FORMULATION AND EVALUATION OF RIVAROXABAN TRANSDERMAL PATCH

[1]T. Gayathri, [2]K. Nishith, [3]B. Udayteja, [4]A. Pavithra, [5]S. Pravalika,

[6]R. Archana.

[1]Assistant Professor, Department of Pharmaceutics, CVM College of Pharmacy, Velichala, Kothapally, Karimnagar, 505451.

[2]B. Pharmacy IV year, CVM College of Pharmacy, Velichala, Kothapally, Karimnagar, 505451.

Address for correspondence

T. Gayathri

Assistant Professor

CVM College of Pharmacy, Velichala, Kothapally, Karimnagar 505451

Telangana.

Email: [1]gayathrithamma1994@gmail.com, [2]nishithkamarapu006@gmail.com.

ABSTRACT

The present study focuses on the formulation and Evaluation of a Rivaroxaban Transdermal Patch designed for controlled and localized drug delivery through the skin. Transdermal drug delivery system offers several advantages, including avoidance of first-pass metabolism, improved patient compliance, and steady drug release over extended periods. Rivaroxaban was used as the model drug, with HPMC as the polymer, PEG 600 as the plasticizer, and IPA as the solvent. Patches were prepared by the solvent casting method and evaluated for parameters like thickness, drug content, folding endurance, and in vitro drug release. The results showed uniformity and sustained drug release, indicating that the patch is suitable for effective transdermal delivery.

Key Words: Rivaroxaban, HPMC, Solvent casting, Transdermal drug delivery system, Sustained release.

INTRODUCTION: [1,2]

Transdermal patches are advanced drug delivery systems designed to deliver medications through the skin and into the bloodstream in a controlled and sustained manner. The occurrence of systemic side effects with some of these formulations is indicative of absorption through the skin. A number of drugs have been applied to the skin for systemic treatment. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. Moreover, it overcomes various side effects like painful delivery of the drugs and the first pass metabolism of the drug occured by other means of drug delivery systems. Many drugs which can be injected directly into the

bloodstream via skin have been formulated. The main advantages of this system are that there is controlled release of the drug and the medication is painless. The drug is mainly delivered to the skin with the help of transdermal patch that adheres to the skin. A transdermal patch has several components including liners, adherents, drug reservoirs, drug release membranes which play a vital role in the release of the drug via skin. Various types of patches along with various methods of applications have been discovered to deliver the drug from the transdermal patch. Because of its great advantages, it has become one of the high research fields among the various drug delivery systems.

Advantages: -

1. Hepatic first pass metabolism, salivary metabolism, and intestinal metabolism are avoided.

2. The ease of usage makes it possible for patients to self-administer these systems.

3. In case of emergency, removing the patch at any point of time during therapy can instantly stop drug input.

4. Since the composition of skin is structurally and biologically same in almost all humans, it is minimal inter and interpatient variation.

Disadvantages: -

1. There is the possibility of skin irritation due to one or many of the formulation components.

2. Binding of the drug to the skin may result in dose dumping.

3. It can be used only for chronic conditions where drug therapy is desired for a long period of time including hypertension, angina, and diabetes.

4. Lag time is variable and can vary from several hours to days for different drug candidates.

5. Cutaneous metabolism will affect the therapeutic performance of the system.

Pathways of Skin Permeation

Drug molecules permeate through the skin surface by the different potential pathways including through the sweat ducts, through the hair follicles and sebaceous glands, or directly across the stratum corneum.

Mechanism of the drug release from transdermal drug delivery system:

Passive Diffusion:

Most TDDS rely on passive diffusion, driven by a concentration gradient. The drug moves from the patch (high concentration) into the skin (low concentration).

Matrix-controlled release:

The drug is dispersed in a polymer matrix. Release occurs by diffusion through the matrix and then into the skin.

Reservoir-controlled release:

The drug is in a reservoir (gel or liquid), separated from the skin by a rate-controlling membrane. The membrane controls the rate at which the drug diffuses out.

Adhesive-controlled release (in some patches):

The adhesive layer itself contains the drug, and release depends on the drug's diffusion from this adhesive layer.

Overall, the release mechanism Ensures a sustained, controlled delivery of the drug into the systemic circulation.

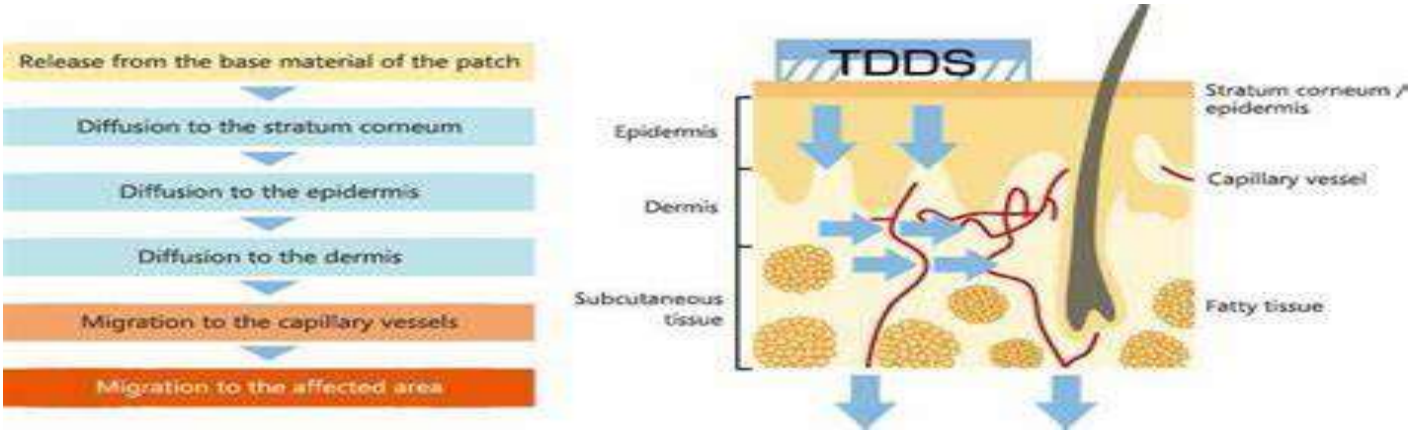

Fig 1: Mechanism of Drug Release

TRANSDERMAL PATCH:

A Transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. It offers controlled drug release over time and is commonly used for medications like nicotine, fentanyl, and hormone therapy. These patches are thin, flexible, and adhesive, containing an active pharmaceutical ingredient (API) that is released at a controlled rate.

COMPONENTS OF THE TRANSDERMAL PATCH:

The Basic Components of Transdermal Patch consist of polymer matrix / Drug reservoir, Active Ingredient (drug), permeation enhancers, pressure-sensitive adhesive (PSA), backing laminates, release liner, and other excipients like plasticizers and solvents.

Fig 2: Components of Transdermal Patch

1. Polymer matrix: Polymers are the backbone of a transdermal drug delivery system.

Systems for transdermal delivery are fabricated as multilayered polymeric laminates in which

a drug reservoir or a drug-polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane. Polymer selection and design must be considered when striving to meet the diverse criteria for the fabrication of effective transdermal delivery systems. The main challenge is in the design of a polymer matrix, followed by optimization of the drug-loaded matrix not only in terms of release properties but also with respect to its adhesion cohesion balance, physicochemical properties, compatibility, and stability with other components of the system as well as with skin.

The polymers utilized for TDDS can be classified as;

i. **Natural Polymers:** Hydroxypropyl Methylcellulose (HPMC), Carboxymethylcellulose (CMC), Methylcellulose (MC), Zein, gelatin, shellac, waxes, gums, natural rubber, chitosan.
ii. **Synthetic Elastomers:** Polybutadiene, Hydrin rubber, Polyisobutylene, Silicon rubber, Nitrilr, Acrylonitrile, Neoprene, Butyl rubber, etc.
iii. **Synthetic Polymer:** Polyvinyl Alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyurea, Polymethylmethacrylate, etc.

2. Drug: The most important criteria for TDDS are that the drug should possess the right physicochemical and pharmacokinetic properties. Transdermal patches offer much to drugs that undergo extensive first-pass metabolism, drugs with narrow therapeutic window, or drugs with short half-life which causes non-compliance due to frequent dosing.

Physicochemical properties:

- The drug must have a molecular weight of less than 1000 Daltons.
- The drug must have affinity for both the lipophilic and hydrophilic phases. The drug must have a low melting point.

Biological properties:

- The drug should have a strong effect at a daily dose of several mg/day.
- The half-life (t1/2) of the drug should be short. The drug should not cause skin irritation or allergic reactions.
- Drugs that are degraded in the gastrointestinal tract, or inactivated by first-pass effects by the liver, are suitable candidates for topical administration.
- Tolerance is not developed below the level of release close to topical administration.
- Drugs that must be used for a long time or cause unwanted effects in non-target tissues may also be formulated for topical administration.

3. Permeation enhancers: To increase the permeability of stratum corneum so as to attain higher therapeutic levels of the drug permeation enhancers interact with structural components of stratum corneum i.e., proteins or lipids. The enhancement in the absorption of oil-soluble drugs is apparently due to the partial leaching of the epidermal lipids by the chemical enhancers, resulting in the improvement of the skin conditions for wetting and for trans-epidermal and trans-follicular permeation. The miscibility and solution properties of the enhancers used could be responsible for the enhanced transdermal permeation of water-soluble drugs.

4. Pressure-sensitive adhesive (PSA): A PSA maintains intimate contact between the patch and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tacky, and exert a strong holding force. These include polyacrylates, polyisobutylene, and silicon-based. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. PSA should be Physicochemically and biologically compatible and should not alter drug release. The PSA can be positioned on the face of the device or in the back of the device and extending peripherally.

5. Backing laminate: The primary function of the backing laminate is to provide support.

Backing layer should be chemically resistant and excipients compatible because the prolonged contact between the backing layer and the excipients may cause the additives to leach out or may lead to diffusion of excipients, drug, or permeation enhancer through the layer. They should have a low moisture vapour transmission rate. They must have optimal elasticity, flexibility, and tensile strength.

6. Release liner: During storage, the release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than a part of the dosage form for delivering the drug. The release liner is composed of a base layer that may be non-occlusive or occlusive and a release coating layer made up of silicon or Teflon. Other materials used for TDDS release liner include polyester foil and metalized laminate.

7. Other excipients: Various solvents such as chloroform, methanol, acetone, isopropanol, and dichloromethane are used to prepare drug reservoirs. In addition plasticizers such as dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol are added to provide plasticity to the transdermal patch.

TYPES OF TRANSDERMAL PATCHES

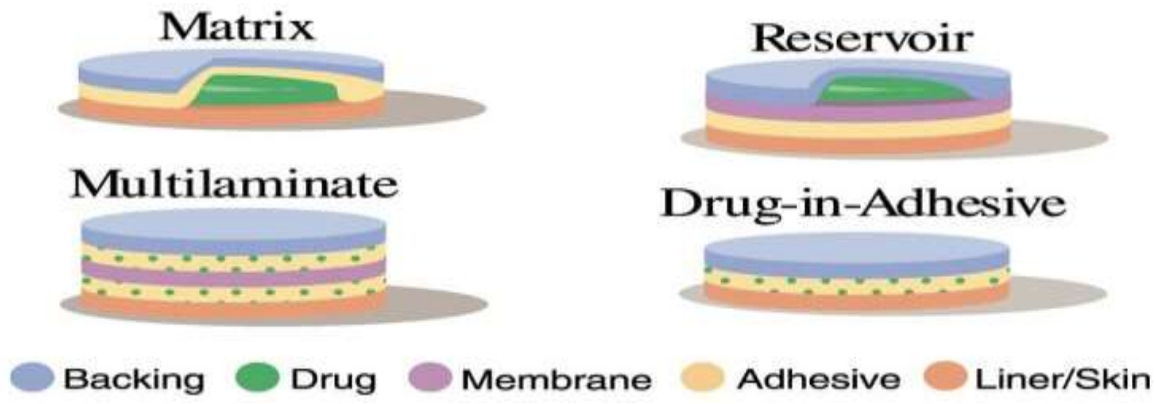

Fig 3: Types of Transdermal Patches

SINGLE-LAYER DRUG IN ADHESIVE:

In this type, the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

a) Multi-layer drug in adhesive: This type is also similar to the single-layer but it contains an immediate drug-release-layer and the other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the release of the drug. This patch also has a temporary liner layer and a permanent backing.

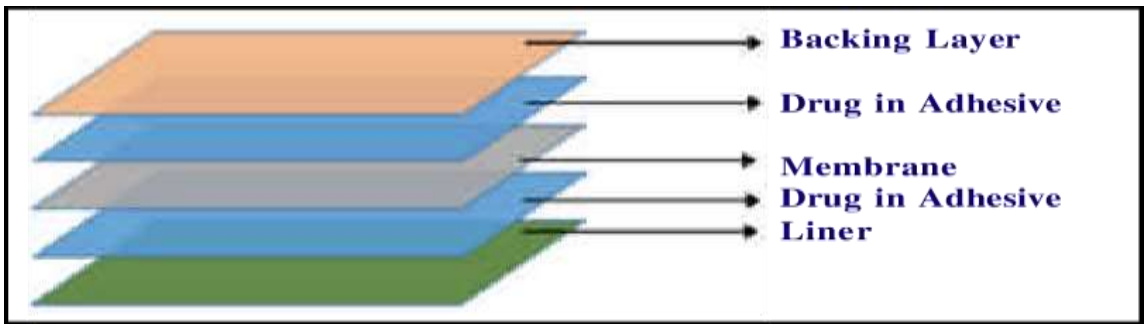

Fig 4: Layers of the Transdermal Patch

b) Vapour patch: The patch containing the adhesive layer not only serves to adhere the various surfaces together but also serves to release the vapor. The vapor patches are new to the market, commonly used for releasing the essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduce cigarette smoking conditions.

c) Reservoir system: In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be microporous or nonporous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel, or dispersed in a solid polymer matrix. The hypoallergenic adhesive polymer can be applied as an outer surface polymeric membrane that is compatible with the drug.

d) Matrix system:

i. Drug-in-adhesive system: This type of patch is formulated by mixing the drug with adhesive polymer to form a drug reservoir. It is then followed by spreading on an impervious backing layer by solvent casting or melting method. The top of the reservoir is protected by unmediated adhesive polymer layers. It may further be categorized into single-layer and multi-layer drug-in-adhesive. The system is considered to be compatible with a wide variety of drugs. Moreover, the system is competent to deliver more than one drug in a single patch. It offers advantages in reduced size and thickness and improved conformability to the application site, helping drive patient preference.

ii. Matrix-dispersion system: The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. It is then altered into a medicated disc with a definite shape and thickness. This drug-containing polymer disk is fixed onto an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of the adhesive rim.

e) Micro reservoir system: The system consists of microscopic spheres of drug reservoirs that release drugs at a zero-order rate for maintaining constant drug levels. A micro reservoir system is a combination of the reservoir and matrix-dispersion system. It is then followed by dispersing the solution homogeneously using high shear mechanical force in a lipophilic polymer to form thousands of microscopic drug reservoirs. Cross-linking agents are added to stabilize the thermodynamically unstable dispersion by in-situ cross-linking the polymer.

CRITERIA FOR DRUG SELECTION OF TRANSDERMAL PATCH:

- Drugs should be selected for their short half-life.
- In transdermal patches, the dose should be chosen to be low (<20mg/ml).
- Drugs should be chosen with lower molecular weight (<400 daltons).
- Drugs should be selected in the partition coefficient(log) between 1.0-4.
- The drug should be chosen in an oral form with low bioavailability.
- Drugs should be selected with a low therapeutic index.
- The drug should be selected as non-irritating and non-sensitizing to the skin.
- Drugs must be selected in their affinity for the lipophilic and hydrophilic phases.

CONDITIONS FOR USING TRANSDERMAL PATCHES:

Transdermal Patches are used when:

- When a patient experiences side effects that are intolerable and cannot take oral medications (dysphagia) and an alternative medication approach is needed.
- Where pain control can be improved by reliable management. Helpful in patients with dementia or who for other reasons are unable to self-medicate with their pain medication.

APPROACHES USED IN THE DEVELOPMENT OF TRANSDERMAL PATCHES:

A. Membrane moderated systems.

B. Adhesive diffusion-controlled system.

C. Matrix dispersion system.

D. Micro Reservoir systems.

RECENT ADVANCES IN THE FIELD OF TRANSDERMAL PATCHES:

1. Patch technology for protein delivery

2. Pain-free diabetic monitoring using transdermal patches

3. Testosterone transdermal patch system in young women with spontaneous premature ovarian failure

4. Transdermal Patch of Oxybutynin used in overactive bladder (OAB)

5. Pain relief

6. Molecular absorption enhancement technology.

EVALUATION OF TRANSDERMAL PATCHES:

Physicochemical Evaluation:-

Thickness: The thickness of the transdermal film is determined by a traveling microscope, dial gauge, screw gauge, or micrometer at different points of the film.

Uniformity of weight: Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Drug content determination: It can be determined by completely dissolving a small area of polymeric film in the suitable solvent of definite volume. The solvent is selected in which the drug is freely soluble. The selected area is weighed before dissolving in the solvent. The whole content is shaken continuously for 24h in a shaker incubator followed by sonication and filtration. The drug in solution is assessed by the appropriate analytical method.

Content uniformity test: The test is applied as the gold standard to determine chemically the content of active constituent for each unit dose. The test is completed by performing an assay to find out the content of drug material contained in the polymeric film of the patch.

Moisture content: The prepared films are weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight.

Moisture Uptake: Weighed films are kept in a desiccator at room temperature for 24 h.

These are then taken out and exposed to 84% relative humidity using a saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with the flatness study. For flatness determination, one strip is cut from the center and two from each side of the patches. The length of each strip is measured and variation in length is measured by determining percent constriction.

Folding Endurance: Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it breaks. The number of times the films could be folded at the same place without breaking gives the folding endurance value.

Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the film is kept fixed with the help of an iron screen and the other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached to the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film.

Water vapor transmission studies (WVT): WVT is determined by taking one gram of calcium chloride in previously dried empty vials having equal diameters. The polymer films are pasted over the brim with the help of adhesive like silicon adhesive grease and then allowed to set for 5 minutes. The vials are accurately weighed and placed in a humidity chamber maintained at 68% .

The vials are then weighed repeatedly up to seven consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch.

Microscopic studies: The distribution of drugs and polymer in the film can be studied using a scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double-sided adhesive tape. The sections are then coated with gold, palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under a scanning electron microscope.

Adhesive studies: The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesive capable of bonding to surfaces with the application of light pressure. The adhesive properties of a TDDS can be characterized by conducting the following factors.

Peel Adhesion properties: It is the force required to remove the adhesive coating from the test substrate. It is tested by measuring the force required to pull a single coated tape, applied to the substrate at 180° angle. The test is passed if there is no residue on the substrate.

MATERIALS:

S.No.	Ingredients	Category
1	Rivaroxaban (RXB)	Active Pharmaceutical Ingredient (API)
2	Hydroxypropyl Methylcellulose (HPMC)	Polymer
3	Isopropyl Alcohol (IPA)	Solvent
4	Polyethylene Glycol (PEG) 600	Plasticizer

METHODOLOGY:

SOLVENT CASTING METHOD:

Solvent casting is a film-forming technique where a polymer and the active drug are dissolved in a suitable solvent, and the solution is poured into a mold or petri dish to evaporate the mold or petri dish to evaporate the solvent, resulting in a uniform, thin polymeric film containing the drug.

Procedure for the Formulation of Rivaroxaban Transdermal Patch by Solvent Casting Method:

- ✓ Initially, 1 mg of Rivaroxaban was accurately weighed and transferred into a clean container.
- ✓ To this, 5 mg of Hydroxypropyl Methylcellulose (HPMC) polymer was added and mixed thoroughly to ensure uniform blending.
- ✓ Following this, 5 ml of Isopropyl Alcohol was added gradually to the mixture, serving as the solvent. The solution was stirred continuously to facilitate the dissolution of both the polymer and the drug.
- ✓ Subsequently, 2 ml of Polyethylene Glycol 600 (PEG 600) was incorporated as a plasticizer to enhance the flexibility of the resulting film.
- ✓ The entire mixture was stirred thoroughly until a clear, homogenous solution was obtained. The resulting solution was then poured into a clean petri plate and placed in a hot air oven at 100 °C for 15 minutes to allow solvent evaporation and film formation.

- ✓ After drying, the former film was carefully removed and cut into desired size and shape for further evaluation and testing.

S.No.	Ingredients	F1	F2	F3
1	Rivaroxaban	1mg	1mg	1mg
2	Hydroxypropyl Methylcellulose	20mg	10mg	5mg
3	Isopropyl Alcohol	10ml	5ml	5ml
4	Polyethylene Glycol 600	5ml	2ml	2ml

RESULTS AND DISCUSSIONS:

Formulation of Placebo Transdermal Patches by Solvent Casting Method Using HPMC and Different Solvents

The image below displays placebo transdermal patches formulated using the solvent casting technique. These patches were prepared without any active pharmaceutical ingredient (drug) to evaluate the base film properties.

Hydroxypropyl Methylcellulose (HPMC) was used as the film-forming polymer due to its excellent film-forming ability and biocompatibility. Polyethylene Glycol 600 (PEG 600) served as a plasticizer to impart flexibility and reduce brittleness of the films.

Three different solvents—Isopropyl Alcohol, Ethanol, and Methanol were individually used to dissolve HPMC and PEG 600, resulting in three separate placebo formulations. The prepared solutions were poured into petri dishes and dried at an ambient temperature to allow complete solvent evaporation and formation of transparent film.

Fig 5: Placebo Polymeric Patches

Each circular film in the image represents a placebo patch prepared using one of the three solvents. The physical characteristics of the patches including clarity, transparency, uniformity, and flexibility were visually compared. Among the three, the patch formulated with Isopropyl Alcohol showed superior physical integrity, smooth surface, and uniform texture, and was therefore selected as the optimized placebo formulation for further development and potential drug incorporation.

This initial placebo formulation study was essential to identify the most suitable solvent system and ensure optimal polymer-plasticizer compatibility before proceeding to drug-loaded patch development.

Results of Formulation Trial 1:

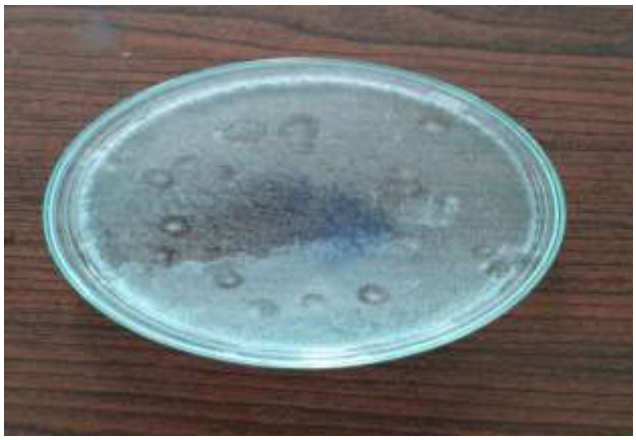

Fig 6: Formulation Trial 1

Results of Formulation Trial 2:

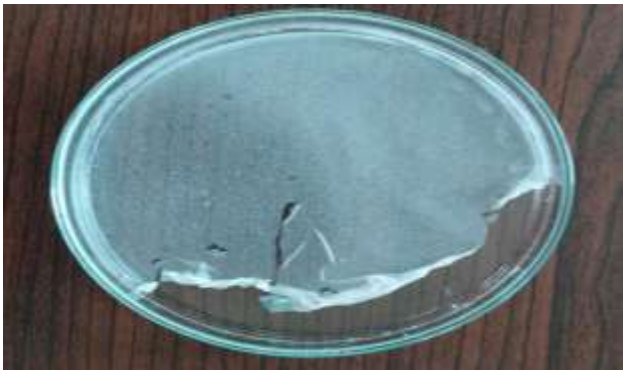

Fig 7: Formulation Trial 2

Results of Formulation Trial 3:

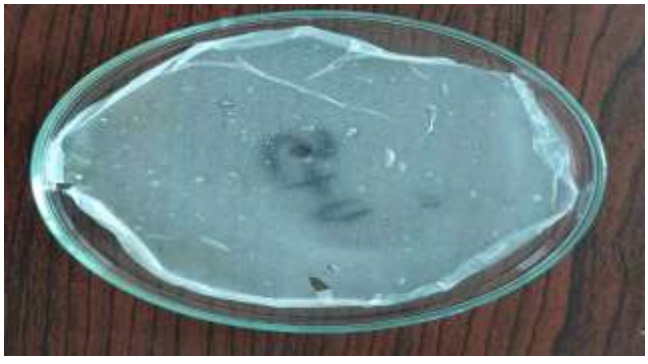

Fig 8: Formulation Trial 3

EVALUATION PARAMETERS:

1. Drug content uniformity of films: The 1 cm^2 patches were cut and put into a beaker with 100 ml of pH 7.4 phosphate buffered saline. A magnetic bead was used to stir the medium. Whatman filter paper was used to filter the contents, and the filtrate's drug content was measured spectrophotometrically at 248 nm using a reference solution made up of drug-free placebo films. To confirm the outcome, the experiment was conducted again.

Procedure:

Accurately weigh and cut a known area of the Rivaroxaban patch (e.g., 1cm^2). Fix the patch on a glass slide using adhesive or place in a tea bag mesh or sample holder to avoid floating. Place the patch in the dissolution vessel containing phosphate buffer. Start the apparatus and allow it to run for a predefined time (e.g., 8 hours or as per release profile). At specific time intervals (e.g., 0.5, 1, 2, 4, 6, 8 hrs), Withdraw 5ml of sample. Replace withdrawn volume with fresh pre-warmed buffer to maintain sink conditions. Filter the withdrawn samples using Whatman filter paper. Measure the absorbance of each sample using a UV-Visible spectrophotometer at wavelength ~249-250 nm (λ max). Calculate the cumulative % drug release using a standard calibration curve.

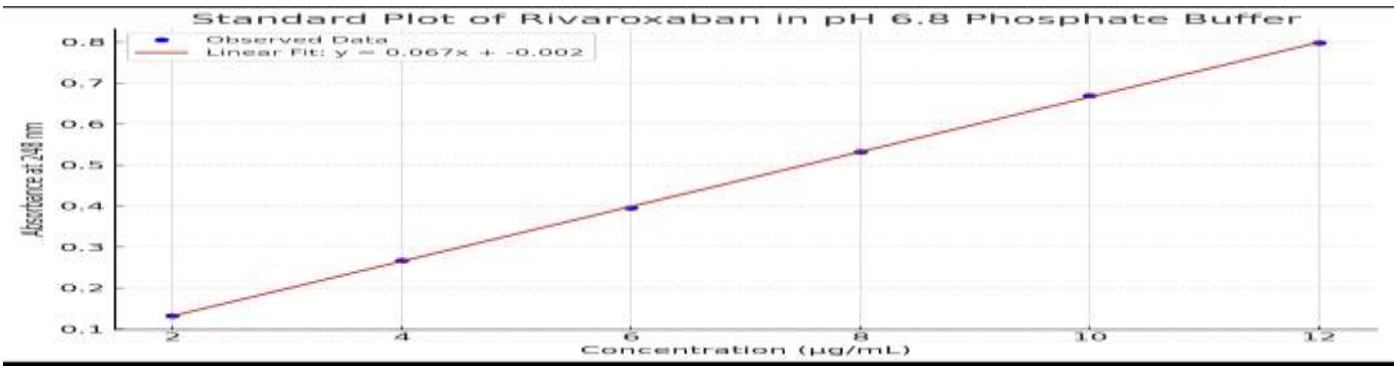

Fig 9: Standard Plot of RXB

Absorbance Values (at 248 nm) of Rivaroxaban:

Concentration (µg/ml)	Absorbance
2	0.13
4	0.27
6	0.39
8	0.55
10	0.67
12	0.80

2. Physical appearance: All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.

3. Thickness of Patch: The thickness of the optimized formulation was assessed using a digital micrometer. Specifically, the thickness of the optimized formulation (F3) was 0.2913±0.3.

4. Folding Endurance: Repeated folding of the transdermal film was used to evaluate the folding endurance of the optimized formulation. Specifically, the folding endurance of the optimized formulation (F3) was 91±2.

5. Tensile Strength: The tensile strength of the film was determined using a universal strength tester. The sensitivity of the device is 1g. It includes two force sensing handles. The bottom is fixed and the top is movable. Film of the test size (4 ×1 cm2) was fixed between these cell clamps and a gradual force was applied until the film broke. The tensile strength of the patch is taken directly from the dial readings in kg. The tensile strength is expressed by following.

Tensile strength of patch =Tensile load at break / Cross section area.

The tensile strength of the prepared transdermal patch was found to be within the acceptable range of 1.0 to 2.0 kg/cm^2 , ensuring sufficient mechanical integrity and flexibility for dermal application.

6. Weight uniformity: For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated.

7. Moisture Content (Loss on drying): The intrinsic moisture present in a substance may affect how stable a dosage form is, particularly if it contains a medication that is water-sensitive. The moisture content is determined using the absolute approach, which results in a weight loss that is recorded throughout the procedure. Each patch from each batch was weighed separately, and the average weight was determined. This weight was taken into account as the starting weight. The patches were then all stored for 24 hours at room temperature in desiccators containing activated silica. When the weight of each individual patch remained unchanged, the final weight was recorded. The difference between the initial and final weights relative to the final weight was used to compute the % moisture absorption. Limits of Moisture content is 2.632-2.854.

% Moisture content= (Initial weight) -(Final weight)/Final weight×100

EVALUATION PARAMETERS TABLE:

CHARACTERISTICS	F1	F2	F3
Weight Variation	5.2±0.5	6.7±0.4	5.6±0.6
Thickness	0.22	0.21	0.29
Folding Endurance	162±6	157±2	91±2
Drug content	87.2±0.02	89.1±0.01	91.4±0.04
Moisture content	2.302	2.431	2.854

Fig 10: Optimized Rivaroxaban Transdermal Patch

CONCLUSION:

In conclusion, TDPs containing RXB were fabricated using the solvent casting technique. A comprehensive evaluation assessed thickness, folding endurance, drug content, moisture uptake, moisture loss, and stability. The results showed promising outcomes, with the improved formulation. Each excipient contributed positively to the formulation's efficacy and acceptability. The TDPs ease of administration enhances patient compliance and therapeutic outcomes, offering a convenient topical delivery method for RXB. Further studies are needed to explore the preclinical and clinical activities of these optimized formulations.

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