SELECTION OF PACKAGING IN GENERIC PRODUCT DEVELOPMENT

Jailani. S[1*], C. K. Dhanapal[2], Noohu Abdullah Khan[3]

Abstract:
The present study aimed to develop suitable packaging material for the generic formulation of Rivaroxaban tablets by packaging material characterization and reverse engineering study of the marketed reference product. The packaging material of the marketed reference product was characterized by description, thickness, total grammage, and an individual grammage of PVC and PVDC layers. The components of the foil were identified using Attenuated total reflection (ATR) assembly and compared with standards. The degradation profile of generic Rivaroxaban tablets was performed by forced degradation study as well as using a photostability study. The packaging material was evaluated for vapour permeation study as per the modified USP method. Based on a short-term stability study and cost-effectiveness of European and Asian source packaging material was proposed. As per ICH guidelines stability study of Rivaroxaban, tablets was performed at accelerated and stress conditions for 6 months. Based on these stability results, the shelf life of the product was predicted. Through the ATR study, it was confirmed that the packaging material was PVC-PVDC. This forced degradation study confirmed that humidity has a high impact on the stability of the product. It has been observed that drug products are light stable and not light sensitive as the directly exposed tablets themselves are stable. It has been observed that among all the packaging materials tested, PVC-PVDC 250/60 showed minimum MVRT and was classified as Class A material. Based on short-term stability testing and cost-effectiveness Asian source PVC-PVDC 250 µ/60 g/m^2 was proposed as the final packaging material and the generic product was packed in blisters made with PVC-PVDC and aluminum foil for Climatic zone III and IV. In both accelerated and stress stability testing the product was found to be stable over 6 months. Overall, 24 month's shelf life is predicted based on the predicted value of assay and impurity levels.

Keywords: generic product, Rivaroxaban tablets, packaging material, PVC, PVDC, shelf life, aluminum foil

[1*]Dept. of Pharmacy, Faculty of Engineering and Technology (FEAT), Annamalai University, Annamalai Nagar, Chidambaram, Tamil Nadu, India.
[2]Dept. of Pharmacy, Faculty of Engineering and Technology (FEAT), Annamalai University, Annamalai Nagar, Chidambaram, Tamil Nadu, India
[3]College of Pharmacy, King Khalid University, Abha, Kingdom of Saudi Arabia.

***Corresponding Author:** Jailani. S
*Dept. of Pharmacy, Faculty of Engineering and Technology (FEAT), Annamalai University, Annamalai Nagar, Chidambaram, Tamil Nadu, India. E-Mail ID: jailanipharmacy@gmail.com

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Introduction:

A drug product that is comparable to a brand or reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use is called a generic product **[1]**. The term "generic" refers to drug products whose patent protection has lapsed and which may be manufactured by companies other than the original inventor. Recent years have seen a rise in the use of generic drug products, mostly as a cost-cutting tool in healthcare. Usually, 20 to 90% less expensive than brand-name counterparts are generic drug products. The developed generic product should be pharmaceutical and bioequivalent as per regulatory guidelines **[2]**. Since primary packaging materials come into direct contact with pharmaceutical products and offer immediate layered protection from the environment, choosing appropriate primary packaging materials is an important step in the development of a successful generic product. Any active material has a unique stability profile for the solid and solution states depending on its chemistry and physical forms. To create a successful generic product, it is essential to choose the right API form, excipients, and packaging materials. These components are crucial to the product's quality, stability, and performance **[3]**. Packaging for pharmaceutical products may also be used to address market appeal (trade dress), patient identification, and patient compliance. This describes the many methods and stages used to choose packaging during the development of generic formulations **[4]**. From a regulatory perspective, HDPE packs are often favored in the US market compared to blister packs in the European market, while in ROW (the rest of the world), manufacturers select packaging based on stability profile with the shelf life of the pharmaceutical product. As a result, there is no legal need that a generic product to utilize the same packaging materials and have the same pack style. It would rely on the generic product's preferred market presentation and stability profile **[3]**. If a generic product uses the same packaging material as the market reference (innovator) product, product stability is still not guaranteed because any variations in other key product parameters, such as API physiochemical properties, excipient physiochemical properties, and manufacturing processes, may lead to different stability profiles from those of the market reference product. Therefore, to determine stability profiles, it is important to research the generic product with several packing materials in addition to the one utilized in the market reference product **[5]**.

To maintain the stability and longer shelf life of the developed generic product, suitable packaging material development is quite crucial. Considering the importance of packaging material development in generic products, we have undertaken this study in the selection of packaging of generic formulation of Rivaroxaban tablets. The development of packaging material was initiated with packaging material characterization and reverse engineering study of market reference product followed by understanding the degradation profile of generic Rivaroxaban tablets by forced degradation study.

Materials and methods:

Materials:

Hydrogen peroxide 30% (H2O2) and Hydrochloric acid (HCl 35-38%) was purchased from macron fine chemicals VWR International Holdings, Inc. Potassium nitrate was purchased from CHD chemicals ltd, Mumbai, India. Sodium hydroxide pellets were obtained from Techno pharmachem, New Delhi. Silica pellets were obtained from Sorb-It India. Morpholine 99% extra pure was purchased from Acros Organics, Belgium. Reference Market Product of Rivaroxaban 20 mg film-coated tablets were purchased from local pharmacy.

Methods:

Generic Rivaroxaban Formulation (Test product) Preparation

The test product, Rivaroxaban 20 mg film-coated tablets, is in-house developed and were prepared by non-aqueous wet granulation process using the following similar excipients as that of reference product, microcrystalline cellulose, lactose mono-hydrate, hypromellose, sodium lauryl sulfate, croscarmellose sodium, magnesium stearate, and Opadry (coating material).

Packaging material Characterization and reverse engineering study of the marketed reference product

Description:

The packaging material of the marketed reference product was characterized for description by visual observation and noted down.

Thickness:

The total thickness of the sample was measured by Digital Vernier Caliper at 10 different locations of the sample. The average thickness was calculated and noted down.

Total grammage:

The sample to be tested was cut into an area of 5x5 cm in a perfect square or rectangle using a template and cutter and weight. A total of 5 pieces from the

different parts of the samples were cut down and the average in gsm was calculated. The following formula was used to calculate the total grammage
Weight (g)

$$GSM\ (g/m^2) = \frac{\text{Weight (g)}}{\text{Area (sq. cm)}} \times 10^4$$

Individual grammage of PVC and PVDC layers:
The sample to be tested was cut into a piece of 10 sq. cm and weighed accurately. This piece was then immersed in acetone and allowed to stand for 1 hour. It was then taken out from the solvent and gently separated the PVDC coating layer from the PVC layer. Both layers were dried at 60^0C and allowed to cool. The weight of each sample was noted down and the GSM of PVC and PVDC was calculated using the same formula used to calculate the total grammage.

Identification of the components of the foil:
A piece of film was cut and a blank scan was performed. After completion of the blank scan. the sample was placed in the Attenuated total reflection (ATR) assembly. The FTIR spectrum was determined by scanning from 3800 cm^{-1} to 650 cm^{-1} and then the sample was removed and the other side of the film was scanned to determine the spectrum from 3800 cm^{-1} to 650 cm^{-1} and the matching spectrums for PVC and PVDC obtained from respective sides.

Degradation profile of Generic Rivaroxaban tablets by forced degradation study:
A study was conducted to demonstrate the effective separation of degradants from an active pharmaceutical ingredient in the formulation. Separate portions of the drug product and placebo were exposed to the following stress conditions to induce degradation. Test samples were prepared and treated with different stress conditions as mentioned below. Assay and total impurity were determined.

a) Acid degradation: Treated sample with 5N HCl solution.
b) Alkali Degradation: Treated sample with 5N NaOH solution.
c) Peroxide Degradation: Treated with 33% Hydrogen peroxide (H_2O_2).
d) Thermal Degradation: Treated at 105ºC for 24 Hours
e) Humidity Degradation: Treated at 95% RH for 24 hours

Photostability studies:
The samples were exposed to the light of an overall illumination of not less than 1.2 million lux hours and near UV energy of NLT 200-watt hours/ m^2 in a photostability chamber, as per ICH Q1B guideline. Assay and total impurity were determined **[6]**.

Comparative Packaging materials evaluation for selection through Vapour permeation study as per modified USP method:
A suitable chamber capable of maintaining 75 ± 5% RH and 25 ± 2°C or a desiccator, containing a saturated solution of 35gm of sodium chloride with each 100 mL of water placed in the bottom of the desiccator. Check whether the desired temperature is attained, then start the study. Desiccant pellets were dried in an oven. Blister packs with respective forming and lidding foils were chosen for the Moisture Vapour Transmission Rate (MVTR) study. Also, control blisters were packed without filling desiccant pellets. The packed blisters with pellets were marked as Test-1, Test-2……. Test-10 and control (empty) blisters as Control-1, Control-2, ……. Control-10. The blisters were loaded in a desiccator and before loading, the temperature, and humidity inside the desiccator were checked and then it was closed. After 7 days, blisters were removed from the desiccator and allowed to equilibrate to room temperature for 1 hour. The weight of the individual blister of the test sample (10 blisters) was recorded and then the weight of the blisters of the control sample together as a bundle was recorded and its average weight was calculated. This weighing of the blisters was continued for up to 28 days and after weighing every time, replace the blisters were replaced inside the desiccator and closed it. The physical appearance of the desiccant pellets (if it is a transparent blister pack), was observed for physical appearance. If the pellets turned pink or if the weight of the blister exceeds 10% of the normal, then the study was terminated and considered the previously recorded values as final. Otherwise, the study was completed for up to 28 days **[7]**. The average rate of moisture vapor transmission, in mg/day, for each blister was calculated using the following formula.

$$[1/(N \times X)]\ [(W_F - W_I) - (C_F - C_I)]$$

Where,
N = number of days expired in the test period (beginning after the initial 24-h equilibration period)
X = number of separately sealed units per pack
W_F = final weight of each test pack (mg)
W_I = initial weight of each test pack (mg)
C_F = final weight of the control packs (mg)
C_I = initial weight of the control packs (mg)

Cost-effective source selection of packaging material:
Based on the MVTR study PVC/PVDC 250/60, aluminum foil as a packaging material was selected. Two sources (European and Asian) were identified and various parameters like GSM, thickness, total thickness, total GSM, heat seal lacquer GSM and comparative price were compared. Based on lower cost one source was selected for the generic product.

Short-term stress stability studies of the generic product:
Short-term stability study of the generic formulation packed in the selected packaging materials at
50± 2ºC temperature and 80± 5% % relative humidity were conducted for 30 days and various parameters were evaluated and compared between the two sources.

Stability study of generic product in final proposed packaging material:
As per ICH guidelines accelerated (40± 2ºC temp and 75±5% RH) and stress stability study at (30± 2ºC temp and 65± 5 % RH) on the generic product was performed in the proposed packaging material for 6 months. The samples were unloaded at a predetermined time interval and various parameters were evaluated and compared with initial results. Using Minitab 19 trial version through regression analysis of stress stability study data of 30± 2ºC temperature and 65± 5% relative humidity condition stability data was extrapolated and shelf life and total impurity were proposed in the final packaging material **[8]**.

Results and discussion:
Packaging material characterization and reverse engineering study of marketed reference product:
During packaging material characterization, it was observed that the innovator product was packed in a blister pack consisting of Aluminium + PVDC + PVC. The blister was transparent and thermos-formed. The brand name and manufacturer details were printed on the lidding foil. The average thickness and grammage of the forming and lidding foil are summarized in **Table 1.**

Table 1: Packaging material characterization

Primary packaging Description		
Transparent thermoformed blister The lidding foil is printed with the brand and manufacturer name details.		
Total foil: Aluminium + PVDC + PVC	460.87	311
Blister – Forming Foil characterization	Grammage	Avg. Thickness (µ)
PVDC layer	62.81	36.67
PVC layer	321.74	243.51
Blister – Lidding Foil characterization	Grammage	Avg. Thickness (µ)
Total: Aluminium	60.88	23.54

Identification of the components of the foil:
Identification of the PVC foil:
To identify the exact nature of the foil, FTIR of the test sample and known sample (PVC) was performed and IR peaks were compared. The FTIR spectrum of PVC showed peaks at 2970 cm −1 consisting of the CH 2 asymmetric stretching vibration mode. The peaks around 1400 cm −1 were due to the C − H aliphatic bending bond. The peak at 1250 cm −1 was attributed to the bending bond of C − H near Cl. The C − C stretching bond of the PVC backbone chain occurred in the range 1000 − 1100 cm −1. The peaks in the range of 600 − 650 cm −1 correspond to the C − Cl gauche bond. Similar peaks were also observed in the test sample with lower intensities as shown in **Figure 1.** Comparing the peaks of the test and standard sample it was confirmed that the material was PVC foil.

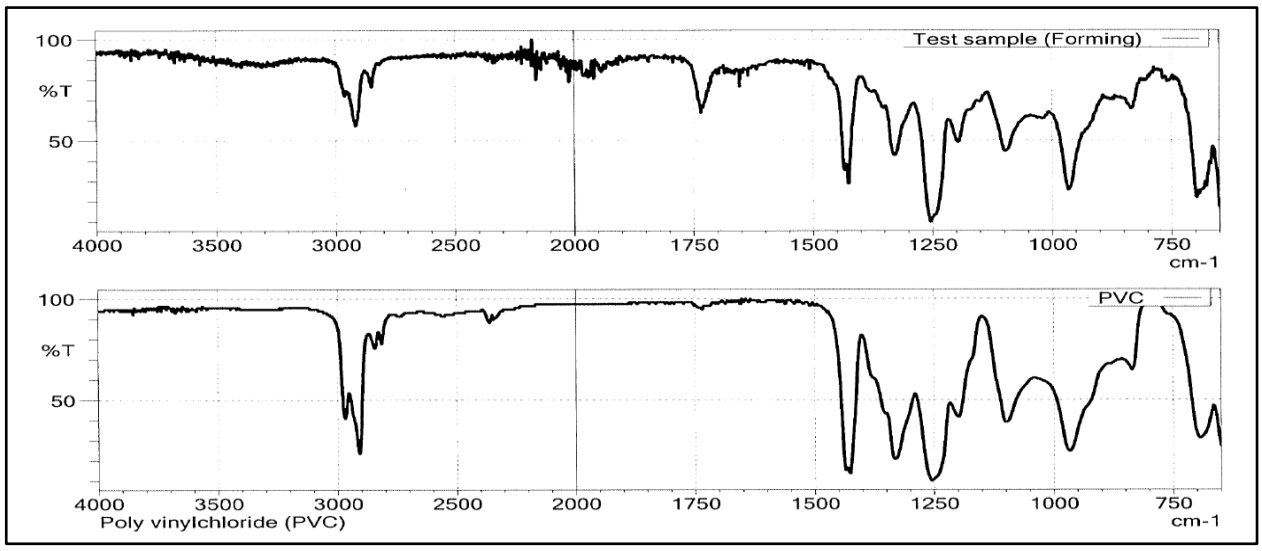

Figure 1: FTIR spectra of PVC and test sample

Identification of the PVDC foil:

To identify the exact nature of the foil, FTIR of the test sample and known sample (PVDC) was performed and IR peaks were compared. In PVDC common peaks were observed in the form of a doublet at 1068 and 1044 cm-1 and a band at 1405 cm-1 due to the CH2 bending. The C-Cl2 stretching vibrations were situated at 600 and 655 cm-1. A very strong absorption band appears at 1616.3 cm−1, which is assigned to C=C stretch vibration absorption, resulting from the conjugative or cumulated C=C bonds of the PVDC. Similar peaks were also observed in the test sample with lower intensities as shown in **Figure 2.** Comparing the peaks of the test and standard sample it was confirmed that the material was PVDC foil.

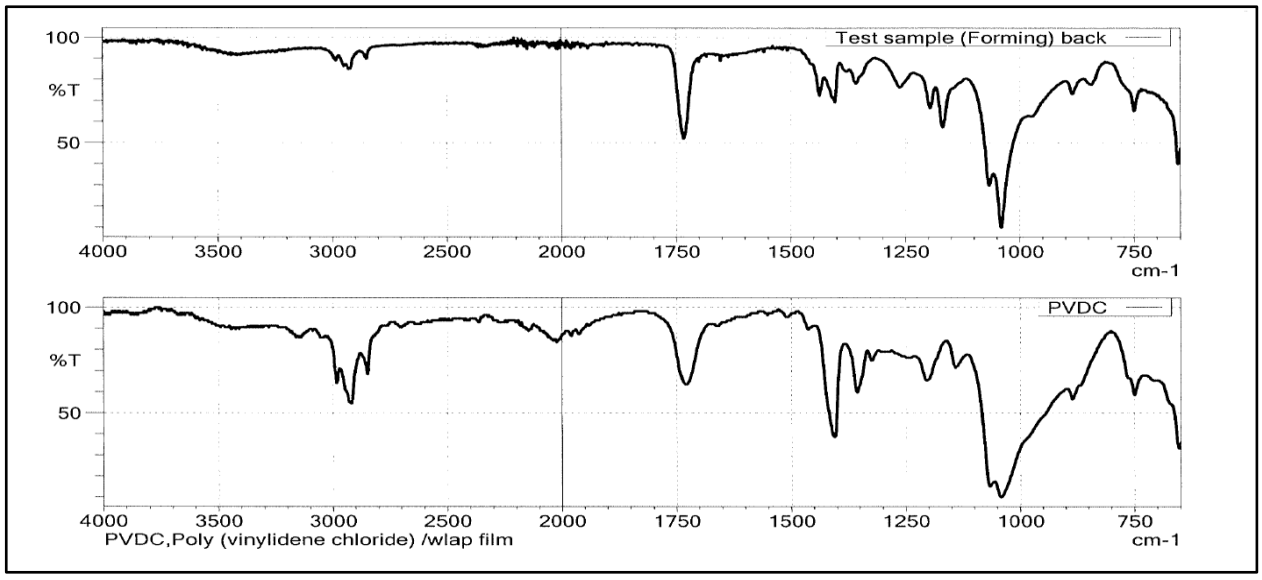

Figure 2: FTIR spectra of PVDC and test sample

Degradation profile of Generic Rivaroxaban tablets by forced degradation study:

In this forced degradation study drug product and placebo samples were exposed to various stress conditions to determine the assay i.e., drug content and total impurities. The details of the force degradation study are summarised in **Table 2.** It has been observed that humidity has a great impact on the assay and impurity profile. Stress testing at highly humid conditions showed significantly lower assay values (92.0%) and higher impurity profiles (7.8%) in comparison to other stress conditions. This forced degradation study confirmed that humidity has a high impact on the stability of the product.

Table 2: Result summary of forced degradation study of Generic Rivaroxaban tablets

Sr. No	Degradation approach	Assay value	Total impurities
1	Initial	101.2 %	0.02 %
2	Stress testing in an Oxidative environment	98.7 %	2.10 %
3	Alkali Degradation	100.3 %	0.68 %
4	Alkali Degradation	101.7 %	0.68 %
5	Stress testing at high temperature	98.6 %	0.56 %
6	Stress testing in high humidity environment	92.0 %	7.80 %*

Photostability studies:

To determine whether a drug product is light sensitive, a photostability study was performed in different packaging configurations as shown in **Table 3.** It has been observed that drug products are light stable and not light sensitive as the directly exposed tablets themselves are stable. Even at direct exposure maximum assay (101.1%) and minimum impurities were observed (0.02 %). Also, the tablets packed in PVC/PVDC blister and blister pack tablets samples inside the market carton pack showed excellent results as shown in **Table 3**. Hence this study suggested that the blister pack would be suitable for this product.

Table 3: Result summary of photostability study of Generic Rivaroxaban tablets

Sr. no	Degradation approach	Assay value	Total impurities
1	Initial	101.2 %	0.02 %
2	Direct light exposed tablets Samples	101.1 %	0.02 %
3	Blister (transparent) packed (PVC/PVDC 250/90) tablets Samples	99.2 %	0.02 %
4	Blister pack tablets Samples inside the Market carton pack	101.2 %	0.02 %

Comparative Packaging materials evaluation for selection through Vapour permeation study as per modified USP method:

Different packaging materials were subjected to an MVTR study to determine the maximum and minimum moisture vapour transmission rate through blisters. The comparative results of MVTR to different packaging materials are presented in **Table 4.** The ideal packaging material should resist moisture vapour transmission to avoid the degradation of the product packed in the packaging material. It has been observed that among all the packaging materials tested, PVC-PVDC 250/60 showed minimum MVRT and was classified as Class A material (No pack exceeds 0.5 mg/day/unit in average blister moisture vapor transmission rate). The graphical representation of the MVRT results of the PVC-PVDC 250/60 is shown in **Figure 3.** Based on this data PVC/ PVDC 250/60 was selected for further studies as well as for stability study.

Table 4: Comparative results of the MVTR with different packaging materials

Sr. No	Pack	Minimum MVTR of a test blister observed in the study (mg/day/unit)	Maximum MVTR of a test blister observed in the study(mg/day/unit)	Classification
1	PVC 250 micron	0.601	0.521	Class B
2	PVC-PVDC 250/40	0.310	0.194	Class A
3	**PVC-PVDC 250/60**	**0.096**	**0.079**	**Class A**
4	PVC-PE-PVDC 250/25/90	0.019	0.042	Class A

***Class A**: No pack exceeds **0.5 mg/day/unit** in average blister moisture vapor transmission rate; **Class B**: No pack exceeds **5 mg/day/unit** in average blister moisture vapor transmission rate; **Class C**: No pack exceeds **20 mg/day/unit** in average blister moisture vapor transmission rate; **Class D**: None*

of the packs meet any of the above average blister moisture vapor transmission rate requirements.

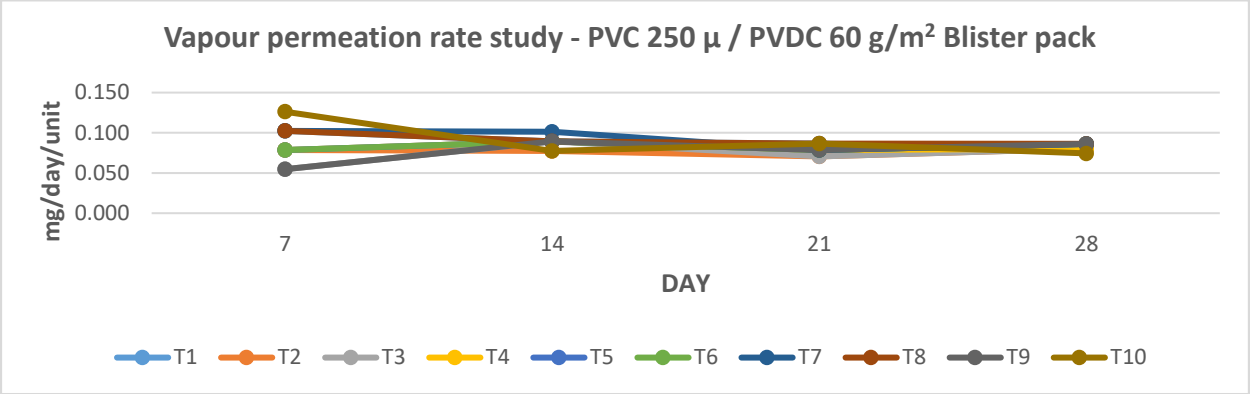

Figure 3: MVRT results of the PVC-PVDC 250 µ/60 g/m^2

Cost-effective source selection of PVC-PVDC 250 µ/60 g/m^2:

Based on the MVTR study PVC/PVDC 250/60, aluminium foil as a packaging material was selected. Two sources (European and Asian) were identified. The comparative physical and economical parameters of the forming and lidding foil obtained from European and Asian sources are presented in **Tables 5 and 6** respectively. With respect to physical specifications both European and Asian sources were found to be acceptable for generic Rivaroxaban tablets. But considering the costing point of view Asian source was selected as it is relatively economical and contributes towards lower product cost.

Table 5: Comparative physical and economical parameters of the forming foil obtained from European and Asian source

Sr. No	PARAMETER	Forming Foil specification	Forming Foil specification
1	Source	European	Asian
2	Material layers	PVC + PVDC	PVC + PVDC
3	PVDC (GSM)	55.5 – 65.5	55.0 – 65.0
4	PVC Thickness (µm)	237.5 – 262.5	235.5 – 265.5
5	Total Thickness (µm)	313.4 – 360.4	290 – 353.1
6	Comparative Price	Relatively expensive	**Relatively economical**

Table 6: Comparative physical and economical parameters of the lidding foil obtained from European and Asian source

Sr. No	PARAMETER	Lidding Foil specification	Lidding Foil specification
1	Source	European	Asian
2	Aluminum thickness	18.4 – 21.6 µ	18.4 – 21.6 µ
3	Aluminum GSM	54.0 ±8% (49.68 – 58.32) GSM	54.2 ±8% (49.86 – 58.54) GSM
4	Heat seal lacquer GSM	6 – 8 GSM	7 – 10 GSM
5	Total GSM	64.0 ±10% (57.6 – 70.4) GSM	61.2 ±10% (55.08 – 67.32) GSM
6	Comparative Price	Relatively expensive	**Relatively economical**

Short-term stress stability studies of the generic product:

The short-term stability study was performed with a generic product packed in PVC-PVDC packaging material obtained from both sources. No significant degradation profile was observed in both pack. The product was found stable in both packs i.e both sources were equivalent in protecting the formulation. So based on the cost Asian PVC-PVDC and aluminium foil were selected for this product and further evaluations were performed. PVC/PVDC Asian source was selected for the final proposed packaging materials for ICH stability studies. The comparative short-term stress stability study results of the generic product are summarized in **Table 7.**

Table 7: The comparative short-term stress stability study results of the generic product packed in European and Asian sources

Sr. No	Parameters	Initial	PVC/PVDC 250/60 Source: European	PVC/PVDC 250/60 Source: Asian	Acceptance Criteria
		0 day	30 days	30 days	
1	Appearance	Brownish, coated tablets	Complies	Complies	No change in initial appearance
2	Water content	3.89%	3.95%	3.98%	NMT 7.0%
3	Disintegration Time	35 seconds	36 seconds	33 seconds	NMT 5 mins
4	Assay	100.1%	100.3%	99.9%	100.0±10%
5	Individual unspecified impurity	0.01	0.020	0.02	NMT 0.20%
6	Total impurities	0.02	0.06	0.04	NMT 1.00%

Stability study of generic product in final proposed packaging material:

Based on short-term stability testing and cost-effectiveness Asian source PVC-PVDC 250 µ/60 g/m^2 was proposed as the final packaging material and the generic product was packed in blisters made with PVC-PVDC and aluminium foil for Climatic zone III and IV. In both accelerated and stress stability testing the product was found to be stable over 6 months. The stability testing results compared with the initial were found to be within acceptable limits. The physical nature, assay, impurity, and R-enantiomer of Rivaroxaban were found to be acceptable for a 6M time frame. This study confirmed that generic Rivaroxaban tablets can be packed in PVC-PVDC 250 µ/60 g/m^2 + aluminium foil blisters. The product was found to be stable in this packaging configuration. The results of accelerated and stress stability testing are presented in **Tables 8 and 9** respectively.

Table 8: Accelerated stability study results with Asian PVC-PVDC 250 µ/60 g/m^2 packaging

Test	Specification	40ºC/75% RH						
		Initial	M1	M2	M3	M4	M5	M6
Description	Brownish, coated tablets	Complies						
Assay	NLT 90.0% and NMT 110.0% of the labeled amount of Rivaroxaban.	101.5	101.0	100.0	99.5	99.2	99.1	98.8
R-enantiomer of Rivaroxaban	NMT 0.5%	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Impurity	Any unknown impurity – NMT 0.2%	0.02	0.02	0.02	0.02	0.03	0.04	0.04
	Total Impurity – NMT 1.0% (excluding Impurity I)	0.03	0.04	0.06	0.07	0.10	0.11	0.13

Table 9: Stress stability study results with Asian PVC-PVDC 250 µ/60 g/m^2 packaging

Test	Specification	30ºC/65% RH						
		Initial	M1	M2	M3	M4	M5	M6
Description	Brownish, coated tablets	Complies						
Assay	NLT 90.0% and NMT 110.0% of the labeled amount of Rivaroxaban.	101.5	101.3	100.6	100.1	99.8	99.5	99.1
R-enantiomer of Rivaroxaban	NMT 0.5%	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Impurity	Any unknown impurity – NMT 0.2%	0.02	0.02	0.02	0.02	0.02	0.03	0.03
	Total Impurity – NMT 1.0% (excluding Impurity I)	0.03	0.03	0.04	0.05	0.06	0.07	0.08

Based on extrapolated Assay data only, 24 months can be assigned as shelf life and based on extrapolated total impurities data only, the product shall be stable for up to 93 months. However, overall, 24 month shelf life is predicted based on the predicted value of assay and impurity levels, the proposed shelf life is 24 months. As shown in **figure 4**, the assay value predicted for 24 months is 93.17 % and the total impurity level predicted is 0.24%.

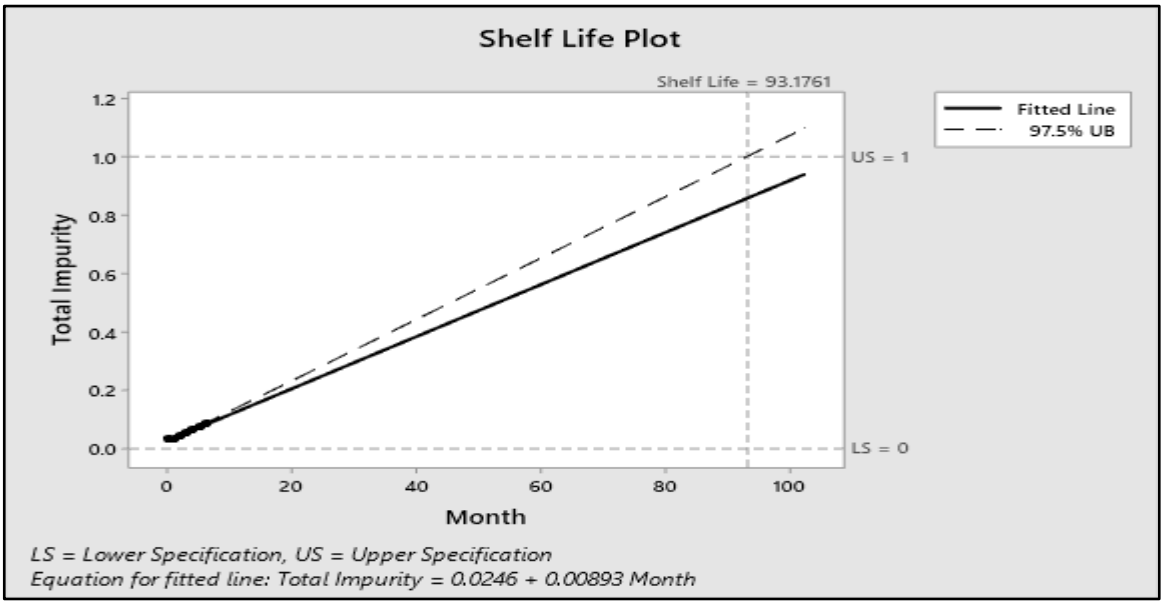

Figure 4: Shelf-life prediction of product stored in PVC-PVDC 250 µ/60 g/m^2 + aluminium foil blisters.

Conclusion:

The Asian source packaging material was found to be economical in comparison to the European source. In both accelerated and stress stability testing the product was found to be stable over 6 months. Overall, 24 months shelf life is predicted based on the predicted value of assay and impurity levels. The present study confirmed that Asian source PVC-PVDC 250 µ/60 g/m^2 was suitable packaging material for the Rivaroxaban tablets based on the MVRT study, accelerated and stress stability study.

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