Research Article

Formulation and Evaluation of Transdermal Patch of Apixaban

Dhaval J. Patel, Ajay M. Vyas, Sanjesh G. Rathi*, Shrenik K. Shah
Department of Pharmaceutics, Saraswati Institute of Pharmaceutical Sciences, Dhanap. Gandinagar, Gujarat, INDIA.
***Corresponding author's E-mail:** rathi.sanjesh@gmail.com

Received: 10-05-2021; **Revised:** 22-07-2021; **Accepted:** 30-07-2021; **Published on:** 15-08-2021.

ABSTRACT

The aim of the present investigation was to develop and evaluate transdermal patch of Apixaban. Formulation development of Apixaban Transdermal patch was initiated using Eudragit S 100 and HPMC E50 LV as matrix controlling polymer for matrix type Transdermal Patch. PEG 400 was selected as plasticizer. Glycerin was selected as permeability enhancer. Preformulation study was performed to check the drug excipient compatibility. The IR spectra of Drug and final formulation found satisfactory. There are no any interaction between drug and excipients. Further the linearity curve was developed in UV for method of analysis. Trials A1-A14 was initiated using different concentration of polymers in the formulation. The prepared patches were transparent and smooth in surface. The weight variation was found well within acceptable range. The thickness of patches was found uniform in nature and the variation is found satisfactory. Further, the surface pH of the patches was found between 6.8 to 7.1 and it is acceptable. The drug content, folding endurance and %elongation results of A1-A14 batches were found well within acceptable range. Initially the trial batches were taken with a single polymer like HPMC and EudragitS100. The drug release was not achieved as per the target drug release profile for 8hours. Hence the combination of these two polymers are taken and found better results than the single polymers. Based on the drug release data, it was observed that the A8 batch was the most satisfactory batch with respect to drug release and other parameters. Hence, the A8 batch selected as optimized batch and Stability study of the same batch initiated.

Keywords: Apixaban, Transdermal Patch, formulation, TDDS.

QUICK RESPONSE CODE →

DOI:
10.47583/ijpsrr.2021.v69i02.009

DOI link: http://dx.doi.org/10.47583/ijpsrr.2021.v69i02.009

INTRODUCTION

Any drug delivery system aim is to provide a therapeutic amount of drug to the proper site in the body and then maintain desired drug concentration. Drugs are administered by various routes such as oral, parental, nasal, transdermal, rectal, intravaginal, ocular etc. Among all of them, oral route is most common and popular but this route of administration have some drawback like first pass metabolism, drug degradation in gastrointestinal tract due to pH, enzyme etc.[1]To overcome these drawback, a novel drug delivery system (controlled drug delivery system)was developed in which a polymer(natural or synthetic)combined with a drug in such a way that drug is released from the material in a predesigned manner.[1] The discovery of Transdermal drug delivery system (TDDS) is a breakthrough in the field of controlled drug delivery system. It becomes a great field of interest. TDDS are self-contained, discrete dosage forms which when applied to the intact skin; deliver the drug, through the skin at control rate to the systemic circulation. In 1965 Stoughton first conceived of the percutaneous absorption of drug substances. FDA approved the first Transdermal system Transderm-SCOP in 1979. FDA approved this for the prevention of nausea and vomiting.[1]In TDDS, the drug is mainly delivered through the skin with the aid of transdermal patch which is a medicament adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and to the blood stream. Now a day TDD is a well-accepted means of delivering many drugs to the systemic circulation in order to achieve a desired pharmacological outcome.[1] The success of this approach is evidenced by the fact that there are currently more than 35 TDD products approved in the USA for the treatment of conditions including hypertension, angina, female menopause, severe pain states, nicotine dependence, male hypogonadism, local pain control and more recently, contraception and urinary incontinence.[1]

Advantages of TDDS[2]

→ Transdermal medication delivers a steady infusion of a drug over an extended period of time.

→ Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic "first-pass" effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc.

They are noninvasive, avoiding the inconvenience of Parenteral therapy.

→ The drug input can be terminated at any point of time by removing transdermal patch.

→ The simplified medication regimen leads to improved patient compliance and reduced inter &intra – patient variability.

→ Self-administration is possible with these systems.

→ They can be used for drugs with narrow therapeutic window.

→ Longer duration of action resulting in a reduction in dosing frequency.

→ Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

Disadvantages of TDDS[2]

→ The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10mg/day, the transdermal delivery will be very difficult.

→ Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin's impermeability.

→ Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.

→ Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.

→ The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

→ Many drugs especially drugs with hydrophilic structures permeate the skin too slowly may not achieve therapeutic level.

→ The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema.

→ The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.

Limitations of TDDS[3]

The drug moiety must possess some physicochemical properties for penetration through skin and if dose of drug is large i.e., more than 10-25mg/day transdermal delivery is very difficult, daily dose of drug preferred less than 5mg/day.

→ Local irritation at the site of administration such as itching, erythema and local edema may be caused by drug or the excipients used in the formulations.

→ Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.

→ Some patients develop contact dermatitis at the site of application due to system components.

→ The barrier function of the skin changes from one site to another, from person to person and with age.

→ Poor skin permeability limits the number of drugs that can be delivered in this manner.

→ A high drug level cannot achieve by this system.

→ Transdermal drug delivery is unable to deliver ionic drugs.

→ Transdermal drug delivery system is restricted to potent drug.

→ It cannot deliver drugs in a pulsatile fashion.

→ Tolerance inducing drugs or those (e.g., hormones) requiring chrono pharmacological management is not suitable candidates.

→ Required significant lag time.

Ideal molecular properties for transdermal drug delivery[4]

→ An adequate solubility in lipid and water is necessary for better penetration of drug (1mg/ml).

→ Optimum partition coefficient is required for good therapeutic action.

→ Low melting point of drug is desired (<200°C).

→ The pH of the saturated solution should be in between 5 to 9.

Skin As Site For Transdermal Drug Administration[4]

The skin of an average adult body covers a surface area of approximately two square meters and receives about one-third of the blood circulating through the body. The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers: the epidermis, the dermis, and the hypodermis . Microscopically, the epidermis is further divided into five anatomical layers with stratum corneum forming the outer most layer of the epidermis, exposing to the external environment. An average human skin surface is known to contain, on the average, 40-70 hair follicles and 200-250 sweat ducts on each square centimeter of skin area. These skin appendages, however, actually occupy, grossly, only 0.1% of the total human skin surface.

Even though the foreign agents, especially the water-soluble ones, may be able to penetrate into the skin via these skin appendages at a rate which is faster than through the intact area of the stratum corneum, this trans-appendage route of percutaneous absorption has, at steady state, a very limited contribution to the overall kinetic profile of transdermal permeation. Therefore, the transdermal permeation of most neutral molecules can

thus, be considered as a process of passive diffusion through the intact stratum corneum in the inter follicular region.

MATERIALS

Apixaban as a gift sample was obtained from Torrent Research Centre, Ahmedabad, Eudragit S100, HPMC E50, PEG400, Glycerin, Acetone was obtained from Balaji Chemicals, Ahmedabad.

METHODS

Pre-formulation Study

Identification of Drug

Physical appearance, color and nature of drug were evaluated.

Melting Point

Melting point of the drug was determined by capillary method and the temperature at which the drug melts was note down.

Solubility

Solubility studies carry out by saturation solubility method in which saturated solution of drug was prepared and transferred in a glass vial. Drug was dissolve in 10 mL of the solvent up to saturation. The solution was sonicating for 15 minutes, than filtered and diluted if required. The amount of the drug dissolved was measure by using UV spectrophotometer. The results of solubility study were recorded.

Dose calculation

Diameter of the Petridish = 9.0 cm

Radius = Diameter /2 = 9.0/2 = 4.5 cm.

Area of Petridish = πr^2 = 3.14 X 4.5 X 4.5 = 63.58 cm^2

Dose is 2.5 mg and film dimension are 2 cm X 2 cm = 4 cm^2

4 cm^2 contain = 2.5 mg of Apixaban

Therefore, 63.58 cm^2 contain (?) = 39.70 mg ~ 40 mg Apixaban.

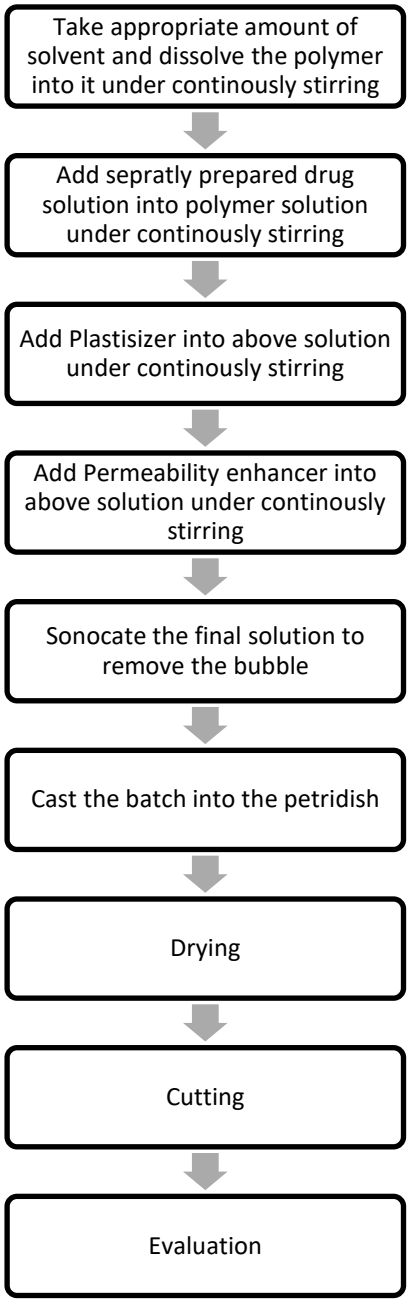
Formulation of Transdermal Patch of Apixaban

In the present study, matrix type transdermal patches of Apixaban were prepared by solvent casting techniques. Circular, glass petri dish having surface area of 63.5 cm^2 were fabricated for casting the patches.

Selection of ingredients

From the literature review and based on the characteristics of Eudragit S 100, it was selected as parent polymer. The further need was to select polymer which can retard the drug release for or near to 8 hrs. Along with Eudragit S100, HPMC E50 LV was selected as release controlling polymer for matrix type Patch. Further, PEG 400 was selected as plasticizer. Glycerin was selected as permeability enhancer.

Manufacturing Process Flow chart



Evaluation of Transdermal Patch of Apixaban

Appearance

Check the visual appearance of the prepared Transdermal patches and record the same.

Thickness

The thickness of the prepared patches was measured using digital vernier caliper with a least count of 0.01 mm at different spots of the patch. The thickness was measured at three different spots of the patches and average was taken and SD was calculated.

Weight Variation

Four-centimeter square of the patch was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

Folding Endurance

Folding endurance was determined by repeated folding of the patch at the same place till the strip breaks. The number of times the patch is folded without breaking was computed as the folding endurance value.

Surface pH

The surface pH of prepared transdermal patch was determined using pH meter. Patch was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the patch. The procedure was performed in triplicate and average with standard deviation was reported.

Drug Content

Drug content test of the patch was carried out by dissolving the 4 cm^2 patch in 100 ml of pH 7.4 phosphate buffer. The prepared solution was filtered and then measured spectrophotometrically at λ_{max} of 279 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded.

Percentage Elongation

The percentage elongation was determined by noting the length just before the break point and calculating the same by using below mentioned equation;

Percentage Elongation = (L1-L2/L1) x 100

Where, L1 is the final length of each patch and L2 is the initial length of each patch

***In Vitro* Diffusion Study**

In Vitro Drug Diffusion studies was carried out using the 20 ml Franz diffusion cell. The synthetic membrane was used as a skin. The membrane was stabilized before mounting to remove the soluble components. The membrane was mounted between the donor and receptor compartments. The receptor compartment was filled with 20 ml of isotonic phosphate buffer of pH 7.4 which was maintained at 37 ± 0.2°C and hydrodynamics were maintained using magnetic stirrer. One patch of dimension 2 cm × 2 cm was previously moistened with a few drops of pH 7.4 phosphate buffer and placed in donor compartment. 1 ml samples from receptor compartment were withdrawn at suitable time interval of 1, 2, 3, 4, 6 and 8 hours which was then replaced with 1 ml of pH 7.4 phosphate buffer. The percentage of drug permeated was determined by measuring the absorbance in UV Visible spectrophotometer at λ_{max} of 279 nm.

Stability study

Stability study was carried out at 40^0C/75% RH condition for 1 month. Each piece of the patch from the optimized formulation was packed in butter paper followed by aluminum foil. After 1 month, the patches were evaluated for the physical appearance, drug content and diffusion study.

RESULTS AND DISCUSSION

Preformulation Study

The results of preformulation study were recorded as below.

Appearance of Drug: White crystalline powder

Colour of Drug: White

Physical state: Crystalline

Melting point: 236 °C

Solubility: Soluble in water and 7.4 phosphate buffer

Obtained results of solubility suggested that Apixaban freely soluble in distilled water and in phosphate buffer pH 7.4. However, transdermal matrix patch apply on the skin, therefore, to evaluate permeation of drug through skin pH, phosphate buffer pH 7.4 was select as a diffusion medium for further study.

Evaluation of Apixaban Transdermal Patches

Formulation and development of Apixaban transdermal patches has been initiated to achieve the targeted objectives. The development batches were taken using HPMC E50 and Eudragit S100 as matrix forming polymers. The evaluation parameters were checked and recorded as below 1

Table 1: Evaluation of Apixaban Transdermal Patches

Batch	Surface	Transparency	Stickiness
A1	Smooth	Transparent	Non-Sticky
A2			
A3			
A4			
A5			
A6			
A7	Rough		
A8			
A9			
A10			
A11			
A12			
A13			
A14			

Based on the appearance results, it was observed that all batches were found non-sticky in nature. The patches were transparent and smooth in surface. It was concluded that all excipients were found in solubilize form and no any undissolved particles are present in the preparation.

Table 2: Evaluation of Apixaban Transdermal Patches

Batch	Weight variation (mg) ± SD	Thickness (mm) ± SD	Surface pH ± SD
A1	102 ± 3.9	0.21 ± 0.05	7.1 ± 0.2
A2	201 ± 4.1	0.25 ± 0.03	6.9 ± 0.4
A3	299 ± 4.5	0.31 ± 0.04	7.0 ± 0.3
A4	101 ± 2.6	0.22 ± 0.09	7.2 ± 0.4
A5	204 ± 4.8	0.24 ± 0.02	7.1 ± 0.2
A6	301 ± 3.9	0.30 ± 0.03	7.0 ± 0.2
A7	105 ± 3.1	0.21 ± 0.06	6.9 ± 0.3
A8	202 ± 3.6	0.26 ± 0.04	6.9 ± 0.2
A9	300 ± 3.2	0.32 ± 0.02	6.8 ± 0.4
A10	348 ± 2.6	0.34 ± 0.04	6.9 ± 0.1
A11	356 ± 1.9	0.35 ± 0.03	6.8 ± 0.3
A12	405 ± 1.4	0.37 ± 0.02	7.0 ± 0.2
A13	411 ± 3.9	0.37 ± 0.04	6.9 ± 0.1
A14	409 ± 2.8	0.39 ± 0.01	7.1 ± 0.2

Table 3: Evaluation of Apixaban Transdermal Patches

Batch	Drug Content (%) ± SD	Folding Endurance ± SD	% Elongation
A1	98.9 ± 3.1	59 ± 10	2.6 ± 1.1
A2	99.1 ± 2.5	72 ± 12	3.9 ± 1.4
A3	99.4 ± 3.6	91 ± 14	4.1 ± 1.3
A4	98.5 ± 3.3	102 ± 15	5.6 ± 2.4
A5	98.2 ± 3.9	114 ± 12	6.8 ± 3.2
A6	99.5 ± 1.8	130 ± 16	7.2 ± 2.2
A7	98.9 ± 1.3	149 ± 18	10.3 ± 3.3
A8	99.2 ± 3.1	169 ± 14	12.5 ± 3.9
A9	99.7 ± 3.8	190 ± 13	14.8 ± 4.4
A10	97.8 ± 2.9	201 ± 11	15.2 ± 1.9
A11	99.2 ± 2.4	220 ± 10	14.7 ± 2.3
A12	99.8 ± 2.6	296 ± 16	17.9 ± 2.5
A13	98.2 ± 1.9	301 ± 14	18.1 ± 2.1
A14	97.6 ± 1.4	325 ± 19	19.3 ± 1.9

Based on the above weight variation, thickness and surface pH results, it was observed that the all A1-A14 batches were found satisfactory in terms of weight variation test.

The weight variation was found well within acceptable range. The thickness of patches was found uniform in nature and the variation is found satisfactory.

Further, the surface pH of the patches was found between 6.8 to 7.1 and it is acceptable.

Based on the above results of drug content, folding endurance and % elongation, it was observed that all A1-A14 batches were well within acceptable range of drug content. The % elongation of all batches was recorded in the above table. Based on % elongation results, it was noted that the elasticity of the film was increased with the increase in amount of polymer. Folding endurance of the A1 to A14 batches were found satisfactory. Higher the amount of polymer gives the higher value of folding endurance.

Polymers in combination gives high folding endurance as compared to single polymer. However, the Eudragit S 100 gives more folding endurance as compared to HPMC polymer. Drug release study of all 14 batches was performed to identify the good polymer and plasticizer combination. Initially the trial batches were taken with a single polymer like HPMC and Eudragit S100. The drug release was not achieved as per the target drug release profile for 8 hours. Hence the combination of these two polymers are taken and found better results than the single polymers. Among all batches, A8 batch which contains HPMC and Eudragit S100 as matrix polymers and PEG 400 as plasticizer gives more than 90% drug release within 8 hours. Further, increase in amount of polymer retard the drug release. As shown in batch A10 to A14 higher amount of polymer not release drug within 8 hours. Hence the desired drug release was expected from HPMC and Eudragit S100 polymers combination. The results were recorded in below table and the comparison also showed in below figure 1.

Table 4: Evaluation of Drug release profile Apixaban Transdermal Patches

Time (Hrs)	1	2	3	4	5	6	7	8
A1	35.9	59.5	76.9	89.5	98.2	99.8	99.9	99.9
A2	32.5	56.7	71.8	84.3	92.8	97.9	98.2	99.7
A3	28.5	52.3	67.2	81.0	89.3	94.2	97.4	98.9
A4	30.2	56.7	69.7	78.3	87.5	92.4	99.7	99.9
A5	26.7	50.9	62.9	73.5	81.6	89.3	98.9	99.7
A6	22.8	47.3	59.2	70.6	76.5	86.7	99.2	99.6
A7	18.9	42.1	54.6	65.9	71.2	80.3	93.4	98.5
A8	21.6	45.9	58.6	68.2	73.3	85.6	92.5	99.7
A9	26.5	48.3	61.3	71.3	77.8	89.3	98.2	98.8
A10	20.9	45.2	54.3	66.1	71.5	80.9	88.3	94.6
A11	18.2	41.3	50.3	61.2	67.5	76.2	82.1	89.9
A12	15.3	35.2	47.2	56.9	64.2	72.3	81.5	88.1
A13	14.1	31.2	44.3	52.3	61.9	70.3	78.9	85.4
A14	11.2	27.3	41.1	49.8	59.1	68.9	75.6	82.6

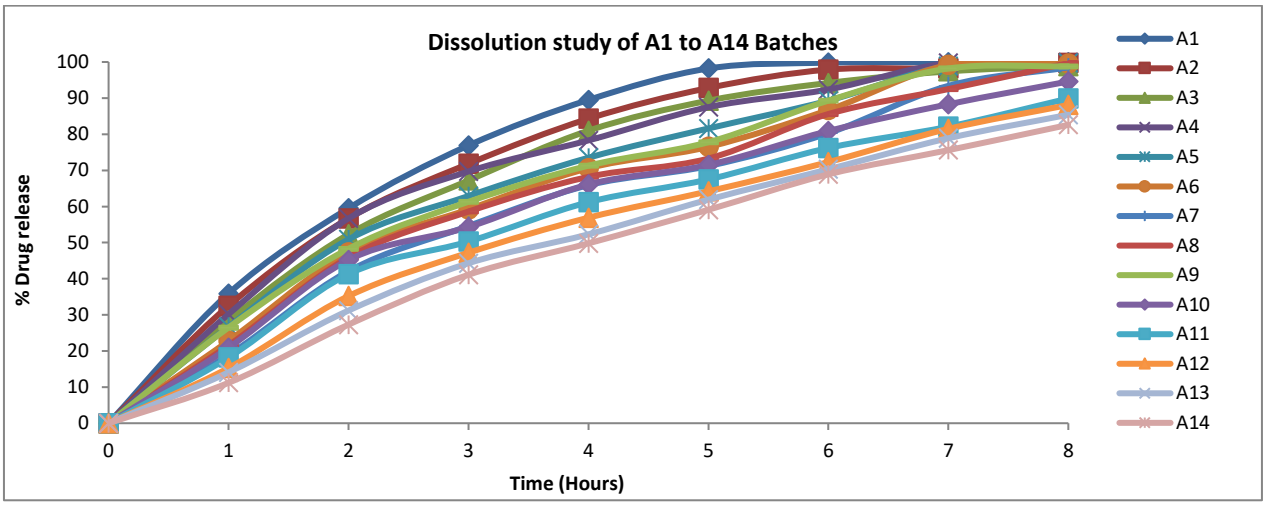


Figure 1: Dissolution study of A1 to A14 Batches

Based on the drug release data, it was observed that the A8 batch was the most satisfactory batch with respect to drug release and other parameters. Hence, the A8 batch selected as optimized batch and Stability study of the same batch initiated.

Drug release kinetic study

The drug release data of the final batch A8 was fitted in to different kinetic models. Among all, the best fitted model explained by Higuchi model because R^2 value of Higuchi model has 0.984.

Table 5: Kinetic modeling data of batch A8

Kinetic Model	Parameters	Value
Zero Order	R^2	0.932
First Order	R^2	0.730
Higuchi	**R^2**	**0.984**
Korsmeyer-Peppas	R^2	0.527
Hixon Crowell	R^2	0.910

Higuchi model was found to best describe the R^2 (coefficient of determination). Korsmeyer-Peppas equation also best suits the dissolution data where the values of "n" were 0.45-0.89 indicating anomalous, non-Fickian, or nearly zero-order release mechanism. Drug release mechanism from prepared floating tablets of A8 batch was elucidated by fitting the in vitro dissolution data in Korsmeyer-Peppas equation. The value of "n" for the optimized formulation was greater than 0.45 indicating non-Fickian case II transport mechanism.

Stability Study

Stability study of optimized batch A8 performed for 1 month at 40 °C/75 % RH and evaluated for various parameters. Resulted parameters are tabulated below;

Table 6: Results of Stability Study of A8

Time	Appearance	% Drug Content	% Drug release in 8 hr
Initial	Complies	99.2 ± 3.1	99.7 ± 1.8
After 1 month	Complies	99.0 ± 3.5	99.2 ± 2.1

From the stability study data, it revealed that the formulation A8 stable at 40 °C/75 % RH condition. Results are well within acceptable limits.

CONCLUSION

The aim of the present investigation was to develop and evaluate transdermal patch of Apixaban. Formulation development of Apixaban Transdermal patch was initiated using Eudragit S 100 and HPMC E50 LV as matrix controlling polymer for matrix type Transdermal Patch. PEG 400 was selected as plastisizer. Glycerine was selected as permeability enhancer. Preformulation study was performed to check the drug excipient compatibility. The IR spectra of Drug and final formulation found satisfactory. There are no any interaction between drug and excipients. Further the linearity curve was developed in UV for method of analysis. Trials A1-A14 was initiated using different concentration of polymers in the formulation. The prepared patches were transparent and smooth in surface. The weight variation was found well within acceptable range. The thickness of patches was found uniform in nature and the variation is found satisfactory. Further, the surface pH of the patches was found between 6.8 to 7.1 and it is acceptable. The drug content, folding endurance and % elongation results of A1-A14 batches were found well within acceptable range. Initially the trial batches were taken with a single polymer like HPMC and Eudragit S100. The drug release was not achieved as per the target drug release profile for 8 hours. Hence the combination of these two polymers are taken and found better results than the single polymers. Based on the drug release data, it was observed that the A8 batch was the most satisfactory batch with respect to drug release and other parameters. Hence, the A8 batch selected as

optimized batch and Stability study of the same batch initiated.

REFERENCES

1. Harneet M, Tarun G, Amit K, Goutam R, "Permeation enhancer strategies in transdermal drug delivery," Drug Delivery, 2016; 23(2): 564-578.
2. Lade S, Kosalge S, Shaikh S, "Transdermal Drug Delivery System: A Tool for Novel Drug Delivery System: An Overview". World Journal of Pharmaceutical Research, 2014; 3(2): 1892-1908.
3. Lincy J, "Review on Transdermal Drug Delivery System."International Journal of Pharma Research and Health Sciences, 2014; 2(4): 261-272.
4. Kesarwani A , Yadav A, Singh S, Gautam H, Singh H, Sharma A, Yadav C, "Theoretical Aspects of Transdermal Drug Delivery System."Bulletin of Pharmaceutical Research, 2013; 3(2): 78-89.
5. Pandey S, Badola A, Bhatt G, Kothiyal P, "An Overview on Transdermal Drug Delivery System." International Journal of Pharmaceutical and Chemical Sciences, 2013; 2(3): 1171-1180.
6. Monoj K, Asmat U, Mehdi H and Khairul M, "Formulation design, development and optimization of Apixaban INN tablet a new era on immediate release drug delivery system", The Pharma Innovation Journal, 2018; 7(10): 298-306.
7. Serpa P, Brooks M, Divers T, Ness S, Birschmann I, Papich M, Stokol T, "Pharmacokinetics and Pharmacodynamic of an Oral Formulation of Apixaban in Horses After Oral and Intravenous Administration", Front Vet Sci,2018; 4(5): 1-15.
8. Maria L, Seda D, Kobi N and Fang Z, "Compounded Apixaban Suspensions for Enteral Feeding Tubes", Hospital Pharmacy, 2017; 52(7): 478-482.
9. Dudhe P, Shelke P, Chavare P, "Determination of Apixaban from Bulk and Tablet Dosage Form by Area Under Curve and First Order Derivative Spectrophotometric Methods", International Journal of Chem Tech Research, 2017; 10(5): 703-711.
10. Gambhire M, Gujar N, Vaidhya A, "Formulation, Optimization and Evaluation of Immediate Release Tablet of Apixaban", International Journal of Chem Tech Research, 2017; 10(10): 424-435.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.