Subscription Agency
Exploring and Distributing Knowledge Globally

Pharmaceutical Sciences
Volume 4 Issue 2, 2024
eISSN No.: 2582-8371

Development and In Vitro Analysis of Matrix-Type Transdermal Patches Containing Aspirin

Sagar K.C[1*], Krishma Paudel[2], Navaraj Khadka[1], Sanjeet Khadka[1], Prajol Paudel[1],
[1]Department of Pharmacy, Kantipur Academy of Health Science, Kathmandu, Nepal
[2]Department of Pharmacy, Hope International College, Lalitpur, Nepal

Corresponding Author
Email Id: sagarkhatrichhetr@gmail.com

ABSTRACT

This study intends to design and evaluate transdermal patches based on a matrix to improve aspirin bioavailability and patient compliance. One effective non-steroidal anti-inflammatory drug that may be used as both an anti-inflammatory and pain relief is aspirin. Due to the drug's significant pre-systemic metabolism, oral treatment is linked to limited patient compliance, a variety of gastrointestinal adverse effects, even at low doses, and frequent high dosage requirements. Transdermal administration, a method that bypasses the stomach, maybe a more practical and secure method for providing aspirin, especially when used continuously.

The drug-excipient compatibility was verified using FTIR analysis. Eight patch formulations (F-1 to F-8) had been developed using a variety of polymers, including carbopol, HPMC K100M and HPMC 15cps by the varying ratio of polymer and DMSO as permeation enhancers. The transdermal drug delivery system for Aspirin, utilizing various polymers like HPMC15cps, HPMC K100M, and Carbopol, demonstrated promising results in all parameters.

The thickness and weight of the patch vary within the same formulation. The drug content ranges from 88.57% to 96.23%, with Aspirin content being fairly uniform. Moisture absorption varies from 5.15% to 16.82%. Folding endurance ranges from 40-68. However, for the in-vitro drug release and drug content results formulation F8 was shown to be the optimized formulation, as a higher percentage of the drug was obtained.

Thus, it can be concluded that transdermal patches are considered appropriate for controlled aspirin release; nevertheless, more investigation is required to confirm their effectiveness using long-term human pharmacokinetic investigations.

***Keywords**: Transdermal patch, Aspirin, HPMC K100M, HPMC 15cps, DMSO, In-vitro release*

INTRODUCTION

The skin provides a handy and easily accessible location for medicine delivery. In light of this, the topic of transdermal drug delivery has attracted a lot of attention and funding in the past and is still doing so now because novel and effective methods of delivering drugs via the skin are constantly being developed. Advanced drug delivery techniques like transdermal drug delivery (TDD) offer the ability to overcome many of the inherent constraints of conventional medicine administration routes [1].

Pharmaceutical Sciences
Volume 4 Issue 2, 2024
eISSN No.: 2582-8371

Transdermal Patches: Transdermal patches, often referred to as skin adhesive patches, are patches that are applied to the skin to provide a precise quantity of medicine. This makes it possible for the medication to enter the bloodstream through the skin. Compared to conventional medication delivery methods like oral or intravenous administration, this non-invasive approach has several advantages. Transdermal patch technology has recently advanced with the goals of increasing drug delivery effectiveness, broadening the spectrum of drugs that may be employed, and raising patient satisfaction. Transdermal patches, also referred to as Transdermal drug delivery systems (TDDS), are specialized medicated patches that work by releasing drugs into the bloodstream through the skin's layers at a controlled rate [1,2]. TDDS dosage forms are designed to enter a patient's bloodstream via their skin and administer a therapeutically effective dose of medication [2].

Key features of TDDS

1) Offers regulated release while preserving the medication's ongoing effectiveness [2].
2) Instead of building up in the dermal layer, the drug leaks out of the patch and absorbs into the stratum corneum, epidermis, and dermis of the skin [2].
3) T[he drug is released through the dermal microcirculation for systemic absorption once it reaches the dermal layer [2]
4) Provides significant benefits over oral and injectable methods, including decreased first-pass metabolism, better patient compliance, and steady drug concentration maintenance [1]

Advantages of TDDS

1) Decrease the frequency of doses and improve patient adherence [3]
2) Transdermal administration provides a prolonged and continuous penetration of a drug over a longer duration, hence preventing first-pass metabolism [4]
3) It doesn't impede the stomach or intestines' liquid flow [4,5]
4) Maintains steady and consistent blood levels, offering long-term management [6,7]
5) Use drug candidates with a short half-life and a low therapeutic index to lessen drug swings in plasma levels [8]
6) Transdermal administration improves the efficacy of many medications by avoiding some of the medication's side effects, such as poor absorption and gastrointestinal discomfort [6]

Disadvantages of TDDS

1) High drug concentrations in plasma or blood could not be attained and drugs with large molecular sizes cannot be synthesized [9].
2) potential for irritation at the application site [10].
3) The skin barrier differs from person to person and might even evolve inside an individual [11].
4) The medication, adhesive, and other chemicals in the patch may irritate the skin locally. To use the transdermal delivery method, a specific clinical need needs to be established [9].

Components of Patches [12,13]: Drugs delivered by transdermal patches enter the bloodstream by diffusing through the skin's layers. Usually, they are composed of many elements:

- **Backing covering:** This impermeable covering keeps medication loss at bay while shielding the patch from the outside world.
- **Drug Matrix or Reservoir**: This layer holds the drug in a solid or solution that may be released gradually.

Pharmaceutical Sciences
Volume 4 Issue 2, 2024
eISSN No.: 2582-8371

- **Rate-Control Membrane:** In certain designs, this membrane controls how much medication is released from the reservoir at a time to provide a steady dose.
- **Adhesive Layer**: In certain patch designs, this layer also holds the medication in place while adhering the patch to the skin.
- **Release Liner:** The adhesive and medication layers are visible once this protective layer is removed before application.

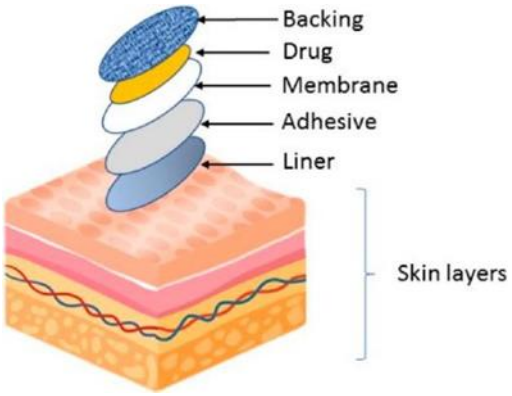

Fig. 1: Different Components of TDDS [12]

Types of Transdermal Patches [13]: Transdermal patches come in a variety of forms, including:

1) **Single-layer drug-in-adhesive patches**: Adhesive and medication are combined to create single-layer drug-in-adhesive patches.
2) **Multi-layer patches:** These allow for a controlled release.
3) **Microneedle patches (MNPs):** These patches pierce the skin with small needles, delivering bigger molecules without the requirement for micronization.

Matrix-type Transdermal Patches [12,13]

Transdermal patches of the matrix type are cutting-edge drug delivery devices intended to apply medicinal substances via the skin for systemic effects. These patches are made of a polymer matrix that holds the medication and enables gradual, controlled release. The drug is uniformly diffused in hydrophilic or lipophilic polymeric material in the matrix diffusion system. The polymer used to make the matrix can be natural, semi-synthetic, or synthetic, and the choice of polymer has a big impact on the patch's overall efficacy and release rate.

Mechanism of Transdermal Patches [14]

Via a diffusion-controlled method, the medication is released from matrix-type patches. The medication diffuses through the matrix and finally penetrates the skin as it dissolves in the polymer. A few examples of things that affect the rate of release are:

- Composition of Polymers
- Solubility of Drugs
- Thickness of Patch

Pharmaceutical Sciences
Volume 4 Issue 2, 2024
eISSN No.: 2582-8371

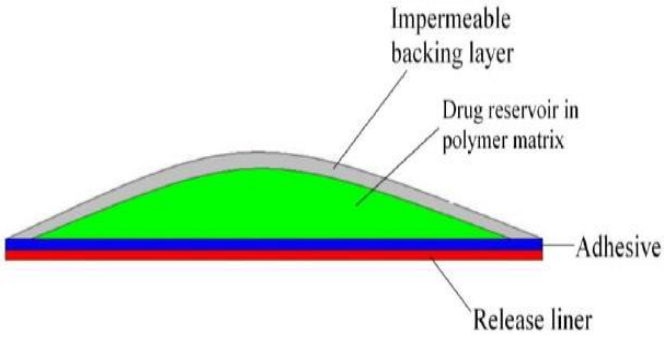

Fig. 2: Matrix diffusion-controlled film [14]

Drug Profile of Aspirin [15,16]: Aspirin is a commonly used medicine under the nonsteroidal anti-inflammatory drug (NSAID) and salicylate categories. Because of its analgesic, antipyretic, and anti-inflammatory qualities, it has several medicinal uses. Aspirin has a half-life of around 13 to 19 minutes in the blood. Salicylic acid, its active metabolite, has a prolonged half-life of 3.5 to 4.5 hours. Aspirin works in several ways to provide its effects.

1) Primary effects: Primary effects include pain alleviation, fever decrease, clotting prevention, and inflammation reduction.
2) Method of action: Reduces the generation of prostaglandins and thromboxane by irreversibly inactivating the cyclooxygenase (COX) enzyme.
3) Specifics of the COX enzyme: acetylation non-selectively inhibits both COX-1 (PTGS1) and COX-2 (PTGS2), but is somewhat more selective for COX-1.
4) Secondary activities include the generation of anti-inflammatory lipoxins by modified COX-2, the uncoupling of oxidative phosphorylation in mitochondria, and the modification of signaling through NF-kB.
5) Comparing aspirin to other NSAIDs: Aspirin differs from other NSAIDs due to its action as an acetylating drug that alters the COX enzyme allosterically.

Rationale of Study [17,18]

Patients sometimes neglect to take their prescribed medication, and even those who comply faithfully become numb to the taste of tablets, particularly if they must take many doses daily. As a result, it is thought that administering medicine via the skin to the general circulation is better than ingesting it orally. Avoiding the gastrointestinal tract would also prevent the pain that usually arises and partial first-pass activation via the liver. Furthermore, the blood level peaks and valleys caused by oral dosage forms are generally not preferable to continuous drug absorption for hours or days. These are the reasons for the transdermal aspirin patch. It is commonly known that using oral aspirin can help prevent heart disease and cerebral vascular disease in the long run. On the other hand, oral administration may cause bleeding and damage to the gastrointestinal mucosa. This issue can be resolved by developing transdermal medication delivery devices. Aspirin undergoes significant pre-systemic hydrolysis in the liver and colon to produce salicylic acid.

Aim of the Study

The current study's goal is to create and assess matrix-type transdermal patches for the controlled administration of aspirin as a model medication to reduce the need for frequent dosage, prevent side effects, and increase aspirin's bioavailability.

METHODS AND MATERIALS

Pharmaceutical Sciences
Volume 4 Issue 2, 2024
eISSN No.: 2582-8371

Materials: Beside Aspirin (drug) different types of chemicals were used in our study like HPMC 15cps, HPMC K100M, Carbopol, Propylene Glycol, Dimethyl sulfoxide (DMSO), Ethanol and methanol.

Instruments and Devices

Equipment used in the Study are as follows:

1) Weighing Balance
2) Magnetic stirrer
3) Hot air oven
4) Desiccator
5) UV-Visible Spectrometer
6) Vernier Caliper
7) Franz Diffusion Cell

Formulation of Transdermal Patch [19]: Using varying ratios of HPMC to carbopol, the matrix type of transdermal patches containing aspirin was created by the solvent casting process. Polymers are dissolved in an organic solvent for solvent casting. Particles with certain sizes are added to the solution, maybe salts. The mixture is shaped to obtain a final geometry. Examples include pouring it over a glass plate to form a membrane or into a three-dimensional mold to form a scaffold. The solvent evaporates, forming a composite substance with the particles and polymer as its constituent parts. Using a magnetic stirrer in a beaker, the polymer (HPMC and Carbopol, each weighing one gram) was dissolved in a combination of ethanol and methanol (1:1). A magnetic stirrer was used to combine the medication with the polymer solution gradually and thoroughly to create a homogenous mixture. DMSO was utilized as a penetration booster and propylene glycol as a plasticizer. Once mixed, the fluid was transferred onto a petri dish. It was stored in an air oven set at 40 to 60 degrees Celsius for a whole day. Following the drying process, the patches were taken off of the Petri plates, sliced into 2 cm by 3 cm pieces, covered with aluminium foil, and kept in storage until they were needed for additional research. Eight formulations in all, designated F1, F2, F3, F4, F5, F6, F7, and F8, were developed.

Table 2: Formulation Table of Transdermal Patch

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Aspirin (mg)	20	20	20	20	20	20	20	20
HPMC K100M: Carbopol	2:1	3:1	4:1	5:1				
HPMC 15 cps: Carbopol					2:1	3:1	4:1	5:1
Solvent (Ethanol: Methanol)	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1
DMSO (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Propylene glycol (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Pharmaceutical Sciences
Volume 4 Issue 2, 2024
eISSN No.: 2582-8371

Physiological Evaluations [20,21]

1) **Thickness variation:** 6 cm2 patches were cut out of the matrix film. The thickness of each of the five patches was measured with a vernier calliper. The data were presented using mean ± standard deviation and average values.
2) **Folding endurance of the patches:** To evaluate folding endurance, the film was folded repeatedly at the same plate until it broke. The number of times the film could be folded in the same spot without breaking was used to calculate the value of folding endurance.
3) **Weight variation:** A random selection of five patches was made, and after weighing each one, average values were determined. The mean ± standard deviation of the data was shown.
4) **Percentage of moisture absorbed:** Accurately weighed patches were placed in a desiccator containing a solution of aluminium chloride for 72 hours. After 72 hours, the patches were weighed again, and the percentage of moisture absorption was determined using the following equation

$$\%\ moisture\ absorbance = \frac{Initial\ weight - Final\ weight}{Initial\ weight}\ \mathbf{x\ 100\%}$$

5) **Percentage of moisture loss:** Accurately weighted patches were kept in a desiccator containing fused anhydrous calcium chloride for 72 hours. After 72 hours, the patches were weighed, and the % moisture loss was calculated using the following equation,

$$\mathbf{\%\ moisture\ loss} = \frac{Initial\ weight - Final\ weight}{Initial\ weight}\ \mathbf{x\ 100\%}$$

6) **Drug Content Uniformity:** After shaking 100 ml of methanol to create a homogenous mixture and adding a 6 cm2 patch, the liquid was allowed to stand for 24 hours. After filtering, the filtrate was then diluted (1 ml in 10 ml methanol). Using a UV-visible spectrophotometer set to 296 nm, the absorbance was determined.
7) **Drug permeation studies (In-vitro release studies) [22]:** To perform in-vitro drug release profiles, a Franz diffusion cell with a cellophane membrane was employed. Before being cut into 6cm^2, the cellophane membrane was immersed in 100 cc of phosphate buffer (pH 7.4) for one day. It was put on the diffusion mobile and allowed to acclimate to the receptor fluid for fifteen minutes.

The diffusion shell is composed of two compartments: a donor compartment and a receptor compartment. Environmental conditions were in touch with the donor compartment. A magnetic stirrer was utilized to agitate the conventions. An area measuring 6 cm by 2 cm moved. at predetermined intervals of time (1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 hours), respectively. Subsequently, the receptor fluid was extracted and replaced with an equivalent volume of phosphate buffer Ph7.4. A UV visible spectrophotometer was used to determine the drug concentration in the sample after it had been diluted as needed with phosphate buffer (pH 7.4).

RESULTS AND DISCUSSION

Analysis was done using a UV Spectrophotometer. At 296 nm, aspirin standard curves in methanol were examined in the 5–50µg/ml range. The standard curve for medication is shown in Figure 3 and the standard curve data is provided in Table 3 below.

In Figures 4 to 5, the FT-IR spectra of the medication in its pure form and in combination with excipients are displayed.

Pharmaceutical Sciences
Volume 4 Issue 2, 2024
eISSN No.: 2582-8371

The findings indicate that the thickness varies between 0.4052 ± 0.03359 and 0.6332 ± 0.06434, whereas the weight variation varies between 0.1556 ± 0.006462 and 0.2468 ± 0.028. The reason for the variance in weight was the addition of polymer in varying ratios and variations in drying rates, both of which affected the weight of the patches. 3.113 to 11.80% of moisture was observed to be lost. The outcome showed that each transdermal system included a certain level of wetness. The range of moisture absorption 5.15% to 16.82% results shows that the addition of plasticizers and the concentration of hydrophilic HPMC increase the transdermal film's capacity to absorb moisture. Research on moisture absorption has shown that HPMC naturally has a high capacity to absorb water. Formulations F4, F7, and F8 exhibited a greater moisture absorption than other formulations as the content of HPMC grew higher. Every patch included 20 mg of the medication. The range of the drug content percentage is 88.57% to 96.23%. The outcome might have differed because of mis-weighed components, inaccurate content pouring, unfavorable laboratory conditions, uneven Petri plate levelling, and insufficient homogeneous mixing. Similar to this, in-vitro drug release profiles were conducted using a Franz diffusion cell with a cellophane membrane. The data obtained was compared with formulations F1, F2, F3, F4, F5, F6, F7, and F8. Cellophane was used as the permeable membrane that was mounted as the donor compartment and phosphate buffer pH 7.4 as the receiver fluid.

In F5, F6, F7, and F8 (HPMC 15cps:carbopol), the results of the permeation investigation indicated that the formulation's percentages were around 78% at 8 hours, 82% at 7 hours, 89% at 7 hours, and 92% at 6 hours. Comparably, the percentages of those who studied through the membrane in the formulation of F1, F2, F3, and F4 (HPMC K 100 M:carbopol) were 57% at 10 hours, 72% at 10 hours, 76.07% at 9 hours, and 85% at 9 hours. Out of all the formulations, formulation F1, with a composition of HPMC K 100 M:Carbopol (2:1), showed delayed drug penetration across the membrane. This may be because the hydrophilic polymer HPMC K 100M concentration, which is known for its very viscous character and is thought to be the most optimal formulation for continuous release of parent drug from patches, is less concentrated. Similarly, the F8 formulation with a 5:1 ratio demonstrated that 92.22% of the medication penetrated the membrane after 6 hours, and the results unmistakably revealed a burst release in the early hours. This might be because the drug interacts less with hydrophilic polymers like HPMC and hydrophobic polymers like carbopol.

Table 3: Concentration versus absorbance

Concentration (µg/ml)	**Absorbance(nm)**
5	0.31
10	0.38
15	0.45
30	0.67
50	0.95

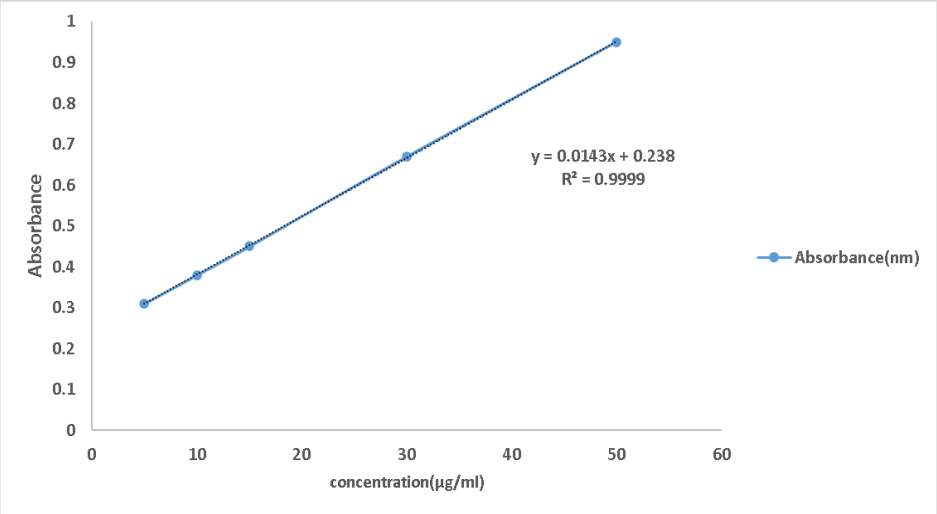

Fig. 3: Standard calibration curve of Aspirin

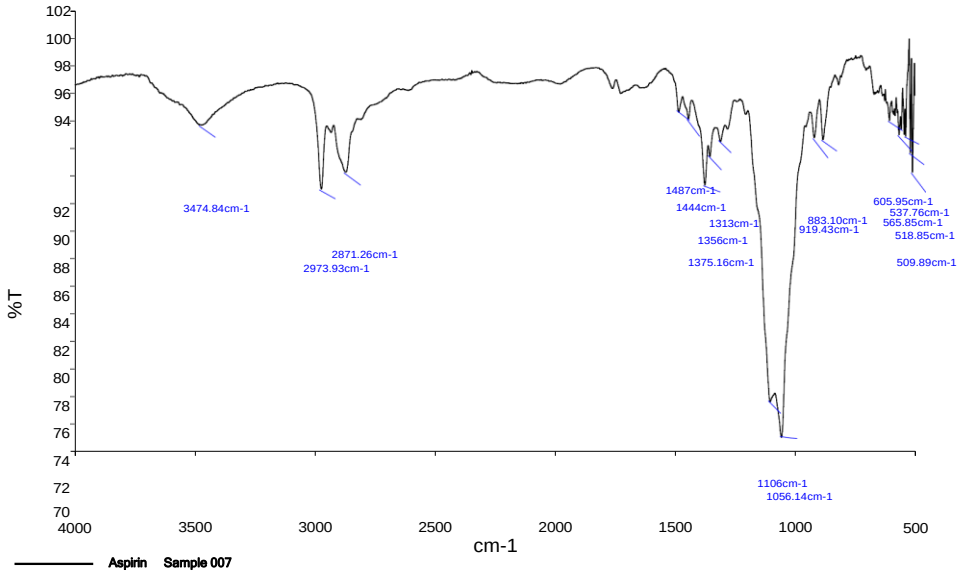

Fig. 4: FTIR Spectra of Aspirin

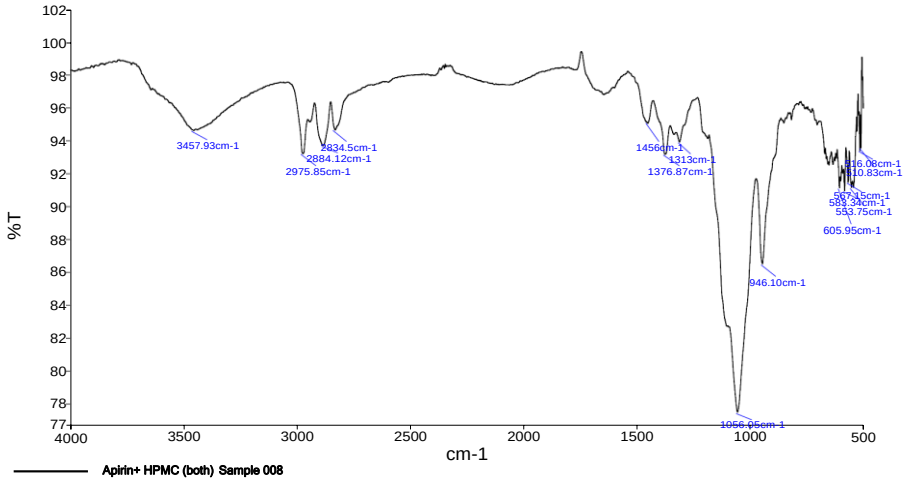

Fig. 5: FTIR Spectra of Aspirin + HPMC (both)

Pharmaceutical Sciences
Volume 4 Issue 2, 2024
eISSN No.: 2582-8371

Table 4: Physiochemical Properties of Prepared Transdermal Patches

Formulation	Weight Variation	Thickness	Folding Endurance	% Moisture loss	% Moisture Absorbance	% Drug Content
F1	0.1556 ± 0.0076	0.4052 ± 0.0410	55	8.28%	5.15%	84.5
F2	0.1754 ± 0.0081	0.4184 ± 0.0355	64	7.83%	6.23%	92.05
F3	0.1976 ± 0.0070	0.4358 ± 0.0564	51	8.28%	7.03%	96.23
F4	0.2008 ± 0.0066	0.4994 ± 0.0624	64	7.06%	10.49%	87.06
F5	0.2108 ± 0.0064	0.5008 ± 0.0643	56	6.11%	7.90%	96.23
F6	0.195 ± 0.0108	0.5834 ± 0.049	40	6.19%	14.70%	83.68
F7	0.2066 ± 0.0286	0.5634 ± 0.059	61	8.52%	15.34%	88.57
F8	0.2468 ± 0.0116	0.6332 ± 0.0335	64	11.80%	16.82%	93.5

Table 5: % Cumulative Drug Permeation

Times (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8
1	2.98	5.01	6.98	11.02	20.1	25.05	28.30	30.5
2	6.06	8.3	12.10	16.64	28.0	21.0	36.36	39
3	10.15	12.2	22.23	30.47	36.0	41.69	52.2	57.20
4	21.02	30.06	27.99	52.6	44.10	57.0	64.06	70.69
5	31.99	41.21	47.88	61.02	59.6	68.01	73.10	83.03
6	37.69	47.69	55.01	68.69	64.01	76.99	80.69	92.22
7	42.3	54.01	62.18	72.25	71.02	82.36	89.66	
8	48.26	59.55	72.04	80.04	78.01			
9	50.99	68.69	76.07	85.69				
10	57.01	72.07						

Pharmaceutical Sciences
Volume 4 Issue 2, 2024
eISSN No.: 2582-8371

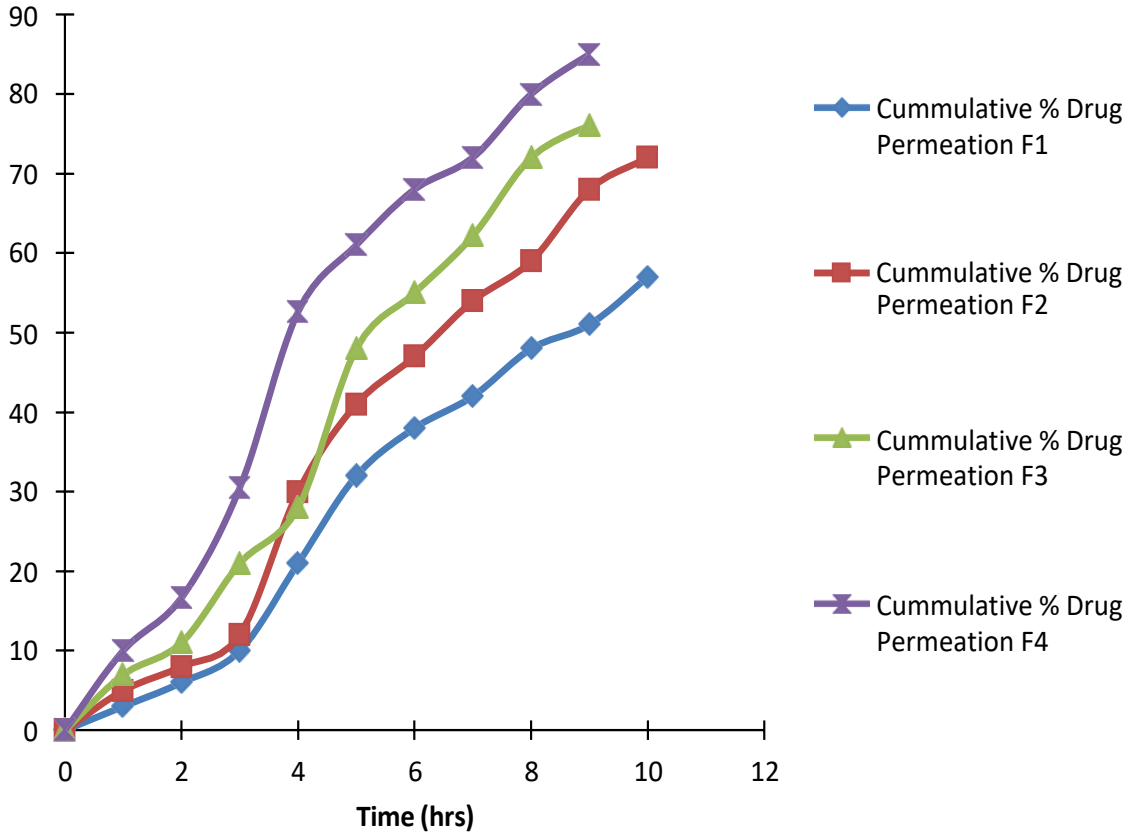

Fig. 6: Comparison of in-vitro % drug permeation vs. time of formulations

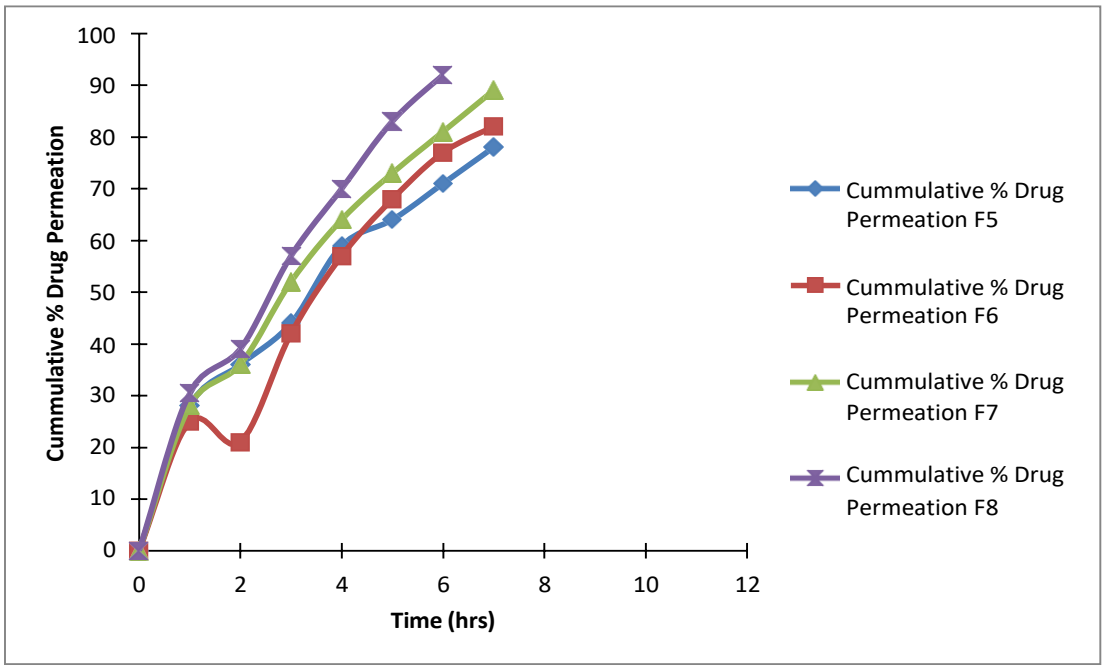

Fig. 7: Comparison of in-vitro % drug permeation vs. time of formulations

Pharmaceutical Sciences
Volume 4 Issue 2, 2024
eISSN No.: 2582-8371

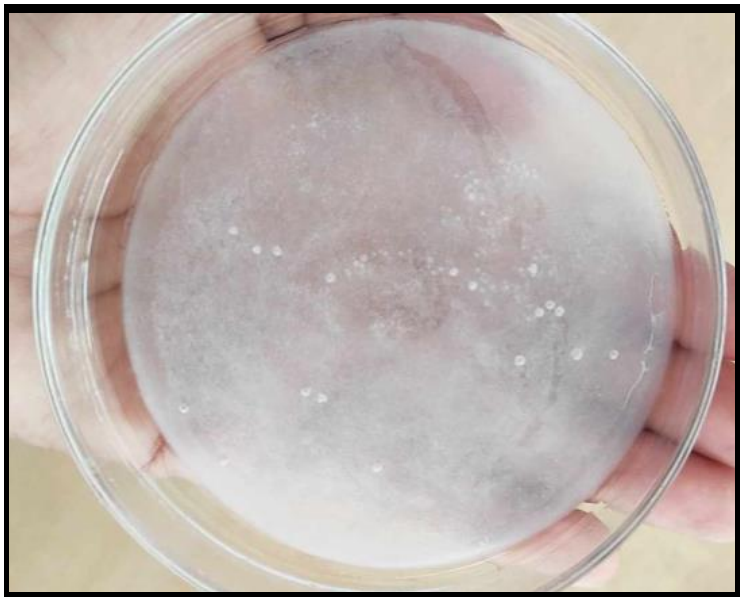

Fig. 8: Final Ready Patch

CONCLUSION

Transdermal drug administration, which emphasizes better style, dosage flexibility, and patient compliance, is a well-liked substitute for oral medicine delivery. The transdermal system's mechanical properties are greatly influenced by the polymers, solvents, penetration enhancers, and plasticizers that are selected. Different grades of HPMC are used to make transdermal patches containing aspirin, an active medicinal ingredient.

After assessing the physiochemical characteristics of the patches, formulation F1 was determined to be the best one for long-term drug release. A better medication flux of almost 92% through the skin was demonstrated by formulation F8. Aspirin was deemed appropriate and effective when combined with the chosen plasticizers, solvents, and penetration enhancers, suggesting that aspirin might be prepared as a transdermal drug delivery system.

LIMITATIONS

1) Despite all attempts being made to properly complete the investigation, a few constraints and limits kept the current project work from being finished.
2) Excipients and polymer compatibility with the main medication are not investigated in this test.
3) There was no research done on skin irritation caused by alternative excipients, the parent medicine, or any interactions.
4) Neither stability tests nor in vivo drug release analyses were conducted.

REFERENCES

1) Shaikh N, Srivastava R. A review on transdermal drug delivery through patches. IP Indian J Clin Exp Dermatol 2024;10(2):113-121. 2]
2) https://www.adhexpharma.com/blog/transdermal-drug-delivery-systems-all-you-need-to-know
3) P Kumar C Sankar B Mishra Delivery of macromolecules through skinIndian Pharm200453717
4) Y Zhang J Yu AR Kahkoska J Wang J B Buse Z Gu Advances in transdermal insulin deliveryAdv Drug Deliv Rev2019139517010.1016/j.addr.2018.12.006

5) P De Vos MM Faas M Spasojevic J Sikkema Encapsulation for preservation of functionality and targeted delivery of bioactive food componentsInt Dairy J2010204292302
6) P Heifer TR Shultz Coupled feedback loops maintain synaptic long-term potentiation: A computational model of PKMzeta synthesis and AMPA receptor traffickingPLoS Comput Biol2018145100614710.1371/journal.pcbi.1006147
7) B Barry EM Aulton Transdermal drug deliveryThe science of dosage forms design, 2nd edn. Harcourt publishersChurchill Livingstone, New York2002499533
8) AC Williams BW Barry Penetration enhancersAdv Drug Deliv Rev201264512818
9) Ramteke K.H, Dhole S.N, *et*.al. (Transdermal Drug Delivery System :A Review), Journal of Advanced Scientific Research,2012, 3(1).22-35
10) J Gupta A Thakur S Thakur Transdermal drug delivery system of Metformin Hydrogen Chloride using Two Different Polymeric CombinationsInt J Heal Biol Sci20192415
11) SG Danby Biological Variation in Skin Barrier Function: From A (Atopic Dermatitis) to X (Xerosis)Curr Probl Dermatol201649476010.1159/000441545
12) Wong WF, Ang KP, Sethi G, Looi CY. Recent Advancement of Medical Patch for Transdermal Drug Delivery. Medicina (Kaunas). 2023;59(4):778. Published 2023 Apr 17. doi:10.3390/medicina59040778
13) https://en.wikipedia.org/wiki/Transdermal_patch
14) https://www.researchgate.net/publication/268384412_Transdermal_drug_delivery_system_An_overview
15) https://en.wikipedia.org/wiki/Mechanism_of_action_of_aspirin
16) Cadavid AP (2017) Aspirin: The Mechanism of Action Revisited in the Context of Pregnancy Complications. Front. Immunol. 8:261. doi: 10.3389/fimmu.2017.00261
17) https://en.wikipedia.org/wiki/Aspirin
18) https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.120.045695
19) Agarwal G, Dhawan.S. et.al. (Formulation, in-vitro, and in-vivo evaluation of matrix type transdermal patches containing olanzapine), Pharmaceutical Development and Technology,2013;18(4):916-925.
20) H.O. Ammar, Ghorab.M, et.al. (Evaluation of Chemical Penetration Enhancers for Transdermal Delivery of Aspirin), Asian Journal of Pharmaceutical Sciences 2007, 2(3) 40
21) Patel. D.P. (Development and Evaluation of Ethyl Cellulose Based Transdermal Films of Furosemide for Improved In-vitro Skin Permeation), National Center for Biotechnology Information, 2009 Apr 21.
22) P.R. Rao, P.V. Diwan, et.al. (Permeability studies of cellulose acetate free films for transdermal use: influence of plasticizers, Pharmaceutica ActaHelvetiae volume 72, issue 1, February1997, pages 47-51.