RESEARCH PAPER

Formulation design and characterization of transdermal patch for controlled delivery of xylometazoline hydrochloride

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ABSTRACT

Background/Aim: Xylometazoline hydrochloride (XYL) is a nasal decongestant, but its effectiveness is restricted by frequent dosing requirements, poor patient compliance, rapid mucociliary clearance and limited residence time. Our research project is to develop xylometazoline hydrochloride-chitosan nanoparticles loaded transdermal patches (XYL-CH-NP-TP) utilizing various combinations of polymers for treating nasal congestion.

Methods: Hydroxypropyl methylcellulose K100M (HPMC K100M) with Polyvinylpyrrolidone (PVP) were combined in various proportions, where polyethylene glycol 400 (PEG 400) serves the purpose of a plasticizer. These patches were fabricated using a solvent evaporation technique and characterized for patch thickness, tensile strength, moisture content, and swelling index were all measured. Furthermore, the optimized patch was evaluated for in-vitro drug release and the data was fitted into different kinetic models. Moreover, the ex-vivo release studies were carried out on goat nasal mucosa and epidermal skin.

Results: 12 formulations were prepared and FTP10 was found to be the optimal choice and evaluated for the different characterization parameters. % Cumulative drug release was determined to be 87.2% with XYL-CH-NP-TP following Higuchi model. Permeation studies through the nasal mucosa of goat showed XYL release of 97.2% for 8 hours. Furthermore, ex-vivo release through goat skin was 95% for 8-hour. Flux of XYL-CH-NP-TP on goat skin was found to be 98.2 µg/cm²/h when compared with XYL solution flux of 57.3 µg/cm²/h.

Conclusion: Hence, these developed XYL-CH-NP permeation packed transdermal patch may be used to improve transdermal permeability by acting as a carrier and treating nasal congestion.

Keywords: Xylometazoline hydrochloride, transdermal patch, nasal congestion, chitosan nanoparticles, HPMC K100M, PVP, controlled drug delivery, ex-vivo permeation.

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Introduction

Nasal mucosa acts as a site for systemic drug administration and facilitates nose to brain drug delivery system.[1] Nasal drops, nasal sprays, semi-solid dosage forms like nasal gel, and solid dosage forms like nasal powders, nanoparticles, are all examples of nasal medication forms which can be transferred to the nasal cavity. Limited volumetric capacity of the nasal mucosa is the major drawback during nasal drug delivery. As a result, drug retention and solubility, are the most important criteria during nasal drug delivery.[2] Recent advancements in nanoparticulate technologies for enhanced drug delivery hold a lot of potential for administering drugs.[3] Polymeric nanoparticles fabricated by various methods have shown increased

permeability to the nasal cavity.[4] Our previous research work has shown that the chitosan nanoparticles prepared from xylometazoline hydrochloride have shown better results in nasal drug delivery. Drug release and permeation studies have shown that XYL loaded nanoparticles have high drug retention within the nasal mucosa. Therefore, XYL-CH-NP shows potential for nasal congestion treatment due to its good mucoadhesive and bio adhesive property.[4]

The small size of nanoparticles enhances drug diffusion through the skin, and nanoencapsulation can help therapeutic medications penetrate the skin. Variables that may be improved by encapsulation include potency of a drug, tolerance and specificity.[5] Transdermal approaches have the advantage of being non-invasive, stable absorption over a longer period contributing to enhanced patient compliance. They eliminate the necessity for recurrent dosing as one patch may deliver the drug for approximately 7 days. Transdermal drug delivery systems (TDDS) are extensively researched topic for the above reasons, nevertheless, there are currently few FDA-approved transdermal pharmaceutical formulations. Drug loaded transdermal patches serve as devices that are applied to the skin to achieve a systemic effect. Recent improvements in nanoparticulate technologies for enhanced drug delivery have a lot of promise for administering active medications.[6] Major drawback in TDDS is to cross the natural skin barrier. To enhance the drug distribution via the dermal and transdermal routes, a variety of strategies have been used, including raising the drug concentration in the vehicle, trying to enhance skin-formulation partitioning using chemical penetration enhancers, and a variety of strategies of physical improvement. Liposome, micro particles and nanoparticles have all been studied as carrier systems.[7] Natural and synthetic permeation enhancers were employed into TDDS for nasal diseases.[8]

Our research proposal is to fabricate the transdermal patch loaded with xylometazoline hydrochloride chitosan nanoparticles (XYL-CH-NP-TP) for the drug release for a long time into the nasal cavity for treating nasal congestion. These patches will facilitate drug release, drug absorption through the skin and improve the drug systemic availability.

Methods

Material

Xylometazoline hydrochloride was given *ex-gratia* by Scott Edil Pharmacia Ltd. (Baddi, India). HPMC K100M and PEG 400 were procured from Moly Chem (Mumbai, India), PVP and Tween 80 were procured from Kemphasol (Mumbai, India). All other reagent and chemicals were of analytical grade.

XYL-CH-NP loaded transdermal patch preparation (XYL-CH-NP-TP)

Solvent evaporation technique was used to make XYL-CH-NP loaded transdermal patch. Different concentration of HPMC, K100M, and PVP were dissolved in distilled water and methanol (50:50) so as to obtain an optimized formulation as shown in **Table 1**. To remove air bubbles and attain a homogenous solution, the mixture was kept overnight on stirring. 10 mL of XYL-CH-NP was added to the aforementioned polymeric solution and agitated for 20 minutes to create a homogeneous suspension. Polyethylene glycol (PEG) was further added to the mixture. The homogeneous solution was evenly poured into 25 cm^2 petri dishes and left to dry at room temperature for 10 minutes. To completely evaporate the solvent, transdermal patches were kept in the hot air oven at 50 ^{0} C for 10 minutes. Furthermore, the prepared transdermal patches were trimmed into 5 cm^2 and finally, the patches were covered with an aluminum foil as a fabric backing film.[9]

Characterization Parameters of XYL-CH-NP-TP

Physical Appearance

Color, smoothness, clarity and flexibility of all the transdermal patches were evaluated.[10]

Tensile Strength

For XYL-CH-NP-TP tensiometer was used to determine the patch tensile strength (Erection and instrumentation, Ahmedabad). The instrument consists of two grips in which the lower one could not be moved, while the upper can move. 2x2 cm^2 patches were placed among the cell grips and force was applied gradually until the patch snapped. The dial value in kg was used to calculate the tensile strength.[11]

Breaking force/ sample cross section area = tensile strength (kg/mm^2) % of elongation at break.

Swelling index

Soaked the XYL-CH-NP-TP in distilled water and with the help of blotting paper excess water was removed and weighed at different time intervals 0.5, 1, 2, 4, 8 and 24 h.[12]

% swelling index was evaluated using the following equation

% Swelling index=(W2-W1)/W1*100

Where W1 = Prior to dipping into the medium, weight of the transdermal patch.

W2= Weight after being submerged onto the medium

Thickness of the films

Digital vernier calipers were employed to determine the thickness of XYL-CH-NP-TP. The measurements were made in triplicates.[13] A digital micrometer was used to measure the thickness of the XYL-CH-NP-TP at five separate places. The average of five values was determined.

Folding endurance

To measure the brittleness of the XYL-CH-NP-TP they were repeatedly folded at the same spot until they were completely broken.[14] To calculate the value of folding endurance of XYL-CH-NP-TP, the patch was folded at the same place without breaking was counted.

Moisture content

XYL-CH-NP-TP were weighed as the initial weight and kept at 25°C in desiccators with silica gel and re-weighed until the final weight remained constant. Moisture content was analyzed by the given equation.[15]

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

Weight variation

Weight variation was done by individually weighing 10 randomly selected patches followed by calculating their average weight. The individual weight should remain consistent and not show significant deviation from the average weight.

Flatness

The length of each longitudinal strip was determined by cutting longitudinal strips from the transdermal patch. The constriction of the strips can be used to determine flatness, with zero % constriction to100 % flatness.[16]

Constriction (%) = S1 − S2 /S1 × 100

where S1- initial length of strip, S2 - final length of strip.

Scanning electron microscopy (SEM)

SEM (Carl Zeiss, supra55, and Germany) was used to determine the shape and surface morphology of the optimized formulation following earlier available protocols according to the literature.[17]

Drug Content

XYL-CH-NP-TP with a patch size of $25cm^2$, equivalent to 10 mg of drug was dissolved in phosphate buffer (pH 6.8) and stirred continuously for 24 h. After filtration and dilution with phosphate buffer % drug content was measured at lamda max of 264nm.

Evaluation Parameters of XYL-CH-NP-TP

***In-Vitro* Drug Release Study**

In–vitro release study was carried out using

900 ml of phosphate buffer (pH 6.8). The study used a circular patch with an internal diameter of 25cm^2(drug equivalent to 10 mg) and a stainless-steel ring to sink the patch at the bottom of the dissolution device. The study was carried out at 37±0.5°C and 100 rpm.

Samples were withdrawn at specific time intervals and substituted with an equal volume of phosphate buffer, and their concentrations were measured using spectroscopy. Various kinetic models were used determine the mechanism of drug release and the exponent n was determined from the slope of the straight line. *In- vitro* drug release data was applied to the following kinetic models such as zero order (% cumulative drug release vs. time), first order (% log cumulative drug remaining vs. time), Higuchi's model (cumulative percent drug released vs. square root of time). Peppas-Korsmeyer model (log cumulative percentage of drug released vs. log time) was also used and if the exponent was found to be 0.5, the diffusion release mechanism was found to be Fickian.[18]

***Ex-vivo* permeation via nasal mucosa**

Fresh nasal mucosa was taken from the nasal cavity of the goat from a nearby butcher. Nasal mucosa was kept in saline buffer with a small amount of gentamycin sulphate to avoid the presence of bacterial growth.[19] Blood and bone cartilage was removed from the nasal mucosa. *Ex-vivo* drug permeability characteristic was investigated using the franz diffusion cell. Acceptor chamber at 37°C was filled with 11 ml of Phosphate Buffer pH 6.8. Hot water was circulated to maintain the temperature within the chamber. Following a 20-minute pre-incubation period, the transdermal patch of 5x5 cm^2(approx. 10mg) was applied to the surface of the nasal mucosa and kept in donor chamber. 0.5ml of sample was withdrawn from the acceptor chamber and replenished with the phosphate buffer at different time points. The samples were filtered and analyzed using UV-visible spectrophotometer. The sampling was carried out in triplicates.[20]

***Ex-vivo* goat epidermal skin permeation**

Preparation of goat skin:

A fresh goat skin was carefully retrieved from a local slaughterhouse and obtained. With a pair of scissors, the hair of the animal was clipped short, and the skin was dissected with a knife from the underlying connective tissue. Excised skin was placed on an aluminum foil, and any subcutaneous tissue was carefully teased off from the skin's dermal side. Using magnifying glass, the skin was examined to ensure that the region used for transdermal permeation experiments was devoid of any surface irregularities such as microscopic holes or cervices.[21]

Permeation through goat skin

The ammonia-free goat skin was mounted to the donor compartment of a modified Franz diffusion cell with a surface area of 2.68 cm^2 and clamped with the Phosphate buffer pH6.8 and filled the acceptor chamber. The diffusion cell was placed on a magnetic stirrer at 37°C. The XYL-CH-NP-TP was put to the goat's skin surface. The contents of the receptor cell were continually stirred at 37^{0}C, extracted for spectrophotometric analysis at appropriate intervals, and the cell was immediately replaced with fresh receptor solution.[22]

Stability Study

Stability tests were carried out in accordance with ICH recommendations. Q1A(R2) For initial, three and six months, the improved formulation of the drug containing XYL was subjected to accelerated stability testing at specified temperatures and relative humidity levels of 40°C+2^{0}C/75% ± 5 % RH. After six months, the samples were visually inspected for any color changes caused by physical and chemical interactions between excipients and the drug.[23]

Results and Discussion

Formulation of XYL-CH-NP-TP

The transdermal patches were fabricated and various trials were carried as shown in **Table 1.** Out of all trials, FTP10 was found to be of good quality and appearance

Table 1: Transdermal Patch Preparation Trials

F.Code	HPMC K100M(gm)	PVP K30 (gm)	PG: PEG (ml) 1:1	Tween 80 (ml)	Water (ml)	XYL-CH-NP
FTP 1	0.5	0.5	7	0.100	QS	10 ml
FTP 2	1	1	3	0.200	QS	10 ml
FTP 3	1.5	1.5	6	0.300	QS	10 ml
FTP 4	2	2	5	0.400	QS	10 ml
FTP 5	2.5	2.5	2	0.500	QS	10 ml
FTP 6	3	3	4	1	QS	10 ml
FTP 7	3.5	3.5	3	1.5	QS	10 ml
FTP 8	4	4	6	2	QS	10 ml
FTP 9	4.5	4.5	8	2.5	QS	10 ml
FTP 10	5	5	10	3	QS	10 ml
FTP 11	5.5	5.5	8	3.5	QS	10 ml
FTP 12	6	6	2	4	QS	10 ml

Characterization Parameters of XYL-CH-NP-TP

Physical Appearance

All the fabricated (FTP1-FTP12) XYL-CH-NP-TP were found to be Smooth and flexible as shown in **Table 2.**

Tensile Strength

The transdermal patches showed a tensile strength between 3.1 and 5.7 kg/ cm^2 **(Table 2).** The tensile strength of the patch gradually increases as the PVP and HPMC concentrations were raised, as determined in the formulation FTP10.

Swelling Index

The transdermal patches swelling index have been shown in **Table 2.** Swelling index investigations revealed that as time passed, the transdermal patch swelling index was increased.[24]

Film Thickness

Table 2 shows the thickness of the transdermal patches. Out of which FTP10 was found to have the thickness of 0.23mm indicates that patches were uniform in size. It shows that as the concentration of the polymer increases; there was an increase in the patch thickness.[25]

Folding Endurance

Folding endurance experimentation determines the capacity of the patches to endure folding. It also indicates the presence of brittleness. Folding endurance was found between 131 and 150 folds which is considered satisfactory and reveals good film property. Folding endurance increases as the amount of polymer increases. This feature was discovered to be helpful for the development of FTP10.[25]

Moisture Content

% Moisture content of the patches varies between 8.4 and 20.5%. The moisture content was observed to increase as the concentration of PVP and the grade of HPMC were increased, as evidenced in formulation FTP10. The formulations showed decrease in moisture content that helps them to stay stable and generate a dry and brittle coating.[26]

Weight Variation

As shown in **Table 2** the weight variation of the patches was calculated and compared with their average weight.

Flatness

The flatness investigation revealed that all

the patches consist of the same length before and after cutting, demonstrating that they all are 97.8% flat. No constriction was observed and all patches have a smooth and flat surface that can be placed onto the skin.[27]

Table 2: Various formulations showing appearance, folding endurance, tensile strength, weight uniformity and average thickness

F.code	Appearance	Folding endurance	Tensile strength	Weight variation	Flatness	Average Thickness	Moisture content	Swelling Index
FTP1	Smooth, Flexible	131	4.5	0.552	98	0.23	8.4	85.2
FTP2	Smooth, Flexible	123	3.2	0.532	97.5	0.25	9.4	86.8
FTP3	Smooth, Flexible	109	3.6	0.542	97	0.27	8.4	85.2
FTP4	Smooth, Flexible	106	3.1	0.548	97.4	0.26	12.33	83.1
FTP5	Smooth, Flexible	112	4.1	0.546	96.7	0.24	11.7	84.7
FTP6	Smooth, Flexible	145	4.6	0.546	98.1	0.22	12.7	87.2
FTP7	Smooth, Flexible	143	3.1	0.547	95.8	0.22	18.5	87
FTP8	Smooth, Flexible	124	5.2	0.545	97.5	0.21	15.6	84.1
FTP9	Smooth, Flexible	93	5.1	0.541	96.2	0.23	20.2	86.3
FTP10	**Smooth, Flexible**	**150**	**5.7**	**0.543**	**97.8**	**0.23**	**20.5**	**95.2**
FTP11	Smooth, Flexible	132	4.7	0.552	96.7	0.24	16.8	87.2
FTP12	Smooth, Flexible	127	4.6	0.551	97.8	0.21	11.5	75.2

Scanning Electron Microscopy (SEM)

Figure 1 shows the image XYL-CH-NP-TP. It reveals that the nanoparticles placed into the transdermal patch have no effect on the size or shape of the patch.

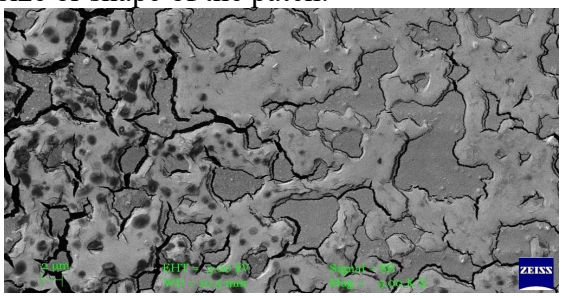

Figure 1: Scanning Electron Microscopy of XYL-CH-NP loaded transdermal patch

Drug Content

The drug content of the transdermal patches was found to be in the range of 84.46%±0.0564 to 86.23%±0.0134 indicating that the process employed to prepare patches consists of uniform drug content.

Evaluation parameters of XYL-CH-NP-TP

***In- Vitro* Drug Release**

In-vitro release of XYL from XYL-CH-NP-TP revealed the slow and continuous release for 12h. **Figure 2 a)** shows that the cumulative drug release, was found to be 87.2% when compared with XYL solution (**Figure 2 b**). The *in-vitro* release profile of the XYL-CH-NP-TP formulation was evaluated using different kinetic models. Among them, the Higuchi model was considered as the best fit, due to its high regression coefficient (R^2). It explains that drug release mechanism from a polymer matrix was diffusion, where the amount of drug released is directly related to the square root of time.[28] When plotted against the square root of time, the drug release from the XYL-CH-NP-TP showed Higuchi kinetics (**Figure 3**).[29]

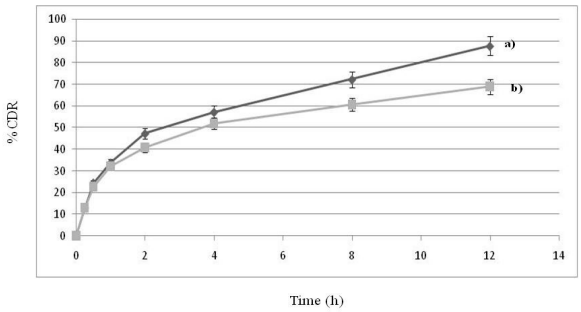

Figure 2: a) % cumulative drug release of XYL from XYL-CH-NP loaded transdermal patch b) % cumulative drug release of XYL from the solution

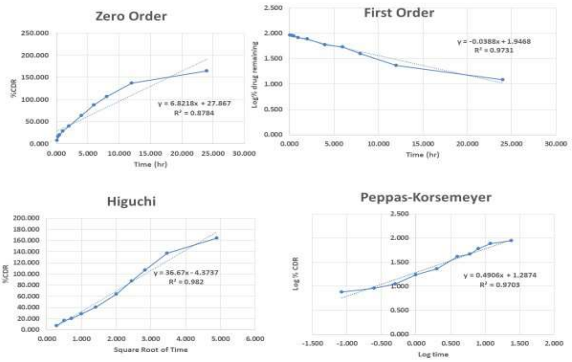

Figure 3: Kinetic model of *in- vitro* release of XYL from XYL-CH-NP a) Zero order b) First order c) Higuchi d) Peppas-Korsemeyer

***Ex-vivo* permeation study via nasal mucosa**

Ex-vivo permeation studies were demonstrated to compare the permeation capacity of the XYL-CH-NP-TP with xylometazoline solution under similar experimental situations. Permeation flux (F) was found to be 982.00 µg/cm²/h, by plotting the cumulative amount of drug permeated (µg) versus time (minutes). **Figure 4** shows the that ex-vivo permeation studies for both (a)XYL-CH-NP-TP and (b) xylometazoline solution. Using Franz diffusion cell, 97.2% drug was permeated through the nasal mucosa within 8 hours.

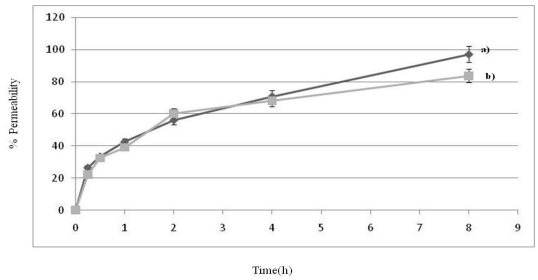

Figure 4: *Ex-vivo* permeation release through goat nasal mucosa a) XYL-CH-NP loaded transdermal patch b) XYL solution loaded transdermal patch

***Ex-vivo* permeation skin study with the help of Goat epidermal skin:**

S. No	TESTS	SPECIFICATION	IMPROVED CONDITION (40°C±2° C/75%RH±5%RH) 1 month		
			SGT-010A	SGT-010B	SGT-010C
1	**Description**	Transluc ent Film	Trans lucen t Film	Trans lucen t Film	Transl ucent Film
2	**pH**	5.5-6.5	6.2	6.4	6.2
3	**Thin ness**	10-20µm	14µm	13.8µ m	13.6µ m
4	**Smoo thing/ Flexi bility**	Plane and ductile	Plane and ductil e	Plane and ductil e	Plane and ductil e
5	**Drug Cont ent**	80-90%	87±0. 23%	86±0. 63%	82±0. 59%

Ex-vivo permeation studies demonstrated the permeation efficiency of XYL-CH-NP-TP compared with XYL solution under similar experimental situations but in this study goat epidermal skin was utilized. Permeation flux (F) was plotted between cumulative drug permeation (µg) against time (minutes). **Figure 5** shows the permeation profile of (a) XYL-CH-NP-TP and the (b) XYL solution loaded transdermal patch. For 8-hour, 95% of the drug from XYL-CH-NP formulation was permeated through goat skin using a Franz diffusion cell. The results clearly indicate that the nanoparticles show significantly enhanced skin permeation compared to the transdermal patch containing xylometazoline solution.

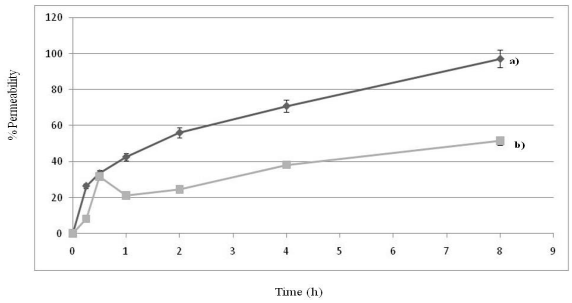

Figure 5: *Ex-vivo* permeation release from goat skina) XYL-CH-NP loaded transdermal patch b) XYL solution loaded transdermal patch

Stability Study

On storage for 6 months, the drug content of the selected transdermal patches were found to be between 85±0.52 % mg/cm^2 compared to 89±0.69 % mg/cm^2 for fresh patches**. Table 3** shows stability study for initial month and **Table 4** shows accelerated stability studies. This suggested that drug content was relatively uniform, with low standard deviation values. During the analysis, no changes in the visual characteristics of the selected XYL-CH-NP-TP, such as shape, clarity, smoothness, homogeneity, or consistency were observed.

Table 3: Stability study for 01 month

Table 4: Accelerated Stability Studies for 3 and 6 months

S. No	TESTS	SPECIFICATION	ACCELERATED NDITION (40°C±2° %RH±5%R 3 month			ACCELERATED NDITION (40°C±2° %RH±5%R 6 month		
			SGT-	SGT-010	SGT-01	SGT-01	GT-010	SGT-010

			010A	B	0C	0A	B	C
1.	**Description**	Translucent Film	Translucent Film	Translucent Film	Translucent Film	Translucent Film	Translucent Film	Translucent Film
2.	**pH**	5.5-6.5	6.2	6.1	5.	5.	6.1	6.3
3.	**Thinness**	10-20µm	15µm	15.8µm	14m	15m	13.n	13.n
4.	**Smoothing/Flexibility**	Smooth & Flexible	Smooth & Flexible	Smooth & Flexible	Sh & ble	Sh & ble	Sm & ble	Sm & ble
5	**Drug Content**	80-90%	8%	87±0.46%	86 9%	84 3%	86 3%	85 2%

Discussion

XYL-CH-NP-TP displayed optimum characterization parameters suitable for adhesion and sustained drug delivery which followed Higuchi kinetic model where the drug was released by the diffusion. Moreover, recent advances in nasal and transdermal drug delivery systems have opened new therapeutic avenues for rhinitis and related conditions. The emedastine transdermal patch, developed as the first of its kind, demonstrated significant efficacy in reducing total nasal symptom scores compared with placebo, with sustained action and favorable safety outcomes.[30] Similarly, combination therapies targeting both symptom relief and epithelial protection have shown promise. A nasal spray combining xylometazoline with hyaluronic acid improved mucociliary function and epithelial protection in vitro, while formulations with xylometazoline and indomethacin effectively reduced vascular congestion, inflammation, and epithelial damage in animal models, highlighting the potential of anti-inflammatory co-formulations.[31] Furthermore, the dual-action spray combining xylometazoline and iota-carrageenan preserved both decongestant and antiviral efficacy, representing a novel strategy against viral rhinosinusitis (xylometazoline–iota-carrageenan study).[32] Collectively, these findings highlight the potential of innovative formulations in providing safer, more effective, and sustained rhinitis management. XYL-CH-NP-TP showed enhanced drug delivery and drug permeation making it a suitable product for nasal congestion

Conclusion

The developed transdermal patch containing chitosan nanoparticles loaded with xylometazoline hydrochloride demonstrated sustained drug release and enhanced permeation for nasal congestion treatment. In vitro studies confirmed prolonged drug release over 24 hours and ex-vivo permeation through goat nasal mucosa and skin significantly showed higher flux and permeability than xylometazoline solution. These findings suggest the XYL-CH-NP-loaded transdermal patch is a promising system for enhanced drug delivery and therapeutic efficacy.

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Conflict of interest

The authors declare that there is no conflict of interest.

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