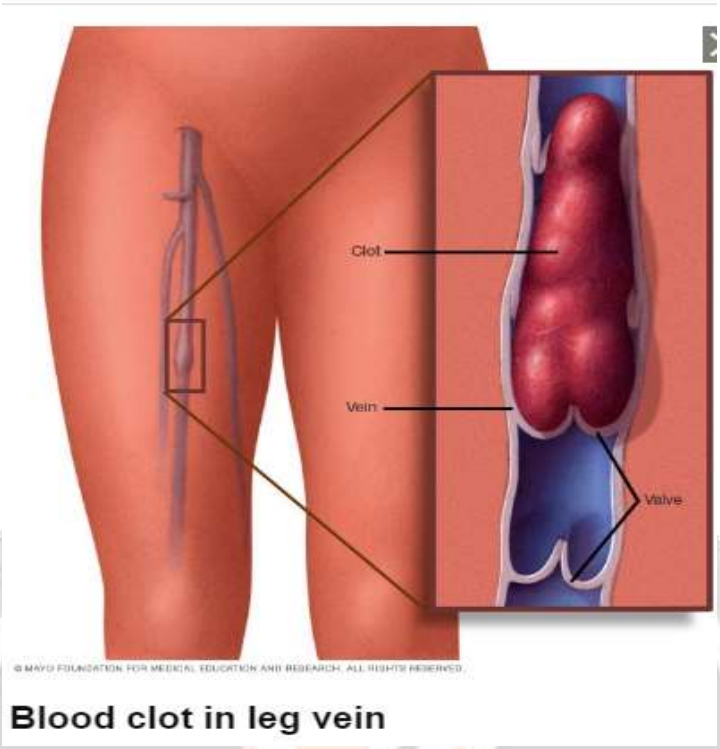
1. INTRODUCTION: DVT is brought on by a blood clot (Thrombus) that develops in one or more deep veins in your body, typically in your legs (deep vein thrombosis). Deep vein thrombosis can be quiet, in addition to generating limb discomfort or edoema. (1)

You may develop them if you have certain medical conditions, including DVT, that modify how your blood clots. If you are immobile for a prolonged length of time, such as after an operation or an accident, on a long vacation, or while you are bedridden, a blood clot in your legs may also form. (2)

Deep vein thrombosis can be very dangerous because blood clots in your veins have the potential to escape, travel through your body, and become lodged in your lungs, obstructing blood flow (pulmonary embolism). Nevertheless, pulmonary embolism can occur even in the absence of DVT symptoms.

The combination of DVT and pulmonary embolism is referred to as venous thromboembolism (VTE).



Blood clot in leg vein

Vein thromboembolism (VTE), which comprises DVT and pulmonary embolism (PE), affects 1 in 1,000 persons on average and results in 60,000–100,000 fatalities annually.(4)

1.1. SYMPTOMS

DVT symptoms might consist of:

- Inflammation of the affected leg. Rarely do both legs experience edoema.
- Leg discomfort. Your calf is where the pain frequently begins and it can feel sore or crampy.
- Skin that is discolored or red on the leg.
- A warm sensation in the affected leg

1.2. The following are the symptoms and warning indications of a pulmonary embolism.

- Sudden breathlessness
- Aches or discomfort in the chest that gets worse when you breathe deeply or cough
- Fainting, feeling faint, or feeling lightheaded
- Quick pulse
- Quick breathing
- Blood in the cough

1.3. CAUSES: A blood clot is the root cause of DVT. Blood cannot flow freely via a vein that is blocked by the clot in your body. Clotting can happen for a variety of causes. These consist of:

- **Injury.** Blood flow can be restricted or blocked by damage to a blood vessel's wall. As a result, a blood clot may develop.
- **Surgery.** During surgery, blood vessels may be damaged, which may result in the formation of a blood clot. Following surgery, bed rest with minimal to no activity may potentially raise your chance of developing a blood clot.
- Lessening of movement or immobility. Blood can build up in your legs, especially the lower ones, if you sit a lot. The blood flow in your legs may slow down if you are immobile for a lengthy amount of time. This may lead to the formation of a clot.
- Specific medicines. Some drugs make it more likely for your blood to clot.

1.4. RISK ELEMENTS: Your chance of getting DVT might be raised by a variety of factors. Your risk of DVT increases with the more of risk factors you have. DVT risk factors include:

1. **Age**. DVT can happen at any age, although it's more likely if you're over 60.
2. Spending a lot of time sitting down, like while driving or travelling. Calf muscles do not contract when your legs are immobile for prolonged periods of time. Blood circulation is generally aided by muscle movements.
3. Paralysis or prolonged bed rest, such as during a protracted hospital stay. Your calves may develop blood clots if your calf muscles are immobile for an extended period of a long time.
4. **Surgery or injury**. Blood clot risk might be increased by surgery or vein injury.
5. **Pregnancy**. The pressure in your pelvic and leg veins rises during pregnancy. Particularly at risk are women who have a clotting disease that was inherited. After giving birth, the risk of blood clots from pregnancy might last for up to six weeks.
6. Hormone replacement therapy or oral contraceptives for contraception. Both can make it easier for your blood to clot.
7. Having a weight problem. Being overweight makes your pelvic and leg veins more compressed.
8. **Smoking.** Smoking has an impact on circulation and blood clotting, which can raise your risk of DVT.
9. **Cancer.** Some cancers raise blood levels of chemicals that make your blood clot. Blood clot risk is also raised by several cancer therapy options.
10. **Heart disease**. Your risk of DVT and pulmonary embolism is increased as a result. Due to their compromised heart and lung health, patients with heart failure are more likely to experience even a minor pulmonary embolism's symptoms.
11. **Bowel inflammation illness**. DVT risk is increased by bowel conditions such Crohn's disease or ulcerative colitis.
12. A personal or ancestor's history of PE or DVT. You may be more susceptible to getting DVT if you or a member of your family has had one or both of these.
13. **Genetics.** A genetic risk factor or condition, such as factor V Leiden, which makes blood clot more readily, can be inherited by certain people. An hereditary condition on its own might not produce blood clots unless paired with one or more other risk factors.
14. No recognized risk factor. A blood clot in a vein can occasionally happen without any obvious underlying risk factors. It is referred to as an unprovoked VTE.

1.5. COMPLICATIONS:

DVT complications include the following

DVT is typically treatable when discovered early with blood thinners and a change in lifestyle. Serious problems may occur in some circumstances.

1.6. RESPIRATORY EMBOLISM:

Pulmonary embolism occurs when a blood clot in a deep vein travel to the lungs (PE). Because the blood flow is constricted, PE can permanently harm the lungs and other organs. Large or numerous clots have the potential to be fatal.

There are frequently no symptoms. There may be symptoms, such as:

1. Shortness of breath (the most typical PE symptom), anxiety, clammy or blue skin, and chest pain. Irregular Heartbeat, Fainting, and Pain in Your Arm, Jaw, Neck, and Shoulder
2. Feeling dizzy; breathing quickly; beating heart; agitation; spitting or coughing up blood; weak pulse

Seek emergency medical treatment if you encounter any of these symptoms.

1.7. SYNDROME POST-THROMBOTIC:

A persistent side effect of DVT is PTS, often referred to as PTS. The vein valves in your body are damaged when a blood clot forms, leading to persistent pain, swelling, and discomfort that can significantly interfere with everyday activities.

After a blood clot forms, symptoms may start to show up six months to two years later and may last for the remainder of your life.

PTS primarily affects your legs and can cause swelling, pain, cramping, heaviness, tingling, itching, and skin discoloration. It can also cause sores or ulcers on the skin.

Although it may be challenging to distinguish PTS symptoms from those of another blood clot, in the majority of PTS instances, resting and elevating your legs will provide some relief. To assist you discover the reason, consult a physician.

1.8. PREVENTION:

Deep vein thrombosis prevention strategies include the following:

Avoid being still. Try to begin moving as soon as you can if you have just had surgery or have been placed on bed rest for any reason. Avoid crossing your legs when sitting for an extended period of time since this might restrict blood flow. Whenever you're driving a long distance, pull over every hour or so and take a stroll.

When flying, get up and move around sometimes. If you're unable to accomplish that, work your lower legs instead.

Quit smoking. Smoking raises the possibility of developing DVT.

Exercise while controlling your weight. DVT is at risk due to obesity. Regular exercise reduces blood clot risk, which is crucial for anyone who spends a lot of time sitting or on the road.

1.9. DVT THERAPIES:

What benefits may you expect from treating a blood clot deep in a vein, or DVT?

1. The growth of the clot will be prevented.
2. It reduces the possibility of chronic problems including swelling and leg discomfort.
3. Treatment also helps to avoid more blood clots.

Medication and self-care will usually solve the problem. But surgery could be necessary. Find out from your doctor which medical treatments are best for you.

1.10. TREATMENT:

A dangerous medical problem is DVT. If you believe you are exhibiting DVT symptoms, call your doctor straight once or visit the nearest emergency facility. An expert in medicine can examine your symptoms.

Treatment for DVT focuses on preventing the clot from spreading. Additionally, therapy may reduce your chance of developing additional clots and possibly avoid a pulmonary embolism.

1.11. MEDICATION:

Your doctor may advise you to use blood-thinning drugs such as **Rivaroxaban, Enoxaparin, Heparin, Warfarin and Fondaparinux.**

Blood clotting is made more difficult by drugs that thin the blood. Additionally, they reduce the size of any current clots and lessen your risk of developing new clots.

Your doctor may prescribe thrombolytic medications if blood thinners are ineffective or if the DVT is severe. The use of this medicine may also be advantageous for those with upper extremity DVT.

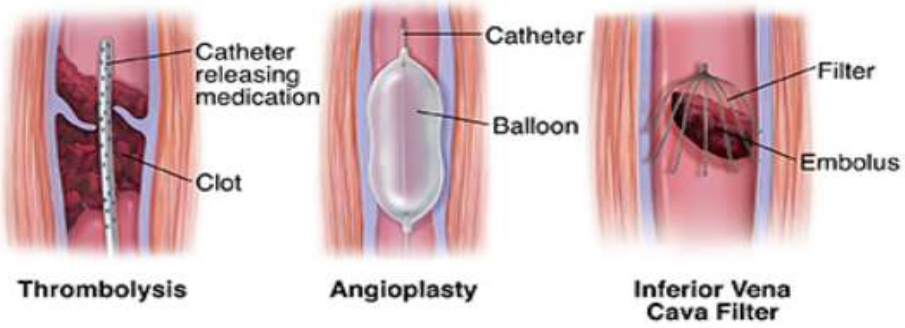
Drugs used for thrombolysis disintegrate blood clots. These will be given to you intravenously (through a vein).

1.12. TREATMENT METHODS FOR DVT: A DVT is a blood clot that develops in a sizable vein in the inner thigh, arm, or other body area. The clot has the potential to break free from the vein and go to the lungs. A pulmonary embolism result from this (PE). The clot may stop the flow of blood to the lungs. It's a medical emergency that might be fatal.

Both DVT and PE are referred to as venous thromboembolism (VTE) by medical professionals. Because the two illnesses are so closely connected, they refer to them as VTE. Furthermore, their treatment and prevention are intimately intertwined.

Most frequently, medications that aid in clot dissolution are used to treat blood clots. They also aid in avoiding problems like pulmonary embolism. But not everyone will experience this. Your doctor could advise having one or several operations, depending on your health as well as the size and location of the blood clot. Blood clots can be

treated with thrombolysis, angioplasty, and vena cava filter implantation. You may get additional information about treating your blood clot, including details on these and other therapies, from your healthcare practitioner. Additionally, he or she may respond to any queries you may have.



THROMBOLYSIS:
A big clot is broken up using this method. In the vein is placed a catheter, a tiny tube. The vein and the clot are both subjected to X-rays. Then, using the catheter, clot-dissolving medication is administered to the clot. A mechanical tool may also be employed in some circumstances to dislodge the clot. Not everyone with a DVT should have this surgery. With you, your healthcare practitioner will go over the advantages and hazards. Thrombolysis is a very successful blood clot therapy in some patients. It does nevertheless run the danger of significant bleeding issues.

ANGIOPLASTY:
The problematic vein may be widened with this surgery, which will also increase blood flow. After the blood clot has been removed, this is done. The vein's narrowing (stenosis) can restrict blood flow and increase the risk of blood clot formation. The afflicted vein is entered using a catheter that has a balloon attached to the end. The catheter is positioned using X-rays. The balloon is inflated to expand your vein once the catheter has been inserted. Your vein may occasionally also be given a stent, a wire mesh device, to assist keep it open. The possibility of this surgery assisting you might be discussed between you and your healthcare professional.

FILTER IN THE INFERIOR VENA CAVA:
A little device called an inferior vena cava (IVC) filter is used to stop an embolus in your lower body from moving up to your lungs. In one of your veins, a lengthy, thin tube (catheter) is inserted. It is utilized to insert the filter into your vena cava, the biggest vein in your body. If this surgery is advised for you, your doctor will go over the risks and advantages with you.

2. MANUFACTURE PROCEDURE: The materials required for the preparation of Rivaroxaban 10mg tablet

- **API:** The active pharmaceutical ingredients that are combined with excipients to form a dose so that it can be administered conveniently by the patient and show its therapeutic activity.
- **Excipients:** These are the extra additives which are used to either increase the bulk, enhance the flavor, mask the unpleasant taste, as a carrier and for several other role.

3. DISSOLUTION PROFILES COMPARED:
It is a graphical depiction of the total release of A.P.I. from a dosage form in terms of [concentration vs. time] in a suitable dissolving media.
Comparing the dissolution profile:

1. A graphic technique

Dissolution Comparison Method:
Graphical technique

In this technique, the solute (drug) concentration vs time graph is plotted in the dissolving medium, which can be a biological fluid.

To compare the extent of dissolution, the concentration of the medication at each point and the form of the two curves are compared.

3.1. COMPARATIVE OF DISSOLUTION METHOD:

Utilizing a validated dissolution method that includes three additional media in addition to the medium specified in the regulatory application, the dissolution profiles of reference and test products are compared. These additional media include pH-1.2 0.1 N HCl or simulated gastric fluid without enzymes, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer, which simulates USP-grade intestinal fluid without enzyme.

3.2. TEXT & METHODOLOGY:

Dissolution Profiles Comparison - Requirements

900 ml of the following dissolving medium should be used to dissolve test and reference goods in USP Apparatus II at 50 rpm:

Dissolution (By UV spectrophotometer):

Dissolution condition:

Apparatus : 2 , Paddle

Medium : 900 mL, 0.1N pH 1.2 HCL acid, pH 4.5 Acetate Buffer solution, pH 6.8 Phosphate buffer solution

Speed : 50 rpm

Temperature : 37 ±0.50C

Time : 5, 15, 30, 45 and 60 minutes

UV spectrophotometer : Detector: UV 250 nm

Dissolution Media: Measure 900 ml purified water.

- 0.1 N pH 1.2 HCl acid solution
- pH 4.5 Acetate Buffer media.
- pH 6.8 Phosphate Buffer media.

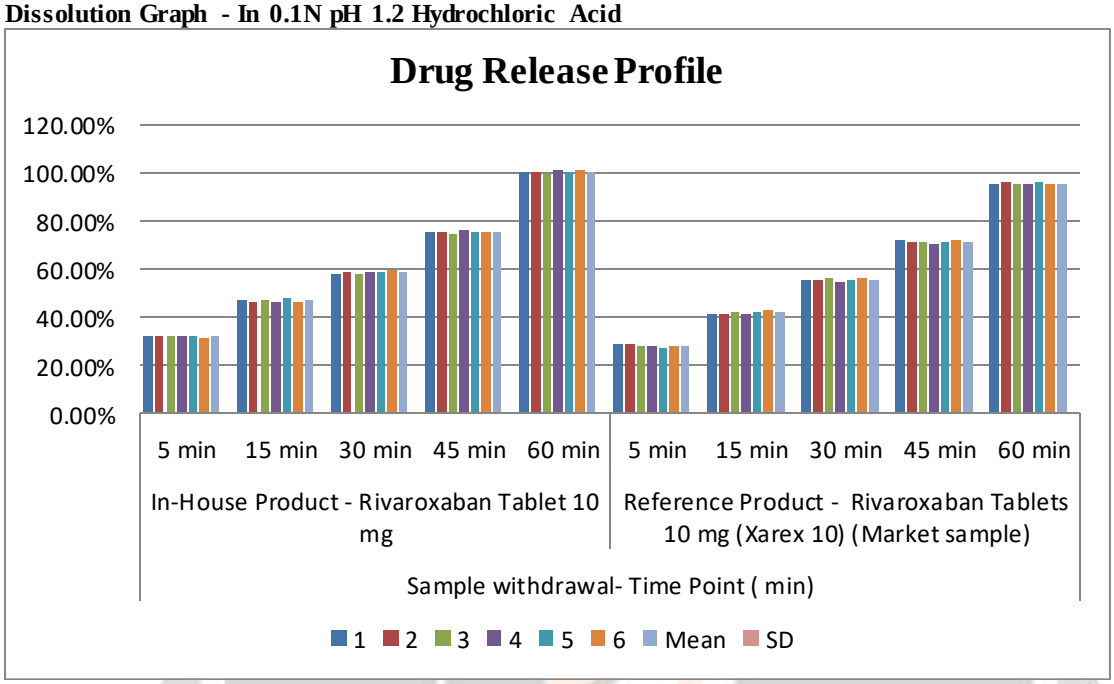
4. RESULT DISCUSSION

4.1COMPARISON OF DISSOLUTION RELEASE RESULTS & GRAPH:

Drug Release data sheet - In 0.1N pH 1.2 Hydrochloric Acid										
Tab No.	**Sample withdrawal- Time Point (min)**									
	In-House Product - Rivaroxaban Tablet 10 mg					**Reference Product** - Rivaroxaban Tablets 10 mg (Xarex 10) (Market sample)				
	5min	15min	30min	45min	60min	5min	15min	30min	45min	60min
1.	32.30%	47.20%	58.10%	75.80%	100.00%	29.00%	41.70%	55.20%	71.90%	95.30%
2.	32.70%	46.80%	58.50%	75.40%	100.40%	28.60%	41.30%	55.60%	71.10%	96.10%
3.	31.90%	47.60%	58.10%	75.00%	99.60%	28.20%	42.50%	56.00%	71.50%	95.70%
4.	32.70%	46.40%	58.90%	76.20%	100.80%	28.20%	41.70%	54.80%	70.70%	95.30%
5	32.30%	48.00%	58.90%	75.40%	100.00%	27.40%	42.10%	55.20%	71.50%	96.50%
6	31.50%	46.80%	59.30%	75.80%	100.80%	27.80%	42.90%	56.00%	71.90%	95.30%
Mean	32.20%	47.10%	58.60%	75.60%	100.30%	28.20%	42.00%	55.50%	71.40%	95.70%

SD	0.4%	0.5%	0.4%	0.4%	0.4%	0.5%	0.5%	0.4%	0.4%	0.5%
% RSD	1.3%	1.2%	0.8%	0.5%	0.4%	1.8%	1.3%	0.8%	0.6%	0.5%

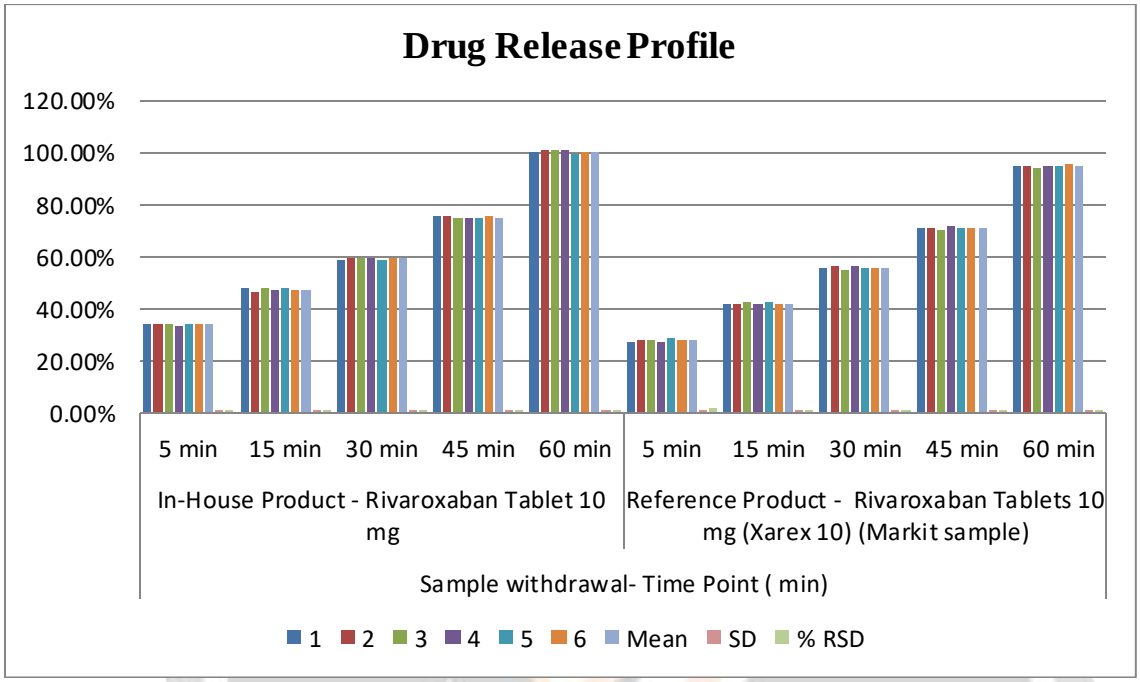
Dissolution Graph - In 0.1N pH 1.2 Hydrochloric Acid



Drug Release data sheet - In pH 4.5Acetate Buffer										
Tab No.	**Sample withdrawal- Time Point (minute)**									
	In-House Product - Rivaroxaban Tablet 10 mg					**Reference Product** - Rivaroxaban Tablets 10 mg (Xarex 10) (Markit sample)				
	5min	15min	30min	45min	60min	5min	15min	30min	45min	60min
1.	33.90%	48.00%	58.50%	75.80%	100.40%	27.30%	41.90%	55.40%	71.20%	94.90%
2.	34.30%	46.80%	59.30%	75.40%	101.20%	27.70%	41.50%	56.20%	70.80%	94.50%
3.	33.90%	47.60%	59.70%	75.00%	100.80%	28.10%	42.30%	55.00%	70.40%	94.10%
4.	33.50%	47.20%	59.70%	74.60%	100.80%	27.30%	41.90%	56.60%	71.60%	94.50%
5	34.30%	48.00%	58.90%	75.00%	99.60%	28.50%	42.70%	55.80%	71.20%	94.90%
6	33.90%	47.20%	59.70%	75.40%	100.00%	27.70%	41.50%	55.40%	70.80%	95.30%
Mean	33.90%	47.50%	59.30%	75.20%	100.50%	27.80%	42.00%	55.70%	71.00%	94.70%
SD	0.3%	0.4%	0.5%	0.4%	0.5%	0.4%	0.4%	0.5%	0.4%	0.4%

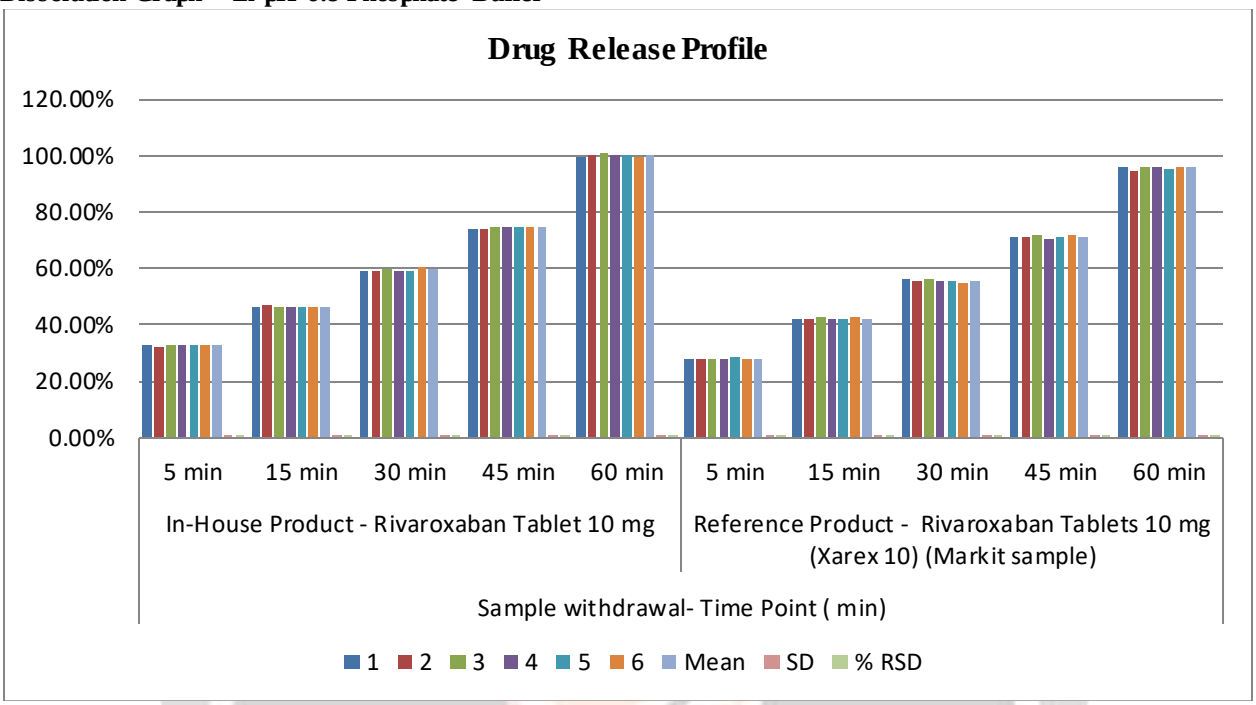
% RSD	0.8%	0.9%	0.8%	0.5%	0.5%	1.6%	1.0%	1.0%	0.5%	0.4%

Dissolution Graph - In pH 4.5 Acetate Buffer



Drug Release data sheet - In pH 6.8 Phosphate Buffer										
Tab No.	**Sample withdrawal- Time Point (minute)**									
	In-House Product - Rivaroxaban Tablet 10 mg					**Reference Product** - Rivaroxaban Tablets 10 mg (Xarex 10) (Markit sample)				
	5min	15min	30min	45min	60min	5min	15min	30min	45min	60min
1.	32.50%	46.60%	59.40%	74.30%	99.60%	27.70%	42.30%	56.20%	71.20%	96.10%
2.	32.10%	47.00%	59.40%	74.30%	100.40%	28.10%	41.90%	55.40%	70.80%	94.90%
3.	32.50%	46.60%	59.80%	74.70%	100.80%	28.10%	42.70%	56.20%	71.60%	96.10%
4.	32.50%	46.60%	59.40%	74.70%	100.40%	27.70%	41.90%	55.40%	70.40%	95.70%
5	32.90%	46.20%	59.40%	74.70%	100.00%	28.50%	42.30%	55.80%	71.20%	95.30%
6	32.90%	46.20%	60.20%	74.70%	99.60%	27.70%	42.70%	55.00%	72.00%	96.10%
Mean	32.60%	46.50%	59.60%	74.60%	100.10%	28.00%	42.30%	55.60%	71.20%	95.70%
SD	0.3%	0.3%	0.3%	0.2%	0.4%	0.3%	0.3%	0.4%	0.5%	0.5%
% RSD	0.8%	0.6%	0.5%	0.3%	0.4%	1.1%	0.8%	0.8%	0.7%	0.5%

Dissolution Graph - In pH 6.8 Phosphate Buffer



4.2 SUMMARY OF DISSOLUTION PROFILE STUDY RESULTS:

Sr. No.	Dissolution Media	Acceptance Criteria	Observation In-House Product - Rivaroxaban Tablet 10 mg	Observation Rivaroxaban Tablets 10 mg (Xarex 10) (Market sample)
1	Hydrochloric Acid pH 1.2	The % RSD dissolution stated amount of Rivaroxaban in each time points (5, 15, 30, 45 & 60min) with 6 dosage units should be not more than 2.0 %	05 min: 32.20% 15 min: 47.10% 30 min: 58.60% 45 min: 75.60% 60 min: 100.30%	05 min: 28.20% 15 min: 42.00% 30 min: 55.50% 45 min: 71.40% 60 min: 95.70%
2	pH 4.5 acetate buffer	The % RSD dissolution stated amount of Rivaroxaban in each time points (5, 15, 30, 45 & 60min) with 6 dosage units should be not more than 2.0 %	05 min: 33.90% 15 min: 47.50% 30 min: 59.30% 45 min: 75.20% 60 min: 100.50%	05 min: 27.80% 15 min: 42.00% 30 min: 55.70% 45 min: 71.00% 60 min: 94.70%
3	Phosphate Buffer	The % RSD dissolution stated amount of Rivaroxaban in each time points (5, 15, 30, 45 & 60min) with 6 dosage units should be not more than 2.0 %	05 min: 32.60% 15 min: 46.50% 30 min: 59.60% 45 min: 74.60% 60 min: 100.10%	05 min: 28.00% 15 min: 42.30% 30 min: 55.60% 45 min: 71.20% 60 min: 95.70%

4.3 CONCLUSION:

Rivaroxaban Tablet 10 mg was created in comparison to Xarex 10 mg tablets, the reference product (Alteus Biogenics Pvt. Ltd.). In addition, the dissolution profile was evaluated since this test was utilized to find formulation elements that affect and have a sizable impact on the bioavailability of the active pharmaceutical component. Dissolution test was employed in the newly designed Labe batch after composition and manufacturing processing

were determined. In order to produce a dose-proportionate product, the same mix was employed to manufacture Rivaroxaban 10mg tablets (In-house product).

In 3 distinct dissolving mediums, the dissolution profile of 10 mg Rivaroxaban tablets was carried out (0.1N Hydrochloride acid pH-1.2, Acetate buffer pH-4.5 and Phosphate buffer pH-6.8). In every dissolving media, the dissolution rate was more than 90% after 60 minutes. Additionally, as both are dosage proportional, the resulting results were compared to reference product data for 10 mg Rivaroxaban tablets (Xarex 10) Studies in vitro and the dissolution profile in many mediums were determined to be appropriate for drug release. Therefore, it is presumed that Rivaroxaban pills, 10 mg, comply with bioavailability standards.

The release profile of multi medium dissolution of Rivaroxaban tablets10 mg (In house product) performed in different time points (i.e.,5, 15, 30, 45, and 60 minutes) is compared with reference sample (Rivaroxaban tablets 10 mg (Xarex 10)), inhouse tablets release pattern better than market sample.

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