Design and Evaluation of Matrix Type and Membrane Controlled Transdermal Delivery Systems of Nicotine Suitable for use in Smoking Cessation

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The availability of nicotine-replacement therapies is very low in India, as there are only a few importers. Currently, negligible forms of transdermal patches are available, they are expensive, and not easily accessible to the common man. In this study, an attempt was made to develop transdermal patches of nicotine, which are cost effective and conducive to the Indian market. Two types of patches, monolayered and bilayered, were prepared. The monolayered patch bore a rate- controlling membrane, whereas the bilayered, served as matrix type. The physical charecteristics of the patches were evaluated by standard techniques. The drug content was found to be uniform in the patches. *In vitro* release studies of transdermal patches showed a biphasic release pattern, with diffusion as the dominating mechanism of drug release for the matrix type, while the membrane-controlled released nicotine, gradually over the 24 h study.

Due to the widespread use of traditional forms of tobacco as well as cigarettes, India has one of the highest rates of oral cancer in the world, and the rates are still increasing. In India, there are an estimated 214 million tobacco users, above 15 years of age. Estimates from the Indian Council of Medical Research, show that about 0.8 million people die every year, from tobacco-related causes, which implies that one death occurs every 40 seconds in the country. If the tobacco use continues unchecked, the annual toll will touch 1.5 million by 2020. Unlike western countries, the availability of nicotine replacement therapies is very low in India, as there are only a few importers. Apart from this, they are expensive, and not easily accessible to the common man. nicotine Transdermal Systems (NTS) are widely available in the western countries, and significant advances have been made in this field. NTS are reported to be well tolerated in clinical trials, because of their ease of use and unobtrusive nature, resulting in better patient compliance. NTS have also been reported to reduce daily cigarette use in subjects who are unable to totally abstain from smoking[1]. Using modern technology and indigenous material, an attempt was made to prepare transdermal patches of nicotine, which are cost effective and appealing to the Indian population, especially to the rural masses.

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MATERIALS AND METHODS

Nicotine was obtained from Merck, Germany HPMC K4M from BDH laboratories, Sodium alginate from S.D.Fine Chemicals, and Ethyl cellulose (20 cps) from Loba Chemie, Mumbai. Carbopol 934 P was purchased from B. F. Goodrich Co. Germany. The rest of the ingredients and reagents were of analytical grade.

Preparation of nicotine transdermal patch:
The solvent-casting technique was used to formulate the sodium alginate patch, containing nicotine. Two types of patches, monolayered and bilayered, were prepared with respect to the drug layer. For the monolayered patch, the drug polymer solution was transferred into a mould of size 4×3 cm^2, previously covered with a backing membrane. The backing membrane was prepared by dipping a polyester cloth into a 4% w/v solution of ethyl vinyl acetate in dichloromethane for two min, and air-drying it for five min. The mould was then kept in a hot air oven and maintained at a temperature of 60° for 4 h. Ethyl cellulose film was used as the rate controlling membrane. The composition of the drug matrix and the rate controlling membrane are

shown in Tables 1 and 2, respectively.

The preparation of bilayered film was similar to that of the monolayered film, except that nicotine was loaded in two separate layers, after which it was crosslinked with calcium chloride. For the preparation of the primary layer, 250 mg of sodium alginate and nicotine, equivalent to 35 mg was used, whereas for the secondary film, 150 mg of sodium alginate and 5 mg of nicotine was used. The bilayered film did not bear a rate controlling membrane. This served as a matrix type of transdermal delivery system.

Preparation of rate controlling membrane:

Ethyl cellulose was dissolved in a mixture of chloroform and dichloromethane. Dibutylphthalate was used as a plasticizer, and the solution was poured within a glass bangle placed on a mercury surface, and left for drying. After 24 h, a membrane of 3×4 cm^2 area was cut, and placed on the patch. Polyisobutylene was applied to the sides of the patch, as an adhesive.

Physicochemical characterisation of the transdermal patch:

To determine the drug content, the patch was placed in 100 ml of Phosphate buffered saline (PBS) solution, and shaken for 5 h (100 rpm) on a shaker. The complete solution was filtered, and then analyzed by UV with the help of spectrophotometer at a λ_{max} of 259 nm.. For content uniformity, the patch was divided into four quadrants of 3 cm^2, and each 3 cm^2 analyzed for the drug content. Weight variation test was caried out on ten patches. The patches were weighed individually, and their average weight and standard deviation was calculated and reported. The thickness of the patches and rate controlling membranes was measured with the help of screw gauge at three different places, and the average value was determined. The percentage moisture absorption was studied by placing pre weighed films in a desiccator containing 100 ml of saturated solution of aluminum chloride, which maintains 79.5% RH. After 3 days, the films were taken out and weighed.[2]

TABLE 1: FORMULATION OF DRUG MATRIX FOR THE TRANSDERMAL PATCH

	Monolayered patch	Bilayered patch
Nicotine	40 mg	40 mg
Sodium alginate	350 mg	400 mg
Water	5 ml	5 ml
Glycerin	0.5 ml	0.5 ml
Chlorocresol	0.1%	0.1%
Calcium chloride solution	–	5%

TABLE 2: FORMULATION OF RATE CONTROLLING MEMBRANES

	A	B	C
Ethyl cellulose	300 mg	250 mg	200 mg
Chloroform	3.0 ml	2.5 ml	2.5 ml
Dichloromethane	3.0 ml	3.0 ml	3.0 ml
Dibutyl Phthalate	60 mg	45 mg	35 mg

***In vitro* release of nicotine from transdermal patches:**

A specially designed rectangular diffusion cell (4×3 cm=12cm^2) was used in the release study. The whole 12 cm^2 patch, along with the backing membrane, was used for the release study. A commercial semipermeable membrane was employed in the study as the permeation barrier. The membrane used was transparent, and regenerated cellulose.

The patch was kept on the sigma/dialysis membrane, previously soaked in the buffer solution for 12 h. The membrane along with the patch, was then firmly tied to the diffusion cell, and was immersed in a beaker containing 200 ml of (PBS) pH 7.4. The experimental set up was placed on a thermostatically controlled magnetic stirrer, and the temperature was set at 37±2°. The contents in the beaker were stirred with the help of a magnetic bead, at a constant speed. The release study was carried out for a period of 24 h. An aliquot of samples were withdrawn at regular predetermined intervals.[3] The drug content was analyzed with the help of a spectrophotometer at a λ_{max} of 259 nm.

***Ex vivo* release of nicotine from transdermal patches:**

Rat skin was mounted on the diffusion cell, with the dermal side in contact with receptor medium, and the subcutaneous side facing the donor compartment.[4] The experimental set up was the same as conducted for the *in vitro* study.

RESULTS AND DISCUSSION

The physicochemical properties of the nicotine transdermal patches are recorded in Table 3. The thickness of rate controlling membranes are shown in Table 4. The drug content analysis of the prepared formulations has shown, that the process employed to prepare the study of the patches, was capable of giving uniform drug content and minimum batch variability. Content uniformity studies proved that the amount of

TABLE 3: PHYSICOCHEMICAL PROPERTIES OF TRANSDERMAL PATCHES

Formulation	Thickness (mm)	Drug content (mg)	% Moisture absorption
F1, F2, F3	1.23±0.31	38.9±0.36	6.62±0.33
F4	1.37±0.22	39.3±0.47	5.77±0.16

Formulation F1 F2 and F3 have the same matrix and differ only in the thickness of the rate controlling membrane. F4 – Bilayered sodium alginate patch crosslinked with calcium chloride

TABLE 4: THICKNESS OF RATE CONTROLLING MEMBRANE

Ethyl cellulose (mg)	Thickness (microns)
200	100±0.14
250	150±0.23
300	200±0.22

Each value represents mean±SD of 3 determinations

nicotine present in each patch of 3 sq. cm., was found out to be fairly uniform, containing 9.86 mg±0.27 of nicotine. Moisture absorption studies showed strong water absorbing capacity, an inherent property of the sodium alginate polymer. This observation would be useful in designing and selecting the final package material.

Sodium alginate, a hydrophilic polymer, was selected for formulating the patch. The main aim of selecting the hydrophilic polymers, was that nicotine is soluble in water. In the casting process, the drug (nicotine) particles become situated at random, within the polymer matrix. It might so happen that some drug molecules get isolated and entrapped by the polymer. When the concentration of nicotine molecules is large, they are more likely to touch each other, and clusters of nicotine molecules can thus extend from the surface deep into the matrix. These clusters result in connected pore space, upon dissolution of the nicotine molecules. Therefore, all nicotine molecules in these clusters can be released. But in a case of isolation of the nicotine molecules, the association with water molecules might come in handy. This can be postulated, because even after the drying of the patch, some water molecules would remain entrapped along with the polymer and nicotine. This association might help in the formation of a bridge or a chain link, to connect it with the other clusters of nicotine molecules, and thus helping in getting out most of the nicotine molecules from the matrix. The other reason for selecting water as a solvent, was that water is a universal solvent, readily available in pure form, and it is also cost effective.

Sodium alginate was the polymer of choice, as it fulfilled the criteria of cost, purity, and acceptability for medical devices, ease of fabrication, stability, and ease of modification. Moreover, since nicotine gradually becomes brown on exposure to air or light without affecting its intended pharmacological action, this change in colour can easily be camouflaged with the natural colour of sodium alginate.

In case of the bilayer film, the bottom layer contained 35 mg of nicotine, and was crosslinked with 5% calcium chloride solution. The top layer was spiked with 5 mg of nicotine, and was not cross- linked with the calcium chloride solution. This would provide the burst effect from the top layer, so that nicotine reaches faster into the systemic circulation, and stops the patient's urge to smoke. Glycerin was used in all the formulations, as it is found that glycerin reduces the primary irritation of moderately irritating drugs[5].

In vitro release studies of the developed formulations are represented in Fig. 1. A comparison of the release graphs of the two formulations (F_1-F_3 and F_4), show that the initial release rate is fast for the bilayer film for the first one hour. This could be due to the fact, that 5 mg of nicotine is present in the top layer of the bilayered sodium alginate patch, which is responsible for the fast release of the nicotine from the systems. The nicotine present in the second layer of sodium alginate (35 mg), starts permeating through the pores created in the upper layer of the

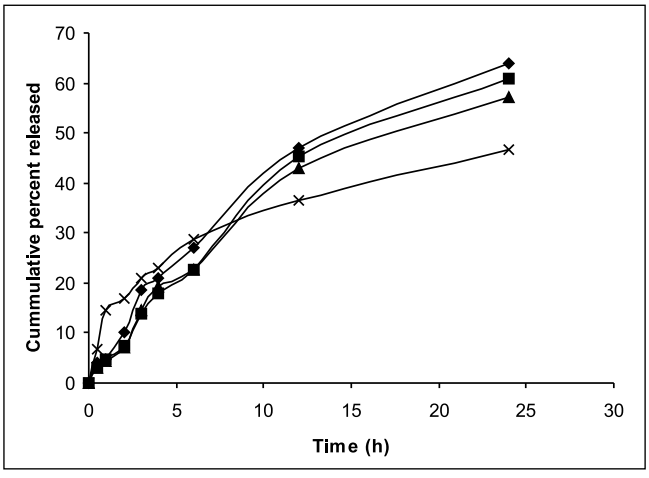

Fig 1: *Ex Vivo* Release profile of nicotine from transdermal patches
F1-Sodium alginate patch with Ethylcellulose rate controlling membrane (thickness 100 microns)
F2-Sodium alginate patch with Ethylcellulose rate controlling membrane (thickness 150 microns)
F3-Sodium alginate patch with Ethylcellulose rate controlling membrane (thickness 200 microns)
Area 12 sq.cm
F4-Bilayered sodium alginate patch crosslinked with calcium chloride

sodium alginate patch, by the diffusion of nicotine into the receptor medium. The cross-linking of sodium alginate with calcium chloride to form calcium alginate, retards the release of nicotine.

In the system containing ethyl cellulose as the rate controlling membrane, the release rate is controlled from the commencement of study. As it is observed, the release rate is steady throughout the 24 h study, because of the rate controlling membrane.

The *in vitro* release data was treated with kinetic equations, such as the first order rate kinetic equation, Higuchi's diffusion equation, and Peppas equation, to understand the release kinetics and mechanism of release from the formulated patch. Results are tabulated in Table 5. It can be inferred, that the incorporated drug was released by the non-fickian type of diffusion, involving swelling of the polymer matrix, as is evident by the slope values of more than 0.5 for the plots of log amount released, Vs log time.

Bilayered Sodium alginate patch

A polymer strand is formed when the sodium alginate patch is dipped in calcium chloride solution. This occurs, because the Ca^{2+} ions replace the Na^{+} ions, and serve as a cross-linking agent, to link two alginate chains together. The resulting cross-linked polymer is insoluble in calcium chloride solution, and this results in the formation of the polymer strand. The release of nicotine from the polymer, depends on the extent of cross linking[6].

Similar to the results obtained through commercial dialysis membrane, the permeation of nicotine through the hairless rat skin, was observed to follow first order kinetics throughout the 24 h of skin permeation study. The flux values for permeation through the rat skin was lower, compared to flux values for permeation through the sigma membrane. It has been reported, that different trends between skin and membrane permeation rate, is due to the difference of pathways. Solutes primarily permeate through water-filled pores in the artificial membrane[7]. Generally, the pore sizes of the artificial membrane are large, compared to that of skin.

In order to get a better insight into the mechanisms underlying the controlled release of nicotine from the transdermal patch, the release kinetics of nicotine was investigated. The results in Fig. 1 indicate that the transdermal system (F1-F3), released nicotine gradually throughout the 24 h study. The release profiles from this transdermal system, follow the polymer matrix diffusion-controlled process. The release of nicotine from the bilayered sodium alginate patch (F4) (Fig. 1) shows a biphasic release kinetic profile, with a mean value of 132 ± (0.33) μg/cm^2/hr, for the first few hrs, which shifts to a lower rate of 32 ± (0.26) μg/cm^2/hr, for the remaining hrs. This shifting phenomena could be attributed to the decrease in the availability of nicotine at the surface. The initial burst, as a result of hydration of the polymer matrix, was followed by steady state permeation. The initial burst is due to the drug on the surface of the matrix. The drug, later diffuses through the pores in the matrix, which is much slower. When a rate-controlling membrane is placed on the device, the initial burst is suppressed due to control release properties of membrane, and release follows the square root of time release kinetics.

The data from *in vitro* release studies of transdermal patches, did not fit zero-order kinetics. When the data was plotted for first order equation, it showed non linearity indicating biphasic release pattern. Further to know the mechanism of release, we plotted Higuchi and Peppas plots, which indicated diffusion as the dominating mechanism of drug release.

Release of the drug from the transdermal patches, is controlled by the chemical properties of drug and delivery form, as well as the physiological and physicochemical properties of the biological membrane.[8] In this study, sodium alginate patches containing nicotine, with rate controlling membranes of different thickness,

TABLE 5: RELEASE RATE KINETICS OF *IN VITRO* RELEASE OF NICOTINE FROM TRANSDERMAL PATCH

Formulation	First order equation		Higuchi equation		Peppas equation	
	K	R^2	n	R^2	n	R^2
F1	3.90×10^{-2}	0.8907	1.829	0.9520	0.729	0.9565
F2	$3.45 \times 10^{-}$	0.9798	1.772	0.9770	1.103	0.9853
F3	2.90×10^{-2}	0.9807	1.589	0.9901	1.317	0.9140
F4	4.60×10^{-4}	0.8939	1.124	0.9926	0.461	0.9824

F1, F2 and F3-Sodium alginate patch with Ethylcellulose rate controlling membrane having thickness 100, 150 and 200 microns respectively. F4 – Bilayered sodium alginate patch crosslinked with calcium chloride

released variable amounts of nicotine through the commercial cellulose membrane and rat skin, in the *in vitro* study fluid. In case of the F4–bilayered sodium alginate patch, there were gradual falls in cumulative amounts of the drug released after 3-4 hr, as depicted in Fig. 1, and a change in kinetic pattern was noticed. This may be because the amounts released were less than those in the first few hrs, where we observed that the release pattern had the tendency to go for the first order kinetics, from zero order kinetics.

Release of a drug from a transdermal drug delivery system, mainly involves factors of diffusion[9]. Diffusion is related to transport of a drug from dosage matrices into the *in vitro* study fluid, depending on concentration[10]. As the gradient varies, the drug is released, and the distance for diffusion increases.

If the release of drug from the transdermal film, when plotted against square root of time, shows a straight line, it indicates that the release pattern is obeying Higuchi's kinetics. In our experiments, *in vitro* release profiles of all the formulations of transdermal patches did not fit zero-order behavior truly, and they could be best expressed by Higuchi's equation for the release of drug from a homogeneous-polymer matrix-type delivery system, that depends mostly on diffusion characteristics. The *in vitro* flux was determined from Fick's law of diffusion $J_s = 1/A(dM/dt)$, where J_s is the flux ($\mu g/cm^2/h$), dM/dt is the amount of drug permeated per unit time, and A is the diffusion area (cm^2). The steady state skin flux was determined from the slope of the linear portion of a cumulative amount-time plot.

The flux values of nicotine from the formulated transdermal patches are shown in Table 6. Transdermal systems were found to deliver nicotine with a permeation rate ranging from (95-197 $\mu g/cm^2/h$). To evaluate any difference in the permeation rate between the developed nicotine transdermal systems, student t test was applied. The flux of nicotine through the sigma membrane was higher,when compared through rat skin ($P<0.05$). Among the formulations F1, F2, F3 and F4, significant difference was observed in flux values ($P<0.05$), indicating that each system is different from the other. The different skin permeation profiles of nicotine, delivered by the developed nicotine transdermal systems, could be explained by the difference in their system designs.

TABLE 6: FLUX VALUES OF NICOTINE FROM TRANSDERMAL PATCHES (µG/CM²/HR)

Formulation	Sigma membrane	Rat skin
F1	197±0.31	152±0.48
F2	122±0.42	110±0.53
F3	108±0.39	95±0.45
F4	127±0.37	132±0.33

Each value represents a mean±S.D of 3 determinations.

When the average rate constants of the formulations were studied, it was observed that formulation F4 showed comparatively lower rates of release of drug. Considering the factors of constant drug release properties, formulation F1, F2 and F3, could be better choice. But when these 3 formulations were compared individually, it was observed that formulation F3 had a much more satisfactory release profile, with better controlled rate of drug release with a flux 95 $\mu g/cm^2/h$. With an area of 12 cm^2, this would deliver about 27 mg nicotine for 24 h.

The recommended initial dosage of transdermal nicotine to assist in cessation of smoking, is upto 22 mg/24 h. Studies have reported that craving for nicotine, however, responded better to higher transdermal nicotine doses. There is evidence, that currently recommended doses of NRT are inadequate for many smokers. Higher doses enhance the likelihood of successful cessation in more dependant smokers.[11] The amount of nicotine released from transdermal systems, has been calculated in trials, with values in the range of 43 to 85%. However, this is not a measure of the amount of nicotine absorbed, since some may be lost at the edge of the system, and therefore would not reach the systemic circulation[12]. Therefore, we selected formulation F3 for further pharmacokinetic studies. This formulation bears a rate controlling membrane, that regulates the release of nicotine to the skin. It showed a flux of 95 $\mu g/cm^2/h$, which would deliver about 27 mg of nicotine for 24 h, using the 12 cm^2 patch. The pharmacokinetic study has been completed, and data compilation is in progress.

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Accepted 25 February 2006
Revised 1 July 2005
Received 4 February 2005
Indian J. Pharm. Sci., 2006, 68 (2): 179-184