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Original Article

Fabrication of Microneedle Patches of Indomethacin Using 3DP Technology

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ABSTRACT

Background: Indomethacin is a Nonsteroidal Anti-Inflammatory Drug (NSAID) that is frequently used for its pain-relieving, anti-inflammatory and fever-reducing properties. It is typically taken orally, but can also be administered rectally or intravenously in certain situations. As with all NSAIDs, indomethacin can have side effects, including gastrointestinal upset, headache, dizziness and skin rashes, the major ones being gastrointestinal bleeding and kidney problems, particularly associated with its prolonged use or at higher doses. Hence, to mitigate the adverse effects of the presently available oral medications, indomethacin needs an alternative way of delivery for local as well as systemic actions. Considering the barrier effects of skin to transdermal drug delivery, microneedle patches of indomethacin have been fabricated on 3D-printed molds as a viable alternative to normal transdermal patches to maximize the local and systemic uses of the drug as an anti-inflammatory agent. **Materials and Methods:** Microneedle and transdermal patches were prepared using the solvent casting method, with a total of eight formulations developed and characterized for parameters such as thickness, drug content and drug release. The patches underwent accelerated stability testing, followed by a skin irritation study conducted on rats to ensure safety. Additionally, a bioavailability study was performed to calculate pharmacokinetic parameters, including AUC, C_{max} and T_{max}. **Results:** Among the formulations, microneedle patch M3 and transdermal patch P3 demonstrated maximum drug release. The pharmacokinetic analysis revealed that M3 exhibited significantly higher values of AUC (2097.15 µg·hr/mL) and C_{max} (93.44 µg/mL) compared to P3, which had an AUC of 1886.32 µg·hr/mL and C_{max} of 90.41 µg/mL. Both patches had a T_{max} of 12 hr. **Conclusion:** These findings indicate that microneedle patches of indomethacin offer a superior and innovative approach for anti-inflammatory applications, with improved drug release and bioavailability compared to transdermal patches. This study highlights the potential of microneedle patches for enhanced therapeutic outcomes, paving the way for further development and clinical exploration.

Keywords: Anti-inflammatory drug, Dermal delivery, Hydroxypropyl Methylcellulose (HPMC), Indomethacin, Microneedle patches, Polyvinyl Pyrrolidone (PVPK30).

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INTRODUCTION

Microneedles are small, needle-like devices typically ranging in size from 50 to 1,000 mm that can penetrate the outer layer of the skin to create tiny channels or pores. These channels can facilitate the delivery of drugs or other substances into the skin, bypassing the stratum cornea and potentially increasing drug absorption and efficacy.[1] Numerous types of microneedles viz. solid, hollow and dissolving microneedles are designed to enter the skin and can be utilized for several purposes such as drug distribution, sampling and aesthetic treatments.[2] Solid microneedles are made of different types of materials, such as silicon, metal, or polymer and can be coated with drugs or other substances to be delivered into the skin. Hollow microneedles have a small channel or lumen that permits for the distribution of fluids or drugs directly into the skin. Dissolving microneedles are made of materials that dissolve when they come into contact with the skin, releasing the drug or other substance they contain. Microneedles have numerous benefits over conventional drug delivery methods, including enhanced drug absorption, increased bioavailability and reduced systemic exposure.[3] They can also be painless or cause minimal discomfort compared to traditional injections, making them more appealing to patients.[4]

Microneedles have been studied for numerous applications, including vaccination, transdermal drug delivery and cosmetic procedures such as skin rejuvenation.[5] The onset of action for indomethacin is relatively rapid, with pain relief often occurring

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within 30 min to 1 hr after administration.[6] The duration of action is typically around 4 to 6 hr, although this can vary depending on the dose and the individual patient. Indomethacin is contraindicated in patients with a history of gastrointestinal bleeding, severe renal impairment, or hypersensitivity to NSAIDs. To overcome such contraindication indomethacin drug is incorporated in microneedles to form a sustained-release product and increase patient compliance. The current research aims to prepare and characterize microneedle patches of indomethacin along with conducting pre-formulation studies, drug characteristics, *in vitro* drug release studies, accelerated stability studies and *in vivo* studies. Moreover, comparative bioavailability and stability studies of microneedles patches and transdermal patches of indomethacin will be conducted to justify that microneedles are having better bioavailability than the transdermal patch.

MATERIALS AND METHODS

Materials

Indomethacin was obtained as a gift sample from Bio Care Health Pvt. Ltd., New Delhi. HPMC, polyvinyl pyrrolidone, Polyethylene glycol 400, Eudragit E 100, DMSO (Dimethyl sulfoxide) and DMF (Dimethylformamide) were supplied by CDH Pvt. Ltd., New Delhi. Analytical-grade ingredients were used in the study.

Methods

Drug Excipient Interaction Study

The FTIR spectra of the physical mixture of drug and polymer were recorded using FTIR 4100 Perkin Elmer, USA to study any kind of interaction.[7] The recorded spectra were matched for any spectral alteration. 4 microneedles patches and 4 transdermal patches have been prepared as composition mentioned in Table 1. M represents the microneedle patches formulation and P represents transdermal patches formulation.

Preparation of transdermal patch

Matrix-type drugs containing transdermal patches of indomethacin were prepared by solvent casting method.[8,9] Accurately weighed required amount of Hydroxypropyl Methylcellulose (HPMC) K-100M and polyvinyl pyrrolidone were solubilized in 10 mL of a mixture of water and methanol (in different ratios, as mentioned in Table 1). The mixture was allowed to stand until a clear solution is formed. The drug was mixed in the polymer solution until the mixture becomes clear. Then PEG 400 was added as a plasticizer to improve the flexibility and handleability of the patch. Additionally, propylene glycol was added which serves as a permeation enhancer to increase drug penetration across the skin. The resultant solution was cast on the previously lubricated petri dish and desiccated at room temperature for 24hr. This drying process allows the solvent to evaporate gradually, leaving behind a solid matrix containing the drug and polymers After 24hr, the dried patches were removed carefully and stored in a desiccator to protect them from moisture and further studies.

Preparation of microneedle patch

The solvent casting method was used for the preparation of the microneedle patch.[10] This method involves the use of a solution containing a biocompatible polymer and a drug or other active ingredient, which is then cast onto a mold containing microneedle-shaped cavities. HPMC K-100M and polyvinyl pyrrolidone are dissolved in a suitable solvent. Indomethacin is also added to the solution. The polymer solution is poured onto a microneedle-shaped mold. The solution is allowed to dry and the resulting film contains the drug or active ingredient and forms the base of the microneedle patch. Once the film is dry, it can be removed from the mold, leaving behind a series of microneedle-shaped cavities. A backing layer, typically made of an adhesive or pressure-sensitive material, is then attached to the film to create the microneedle patch.

Characterization and Evaluation of MNs and Transdermal Patches Physical evaluation parameters

The prepared formulation was subjected to physical evaluation parameters viz. thickness, drug content, % moisture content and % moisture uptake.

In vitro Drug Release Studies

In vitro, drug release studies are important for assessing the performance of microneedle patches in delivering drugs to the body. The patch was placed on the donor compartment and phosphate buffer pH 7.4 was added to the receptor compartment. At predefined time intervals, samples of the receptor medium were collected and the quantity of drug released was determined using a UV spectrophotometer. The cumulative amount of drug released over time was plotted to generate a drug release profile and that can be further used to determine the release kinetics of the patch.[11]

Accelerated stability studies of Transdermal patch and Microneedle patch

The patches stored in plastic casings were placed in a triple stability chamber maintained at three different conditions for 45 days. The stability chamber should be equipped with a monitoring system to measure the temperature and humidity inside the chamber.[12] The microneedles and transdermal patches were withdrawn at 15, 30 and 45 days. Drug content and morphology of microneedles and transdermal patches were evaluated at predetermined time intervals.

In vivo study

The study utilized Wistar albino rats of both sexes with average weights ranging from 180 to 250 g. These rats were obtained from a breeder located in the Central Animal Facility at Ansari

Nagar, AIIMS, New Delhi-110029. The rats were housed under standard environmental conditions and provided with a balanced diet and unrestricted access to water.[13] The study on the animals was conducted by adhering to the guidelines outlined in the principles of laboratory Animal Care (IAEC). Each group in the study consisted of 5 rats, resulting in a total of 2 groups (n=2).

Skin irritation study

The skin irritation study was done on rats using four rats per group. To ensure immobility during the experiment, the rats were anesthetized with a ketamine hydrochloride injection (0.2 mL) at least 2 hr before administration. Before applying the sample, the abdominal region of the rats was shaved using hair removal cream 24 hr in advance. A cotton wool soaked in methylated spirit was used to disinfect the shaved area, preventing contamination. In each group of rats, a pure drug of indomethacin (0.1 g) and distilled water (0.5 mL) (control group) were topically applied on the shaved skin surface. This process was repeated for the microneedle patches and transdermal patches containing the same drug. To maintain contact with the skin, a ZnO adhesive plaster and a non-occlusive bandage dressing were used for 24 hr. After 24 hr, the bandage and test patches were removed and the skin surface was rinsed with distilled water. 1 hr later, the sites were examined for any signs of skin irritation. The sites were observed 24 hr after application and subsequent observations were made at 48, 72 hr, 4 days and 5 days thereafter.

Bioavailability study

Wistar albino rats were kept in a standard laboratory environment with a 12:12 hr dark/light schedule. All rats were administered ketamine anesthesia at a dosage of 20 mg/kg via intramuscular injection. Microneedle formulations in the form of patches were applied to the shaved area of each group of animals and kept in place for 9 hr. Each group of animals received topical treatment with their respective microneedle formulation of the drug for 9 hr. Blood samples were collected from the orbital sinus three times at intervals of 3 hr.[14] After 9 hr, the patches were removed and the collected blood samples were immediately used for drug analysis using HPLC.

Statistical analysis

Statistical analysis, specifically one-way ANOVA, was conducted to evaluate the significance of differences between formulations and p-values were calculated to confirm statistical relevance. $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Drug Excipient Interaction Study

Perkin Elmer FTIR-1100 spectrophotometer by KBr disk method was used to study any incompatibility in the physical mixture of indomethacin and polymers due to its ability to provide high-quality spectra of solid-state samples with minimal noise. The spectral analysis demonstrated the existence of all the distinctive peaks in comparison to the standard peaks. The absence of incompatibilities was confirmed by ensuring that no significant peak shifts, disappearance of peaks, or new peaks were observed in the physical mixture or formulation spectra compared to the pure drug spectrum (Figures 1-3).

Preparation and evaluation of microneedle and transdermal patch

4 microneedles patches and 4 transdermal patches have been prepared and accordingly been evaluated in triplicate. M corresponds to microneedle patches formulation and P corresponds to transdermal patches formulation. The formulations were subjected to evaluation for numerous parameters viz. thickness, drug content, % moisture content, % moisture uptake and % drug release (results have been depicted in Table 2). Formulations M3 and P3 were found to have the maximum % drug release among all eight formulations. Hence, a comparative release profile was prepared from the dissolution profile data and graph of different formulations of microneedle patches and transdermal patches. It can be concluded that microneedle patch formulation has a rapid onset of action and a better percentage drug release in the required therapeutic period, compared to the transdermal patches of the same composition (as depicted in Figure 4). The rapid onset of action observed with microneedle patches is attributed to the bypassing of the stratum

Table 1: Formulation batches of microneedle patches and transdermal patches.

Name of Ingredient	Quantity of each formulation							
	M1	M2	M3	M4	P1	P2	P3	P4
Drug (Indomethacin) (mg)	100	100	100	100	100	100	100	100
HPMC K 100 M (mg)	3	3.5	2.5	2	3	3.5	2.5	2
Polyvinyl Pyrrolidone (mg)	2	1.5	2.5	3	2	1.5	2.5	3
Methanol (mL)	6	7	5	4	6	7	5	4
Water (mL)	4	3	5	6	4	3	5	6
Polyethylene Glycol 400	q.s.							
Propylene Glycol	q.s.							

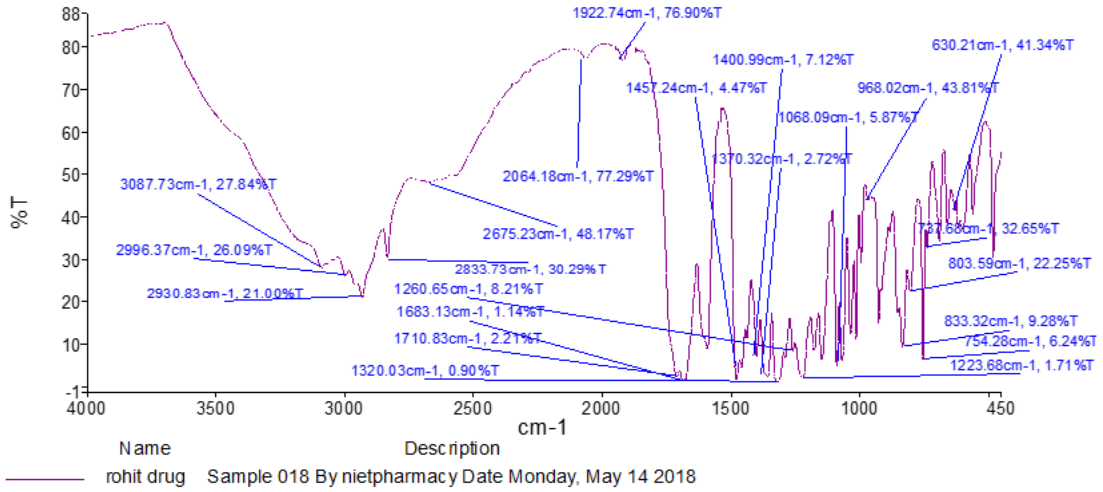

Figure 1: FTIR Spectra of the drug Indomethacin.

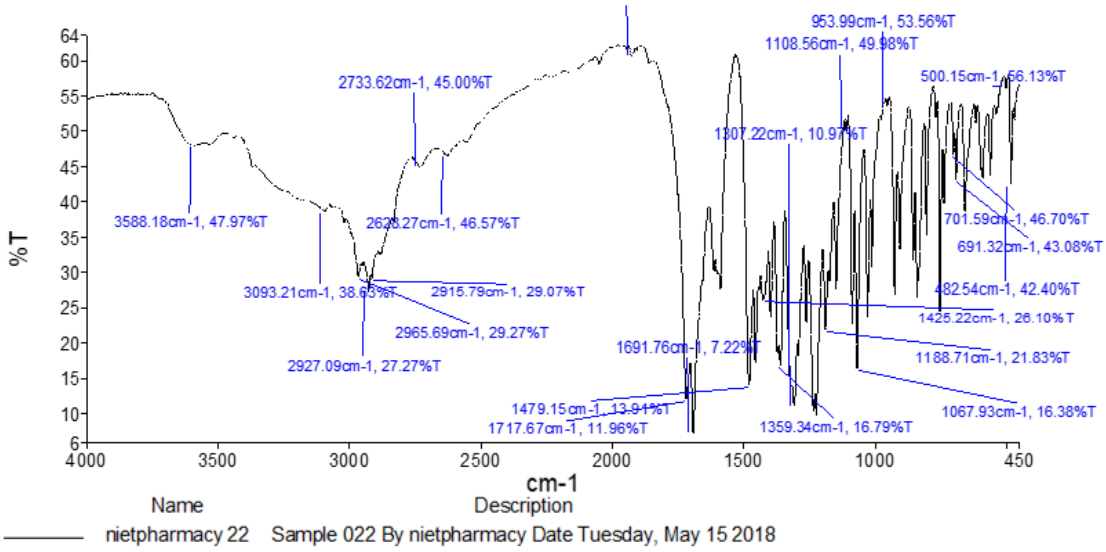

Figure 2: Observation of FTIR Spectroscopy of the drug Indomethacin with Polyvinyl Pyrrolidone (PVP).

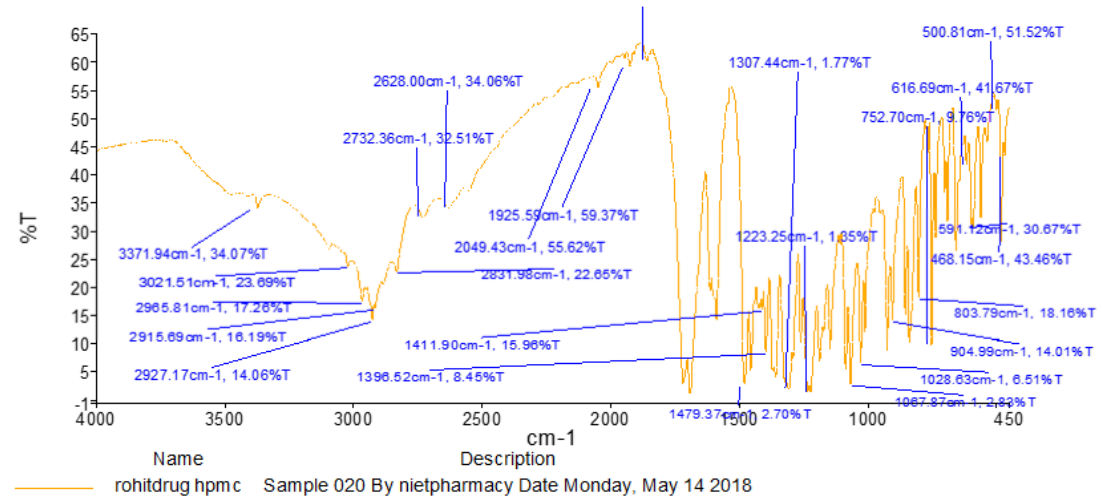

Figure 3: Observation of FTIR Spectroscopy of drug Indomethacin with HPMC K 100 M.

Table 2: Evaluation parameters of M3 and P3.

Formulation	Thickness (mm)	Drug Content(%)	Moisture Content (%)	Moisture Uptake (%)	Drug Release (%)
M1	0.12±0.01*	97.6±0.05	3.66±0.52	6.86±0.08	57.49±1.15*
M2	0.13±0.15*	94.8±0.18	2.84±0.42	5.78±0.78	60.6±0.32*
M3	0.12±0.05*	95.6±0.17	3.76±0.12	5.62±0.14	64.58±0.56*
M4	0.14±0.07*	94.4±0.58	3.71±0.57	6.51±0.65	62.18±0.78*
P1	0.18±0.24*	96.5±0.96	2.75±0.16	6.78±0.39	55.66±0.22*
P2	0.20±0.34*	94.6±0.29	3.37±0.56	5.67±0.69	56.08±0.11*
P3	0.20±0.08*	92.8±0.16	4.45±0.19	7.28±0.28	57.22±0.98*
P4	0.16±0.10*	93.6±0.98	3.65±0.65	5.57±1.32	54.85±0.79*

(*n*=3, Values are presented as mean±S.E.M, *$p<0.05$).

Table 3: Accelerated stability study of M3 and P3.

Formulation	Time (days)	Appearance			Drug content		
		25°C/60%RH	30°C/65%RH	40°C/75%RH	25°C/60% RH	30°C/65% RH	40°C/75% RH
Microneedle Patch (M3)	0	Uniform	Uniform	Uniform	93.42±0.21	93.42±0.13	93.42±0.28
	15	Uniform	Uniform	Uniform	93.40±0.41	93.40±0.43	93.41±0.24
	30	Uniform	Uniform	Uniform	93.40±0.23	93.22±0.32	93.20±0.17
	45	Uniform	Uniform	Uniform	93.40±0.89	93.14±0.73	92.12±0.19
Transdermal Patch (P3)	0	Uniform	Uniform	Uniform	91.22±0.65	93.28±0.38	93.28±0.27
	15	Uniform	Uniform	Uniform	91.20±0.24	93.28±0.96	93.28±0.35
	30	Uniform	Uniform	Squeezed	91.19±0.17	93.16±0.57	92.74±0.49
	45	Uniform	Squeezed	Squeezed	91.19±0.82	93.11±0.94	91.94±0.52

(*n*=3, Values are presented as mean±S.E.M).

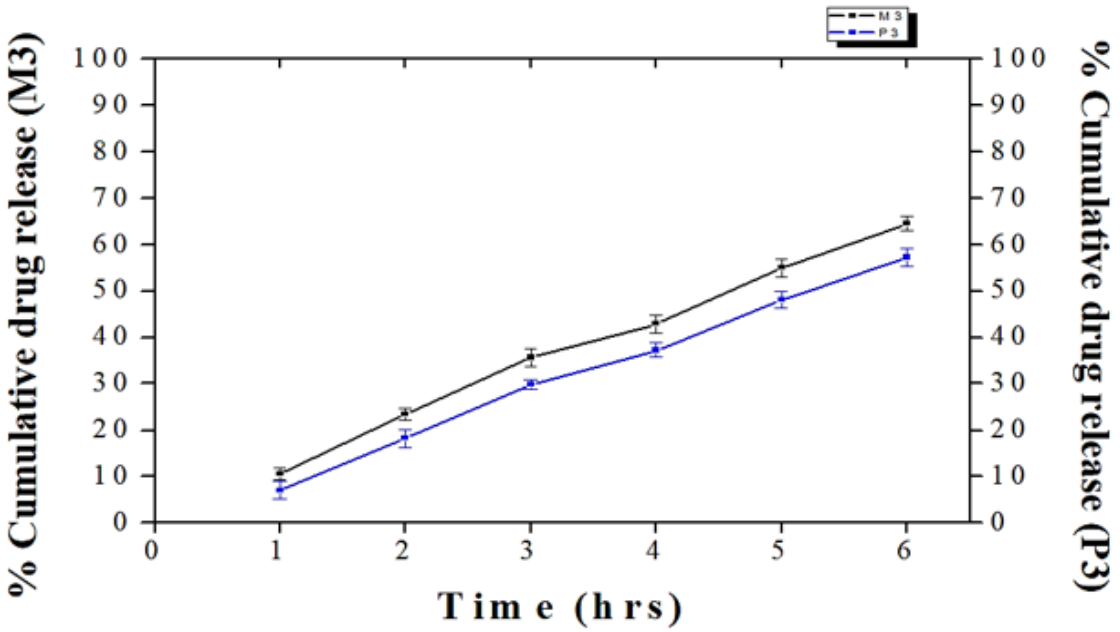

Figure 4: Comparative Percent drug release study of Microneedle Patch (M3) and Transdermal Patch (P3) Formulations.

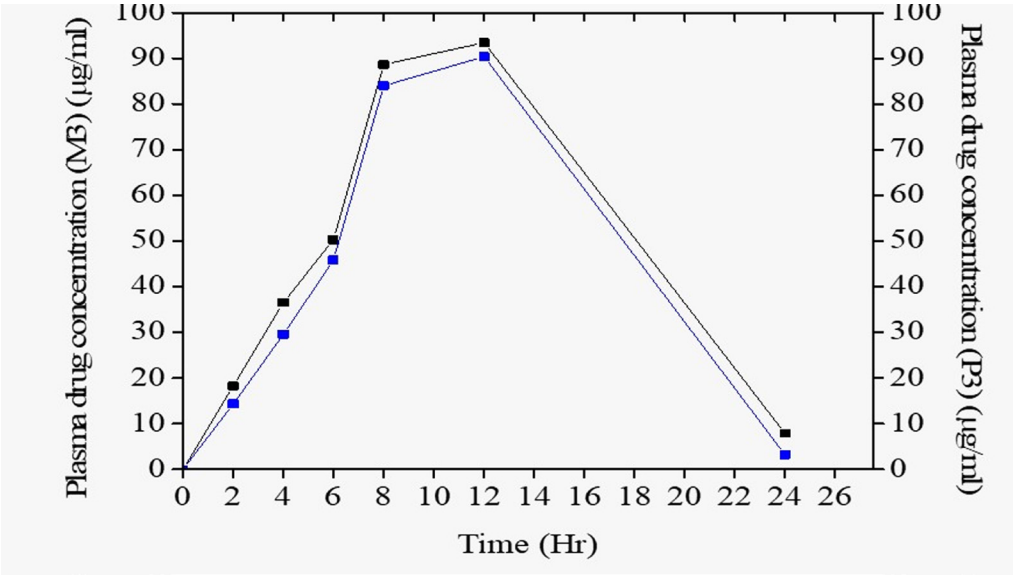

Figure 5: Comparative plasma drug conc. vs time plot of M3 and P3.

Table 4: Pharmacokinetic data of M3 and P3.

Parameters	M3	P3
C_{max}	93.44 µg/mL	90.41 µg/mL
T_{max}	12 hr	12 hr
K_a	4.95	3.87
AUC	2097.15 µghr/mL	1886.32 µghr/mL
MRT	24 hr	22.3 hr
K_e	7.9	6.38

corneum, enabling direct delivery of the drug to the dermis, where systemic absorption occurs more efficiently.

Accelerated stability studies of M3 and P3

It was observed that the microneedle patch formulations showed no significant alteration in morphology as well as drug content when the samples were kept at accelerated conditions of 40C±2°C, 75±5% RH for 4 hr (as shown in Table 3). Compared with transdermal patches it also does not show any significant changes in their appearance but drug content varies up to 90% content availability as compared to microneedle patch formulations which have drug content of about 93% (minimum value).

In vivo study

Skin irritation study

No indications of dermal toxicity were observed, as there were no signs of redness, erythema, edema, or any type of skin damage. Throughout the 5-day observation period, the test samples did not induce moderate or severe toxicity. So from the study, it could be considered that the API and the drug loaded in microneedle patches as well as transdermal patches are safe for the skin and no contraindication or allergic condition had been observed.

Bioavailability study of M3 and P3

The plasma drug concentration-time profile was plotted (Figure 5) and various pharmacokinetic parameters[14] viz. C_{max}, T_{max}, AUC, K_a and K_e were calculated (values are given in Table 4).

CONCLUSION

The field of transdermal drug delivery is continuously advancing and aims to deliver macromolecules either systemically or locally. However, a major challenge is the limited permeability of drugs through the stratum corneum. To overcome this challenge, microneedles are used. Microneedles play a dual role by acting as a bridge between hypodermic syringes and transdermal patches, combining the advantages of both these drug delivery methods.[15] Numerous evaluation parameters have been studied for both microneedles and transdermal patches, using *in vitro* and *in vivo* approaches under similar experimental conditions. These evaluations analyze the physical, chemical and bioavailability aspects to determine which method is more effective for delivering therapeutics in the transdermal drug delivery system.[16] In a nutshell, microneedles are a superior and cost-effective alternative to transdermal patches, potentially revolutionizing the arena of transdermal drug delivery systems.[17,18] Their efficacy and affordability make them a promising option for overcoming the limitations of traditional patch-based drug delivery.

FUTURE SCOPE

The findings of this study provide a promising foundation for advancing the application of microneedle patches as an alternative delivery system for indomethacin. Future research could focus on clinical trials, optimization and scalability, personalized medicine, combination therapies and patient compliance studies. These avenues can further establish microneedle patches as a game-changing technology in transdermal drug delivery,

enhancing therapeutic outcomes and minimizing adverse effects associated with conventional NSAID formulations.

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ABBREVIATIONS

AUC: Area under the curve; **ºC:** Degree Celsius; **C_{max}:** Maximum plasma concentration; **FTIR:** Fourier transform infra-red; **hr:** Hours; **HPMC:** Hydroxypropyl methylcellulose; **min:** Minutes; **mL:** Milliliter; **M3:** Microneedle Patch; **T_{max}:** Maximum time; **P3:** Transdermal Patch.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

Microneedles are tiny, minimally invasive devices used in various fields, including medicine, cosmetics and biomedical research. One of the primary applications of microneedles is in transdermal drug delivery. By piercing the outermost level of the skin, known as the stratum corneum, microneedles create channels that allow drugs or other therapeutic substances to penetrate deeper into the skin. Overall, microneedles offer a versatile and minimally invasive approach for drug delivery, diagnostics and cosmetic treatments. Their potential to enhance therapeutic outcomes, improve patient compliance and enable precise tissue targeting make them an exciting area of ongoing research and development.

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