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Development and evaluation of matrix type transdermal patches of aspirin

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ABSTRACT

Objective of the present study involves development and evaluation of matrix type transdermal patches for controlled delivery of aspirin as a model drug in order to avoid it,s frequent dosing , avoidance of adverse effects and improving the bioavailability of aspirin.Transdermal patches were prepared by using different polymers i.e. Eudragit RS 100, chitosan ,polyethylene glycol 4000 and polyvinylpyrrolidone K30. Transdermal patches were evaluated in terms of physical properties and in-vitro release studies by using phosphate buffer of pH 5.0 and *in-vitro* skinpermeation studies was performed by using rat skin and phosphate buffer of pH 7.4 for 11 hrs. The effect of penetration enhancer (20 % propylene glycol) was estimated on the *in-vitro* skin permeation profile of the patches.

Key words: Matrix type transdermal patches, Aspirin, model drug.

INTRODUCTION

Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate1.A transdermal drug delivery device, which may be of an active or a passive design is a device which provides an alternative route for administering medication.These devices allow for pharmaceuticals to be delivered across the skin barrier2. Transdermal patch is a medicated adhesive pad that is placed on the skin to deliver a time-release dose of medication through the skin into the bloodstream. It is also called skin patch. In theory, transdermal patches work very simply. A drug is applied ina relatively high dosage to the inside of a patch which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood the drug will keep diffusing into the blood for a long period of time maintaining the constant concentration of drug in the blood flow.

Advantages

1. The system avoids chemically hostile GI environment.
2. It doesn't have GI distress or other physiologic contraindications of oral route.
3. It provides controlled administration of a therapeutically effective dose at a desired rate of delivery.
4. It allows effective use of drugs with short biological half-lives.
5. It allows administration of drugs with narrow therapeutic window.
6. It maintains drug concentration within an optimal therapeutic range even during prolonged therapy.
7. It leads to the reduction of adverse drug effects.

8. It maximizes the efficacy – dose relationship.
9. It minimizes the need for frequent drug administration.
10. It leads to better patient compliance due to reduction in the frequency of dosing.
11. It by passes hepatic first pass metabolism.
12. It interrupts drug input promptly when toxicities occur (easy termination of drug therapy by mere removal of patch.).
13. It has better cost benefit ratio.
14. Self-application is possible.

Limitations of Transdermal Drug Delivery Systems3

The route is unsuitable when

1. The drug dose is large.
2. The drug has large molecular size (makes absorption difficult: should ideally be below 800-1000).
3. The drug is skin sensitizing and irritating.
4. The drug is metabolized in skin.
5. The drug undergoes protein binding in skin.
6. The drug is highly lipophilic or hydrophilic.

Aspirin is rapidly absorbed in the stomach and upper intestine. The oral bioavailability of regular aspirin tablets is approximately 40-50% over a wide range of dose. A considerably lower bioavailability has been reported for enteric-coated tablets and sustained–release, microencapsulated preparations (Pedersen *et al.,* 1984). Orally administered aspirin requires high and frequent dosing because it undergoes extensive presystemic hydrolysis in the gut and liver into salicylic acid which is devoid of antiplatelet activity. Continuous exposure of new platelets to aspirin is necessary to achieve inhibition of platelet aggregation (Krishna *et al,* 2000)4. The major side effects of NSAIDs are gastric irritation and ulceration due to inhibition of cyclooxygenase (Fowler, 1979)5. It has also been reported that (Dr. Krishna *et al.* 2000), the efficacy of the asprin (considering the pharmacokinetic parameters), when administered transdermally using a controlled release transdermal preparation of aspirin was better than the conventional multiple oral dosage. Since long-term very frequent oral dosing with aspirin tablet (every 2-3 hrs) is not practical. In the present study, the matrix type patches of aspirin were prepared using different polymer i.e. chitosan, Eudragit RL 100, PEG 4000, with and without penetration enhancer (propylene glycol) in order to overcome these drawbacks of aspirin. Aspirin could be delivered transdermally by patch at a dose that suppresses platelet COX, but low delivery rates due to extensive hydrolysis in skin, have been reported. The low bioavailability of dermal aspirin and the avoidance of direct contact with COX-1 expressed on gastric mucosal cells may provide a safer means of inhibiting platelet function (Keimowitz, 1996)6. The goal of present study was to design transdermal delivery of aspirin characterized by high therapeutic efficacy and safety. Two main strategies were implemented. In the first strategy matrix type patches of aspirin were formulated with different combinations, in order to optimize drug release and permeation through skin. The second strategy involved incorporation and evaluation of penetration enhancer (propylene glycol).

Aspirin was selected as a candidate for the drug delivery because

a. It has a low molecular weight 180.157 g/mol
b. It has a low melting point i.e. 1350C.
c. It has an elimination plasma half-life of 15-20 min.
d. It causes gastric irritation and ulceration due to inhibition of cyclooxygenase (Fowler, 1979)[6].
e. It is used for a long period.
f. It undergoes extensive first pass metabolism
g. It has log P (lipophilic character) value of 1.426.

EXPERIMENTALS

Material

Aspirin was obtained as a gift sample from Elder Pharmaceuticals (Pvt) Ltd Mumbai. Eudragit RS 100 (Rhom Pharma GmbH, Germany), Chitosan was obtained as a gift sample from Fischeries Research Center, Cochin, India. PEG 4000 (C.D.H. Delhi). Acetic acid (Glaxo India Ltd. Mumbai) and dichloromethane (C.D.H. Delhi) were used as the solvent. Castor oil and glycerine were used as the plasticizer. Propylene glycol (C.D.H. Delhi) was used as the Penetration enhancer. All the reagents and solvents used were of analytical grade.

General procedure for fabricating the drug free films

A fixed volume of polymer solution with plasticizer was poured onto a glass petridish of area 56.77 cm2 (inner diameter 8.5 cm and height 2 cm). The Petridish was placed on an even and smooth surface to ensure uniform spreading of the polymer solution. It was then placed in an oven. An inverted funnel was placed on the Petridish to facilitate the evaporation of the solvent at the controlled rate over the drying periods of 12 hrs at 40 °C. The film thus formed was retrieved by cutting along the edges with a sharp razor blade.

General procedure for fabricating the drug loaded polymeric films

The compositions of the patches are shown in Table 1. The drug loaded polymeric films were prepared in a similar manner described above except that a weighed quantity of the drug aspirin was dissolved to the polymer solution containingthe plasticizer.For the preparation of the patches containing penetration enhancer (20% propylene glycol) was incorporated by proper mixing rest compositions of the transdermal patches remains the same.

Table 1: Compositions of the Transdermal Patches (without drug)

Batch code	Polymer Ratio	Solvent	Plasticizer (% to the weight of Polymer)
A	CH : 100	Acetic acid(1 %w/v)	Glycerine (20%)
A1	EuRS100 : PVPK30:: 80:20	Dichloromethane (2%w/v)	Castor oil (20%)
A2	EuRS 100 : PVPK 30 :: 70: 30	Dichloromethane (2%w/v)	Castor oil (20%)
A3	EuRS 100 : PVPK 30 :: 60 : 40	Dichloromethane (2%w/v)	Castor oil (20%)
B1	CH:PEG 4000 :: 80:20	Acetic acid(1%w/v)	Glycerine (20%)
B2	CH:PEG 4000 :: 20: 80	Acetic acid(1%w/v)	Glycerine (20%)
B3	CH:PEG 4000 :: 70:30	Acetic acid(1%w/v)	Glycerine (20%)
B4	CH:PEG 4000 :: 30:70	Acetic acid(1%w/v)	Glycerine (20%)

CH-Chitosan , PVPK30 –Polyvinylpyrrolidone K30, EuRS 100-Eudragit RS 100, PEG 4000- Polyethylene glycol 4000

Evaluation

The prepared transdermal patches were evaluated in terms of the physical properties, *in-vitro* release and *in-vitro* skin permeation studies. For the evaluation of the patches a particular number of the patches were selected in order to find out the standard deviation to check the versatility of the results in the batches.

Physical properties

Thickness[7]

The thickness of each film was measured at five different places by means of a screw gauge. The data shown in table-2 are the average of the thickness of five measurements.

Weight uniformity[7]

Five patches (area = 2.009 cm2) of each film were weighed accurately and the average weight of the patch was found out. The observations are recorded in Table 2

Content uniformity[7]

To determine the amount of aspirin in the patches, the patch of 2.009 cm2 area was dissolved in 10ml of phosphate buffer solution (pH 7.4) and then after dilution the amount was measured spectrophotometrically at 296 nm. Results are shown in Table 2.

Folding endurance[7]

The folding endurance of the patch was determined by repeatedly folding one patch at the same place up to 290 times, which was considered satisfactory to reveal good patch properties. The number of times the patch could be folded at the same place without breaking gave the value of folding endurance.

Table 2: Physical characterization of transdermal patches

Batch code	Physical apperance	Thickness (mm)±SD[b]	Mass uniformit y(mg)±SD[b]	%Drug content± SD[a]	%Moisture content ±SD[a]	%Moisture Absoprtion SD[a]	%Moisture loss ± SD[a]	Water vapour transmission Rate (g/cm²/ hrs)±SD[a]	Folding endrance[a]	Flatness
A	Smooth flexible	0.036±0.01	44.5+0.034	97.19+0.056	3.11±0.114	7.330±0.134	3.359±0.104	1.757×10^{-4} ±0.237	>230	100%
A1	Smooth tough	0.032 ±0.007	47.7 ±0.002	97.80±0.078	2.60 ±0.103	4.047 ± 0.089	2.844 ±0.157	1.499×10^{-4} ±0.312	> 275	100%
A2	Hard and tough	0.038 ±0.007	45.8 ±0.001	97.65±0.098	2.736 ±0.106	4.055 ± 0.071	3.199 ±0.087	1.601×10^{-4} ±0.438	> 275	100%
A3	Hard and brittle	0.040 ±0.006	47.2 ±0.001	97.32±0.125	2.743 ±0.130	4.148 ± 0.034	3.438 ±0.046	1.693×10^{-4} ±0.467	> 275	100%
B1	Smooth flexible but wrinkled	0.038 ±0.005	47.3 ±0.002	96.99±0.098	3.318 ±0.154	7.994 ± 0.098	3.532 ±0.099	1.882×10^{-4} ±0.238	> 230	100%
B2	Smooth tough	0.034 ±0.008	45.7 ±0.003	96.85±0.092	3.364 ±0.072	8.106 ± 0.073	3.688 ±0.168	2.522×10^{-4} ±0.136	> 230	100%
B3	Hard and tough	0.036 ±0.010	47.1 ±0.002	96.79±0.096	3.224 ±0.068	8.078 ± 0.148	3.642 ±0.168	2.034×10^{-4} ±0.358	> 230	100%
B4	Hard and brittle	0.036±0.004	47.0 ±0.001	96.65±0.087	3.359 ±0.109	8.102 ± 0.007	3.659 ±0.116	2.439×10^{-4} ± 0.453	> 230	100%

Percentage moisture loss[7]

The films were weighted accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula.

$$\%M.L. = \frac{\text{Initial Weight - Final weight}}{\text{Initial Weight}} \times 100$$

Percentage moisture content[7]

The prepared films were weighed individually and kept in a dessicator containing silica at room temperature and the films were weighed again and again until they showed a constant weight. The percentage moisture content was calculatedusing the following formula.

$$\%M.C. = \frac{\text{Initial Weight - Final weight}}{\text{Initial Weight}} \times 100$$

Percentage moisture absorption[8]

The films were weighed accurately and placed in the desiccator containing 100 ml of saturated solution of aluminium chloride which maintains 79.50% RH. After 3 days the films were taken out and weighed. The percentage moisture absorption was calculated using the formula.

$$\%M.A. = \frac{\text{Initial Weight - Final weight}}{\text{Initial Weight}} \times 100$$

Water vapour transmission rate (WVTR)[8]

For this study vials of equal diameter were used as transmission cells. These cells were washed thoroughly an dried in an oven. About 1.0 g of fused calcium chloride was taken in the cells and the polymeric films measuring 2.009 cm2 area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight is recorded and then kept in a closed desiccator containing saturated solution of potassium chloride (200ml), containing humidity between 80-90% RH. The cells were taken out and weighed after 1, 2, 3, 4, 5, 6, and 7th day of storage. From increase in the weights the amount of water vapour transmitted and rate at which water vapour transmitted were calculated as shown below.

$$WVTR = \frac{\text{Initial Weight - Final weight}}{\text{Time} \times \text{Area}}$$

Flatness[8]

Longitudinal strips of 1.6 cm in length were cut out from the prepared medicated film and than variation in the lengths due to the nonuniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero percentconstriction was considered to be equal to a hundred percent flatness

$$\text{Constriction}(\%) = \left(\frac{11\text{-}12}{l_2}\right) \times 100$$

l_1 = final length of each strip, and l_2 =initial length

***In-vitro* release studies**

A modified Franz-diffusion cell which is also called Keshary – Chein cell was fabricated to study the *in-vitro* release profile as well as the permeation of aspirin from the films of diffusion cell with an improved efficiency in fluid mixing. The diffusion cell consists of two cylindrical compartments in vertical arrangement, a donor compartment which was exposed to ambient temperature and a receptor compartment, which was maintained at 37°C . The receptor compartment has a sampling port for removing samples at different time intervals. The two compartments were held together ith the help of rubber bands. The solution hydrodynamics in the receptor compartment was kept constant by the rotation of the magnetic bead. For the *in-vitro* study the patches were stuck to an aluminum foil which was previously cut to have a diameter of 2 cm and a slightly larger patch was fixed using an water-impermeable adhesive to ensure that the receptor fluid does not come in contact with the sides of the films. Before placing the patch fixed on to the diffusion cell, the mouth of the cell was coated with a thin layer of silicone grease to prevent leakage of the receptor fluid 1 ml of the receptor fluid was withdrawn at periodic interval for 11 hrs. It was immediately replaced with 1 ml of fresh drug free buffer (pH 5.0) solution to maintain constant volume. The fluid removed, after suitable dilution with phosphate buffer was analyzed spectro-photometrically at 296 nm and the concentration were noted from the calibration curve .

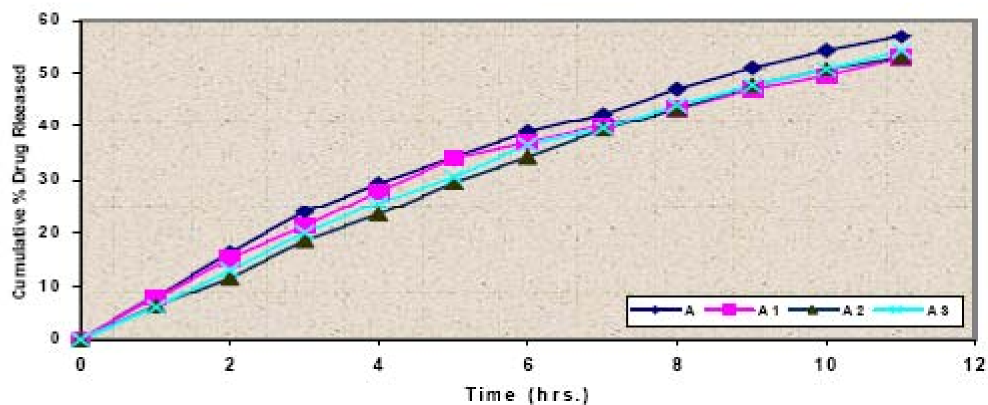

Fig. 1: Cumulative percentage of in-vitro drug released from batch A to A3

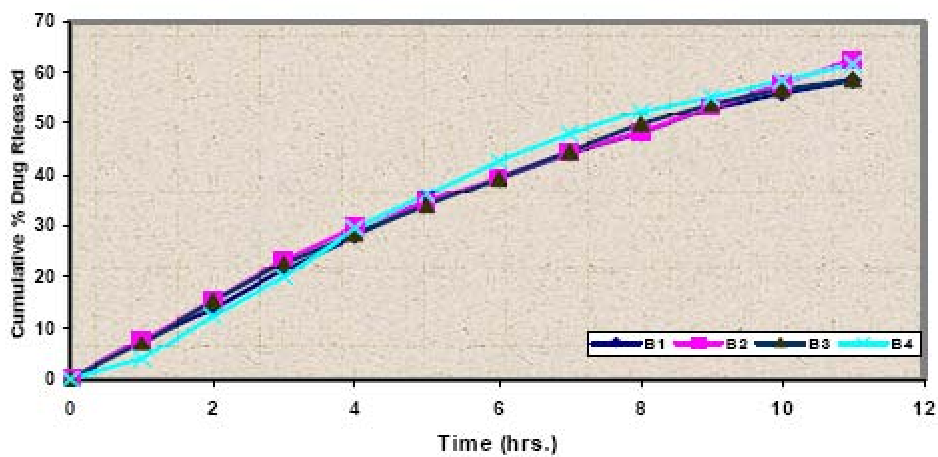

Fig. 2: Cumulative percentage of in-vitro drug released from batch B to B4

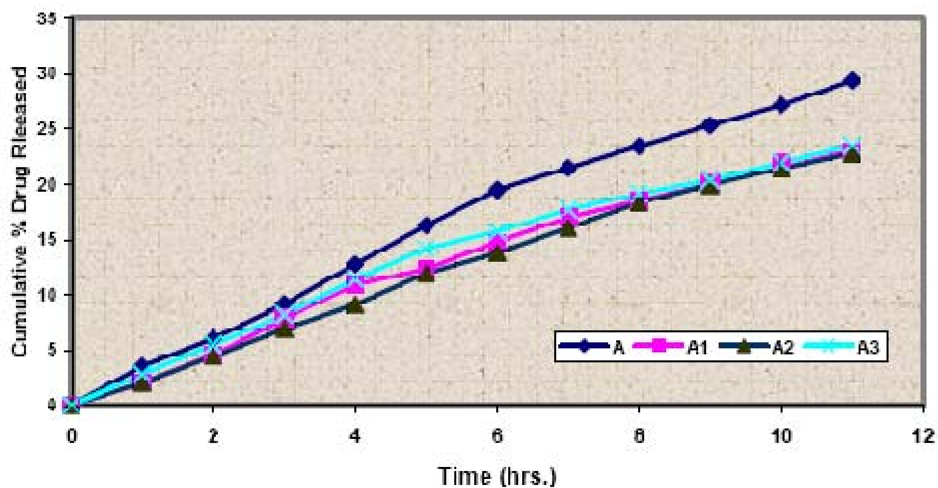

Fig. 3: Cumulative percentage of drug permeated across excised rat skin from batch A to A3

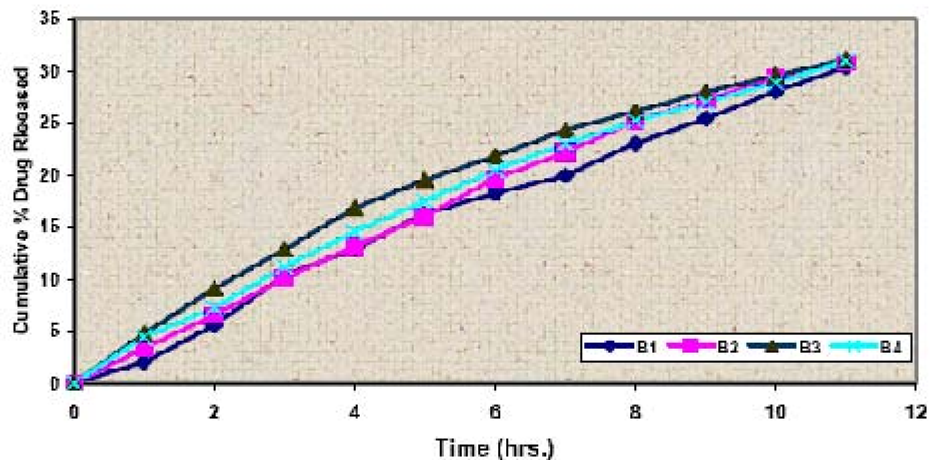

Fig. 4: Cumulative percentage of drug permeated across excised rat skin from batch B1 to B4

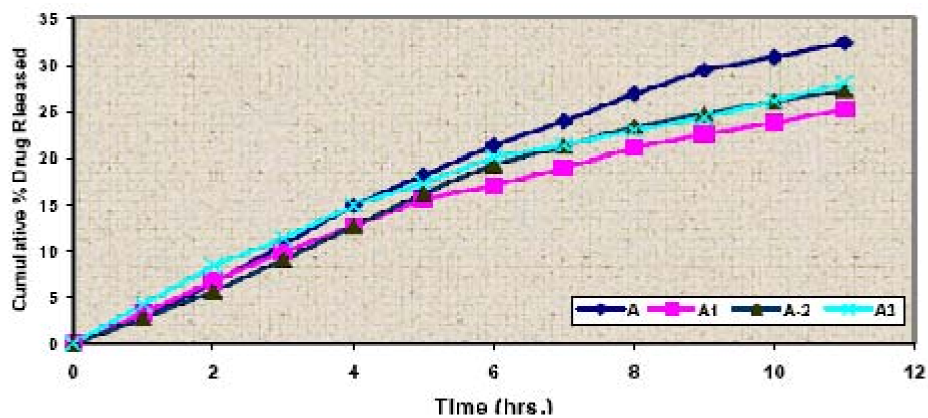

Fig. 5: Permentation of drug from batch A to A3 containing penetration enhancer (20% Propylene Glycol) across excised rat skin

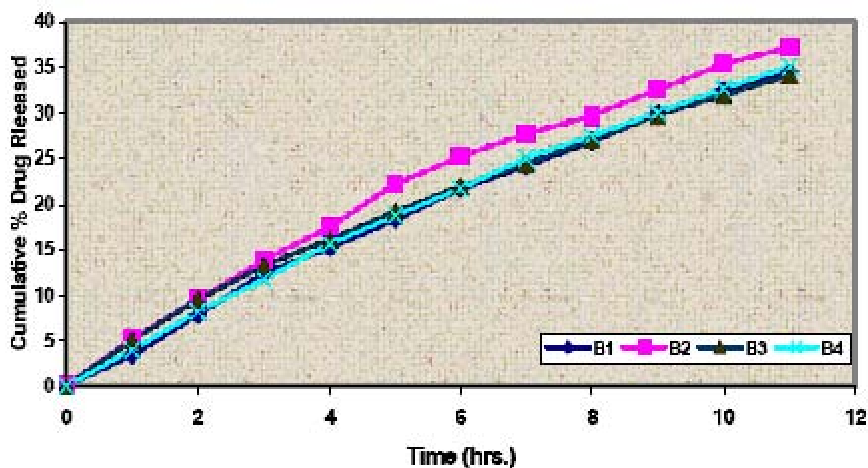

Fig. 6: Permentation of drug from batch B1 to B4 containing penetration enhancer (20% Propylene Glycol) across excised rat skin

Preparation of rat skin for permeation studies

Albino rats of both sexes weighing between 150 - 200 gms were used for the studies. The rats were sacrificed by giving overdose of inhalation of chloroform. Then the hairs from the abdominal region were removed first by using a scissor. Special care was taken while removing the hairs so as not to disturb the stratum corneum. Complete removal of the hair was accomplished by using depilatory cream. After an interval of 10 minutes of applying cream the abdominal region was cleaned thoroughly with a wet cotton swab gently in order to remove any traces of depilatory. A piece of full thickness skin sample was excised from the hairless abdominal region. The dermal side of the skin was cleaned off any adhering subcutaneous tissues and /or blood vessels and the skin free from any adhering subcutaneous tissues was used for the permeation studies.

***In-vitro* permeation studies across freshly excised Rat skin**

Freshly excised rat skin (with stratum corneum intact) prepared as described above was mounted on the receptor compartment of the permeation cell, with the stratum corneum facing upwards and the dermis side facing downwards into the receptor compartment. Films of area 2.009 cm2 were cut with the help of cork borer and films were placed on the skin in intimate contact with the stratum corneum. A sheet of aluminium foil was kept over the film, which acted as the backing membrane as well as to fix the film properly in intimate contact with the skin. The donor compartment was kept on the receptor compartment and secured tightly with the help of rubber bands. Phosphate buffer pH 7.4 containing the 20 % w/v PEG 400 and 0.002 % gentamycin as the anti-bacterial agent serving as the elution medium, was placed in receptor compartment through the sampling port and checked for the absence of any air bubble under the skin. A magnetic bead was rotated at a constant speed for maintaining the hydrodynamics of the receptor fluid constant throughout the study and the temperature of the receptor fluid was maintained at 37 ºC with the help of a thermostat.The amount of drug that released from the transdermal patch and permeated through the skin was determined by removing 1 ml samples at periodic interval for 11hrs. The samples were replaced with the same volume of drug free phosphate buffer containing 20 % PEG 400 to keep the volume of the receptor compartment constant and also to ensure an intimate contact between the dermal surface of the skin and the uniformity studies proved that the receptor solution. The aliquots removed were analyzed spectrophotometrically after suitable dilution and the absorbance were noted at 296 nm using drug free phosphate buffer as the reagent blank and the concentrations were noted from calibration curve.

RESULTS AND DISCUSSION

Matrix type transdermal patches of aspirin were formulated using different polymers i.e. chitosan, PVPK30, PEG4000, Eudragit RS100, in different ratios. The prepared patches were evaluated for the physical properties, *in-vitro* drug release studies*, in-vitro* skin permeation studies.

Physical properties of transdermal patches

Thickness, weight uniformity and % drug content

Though the average thicknesses were almost uniform within same formulation a small variation in thickness was observed with different formulations. The variations in thickness may be attributed to viscosity of polymer solutions of different formulations. The other reasons may be due to lack of temperature control which have affected the controlled evaporation of solvent from the wet film surface. An increase or decrease in thickness had a direct relationship with weight of the patch and drug content.The % drug content analysis of 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 amount of aspirin in each patch of 2.009 cm2 was found to be fairly uniform containing 13-15 mg of aspirin.

% Moisture loss (% ML), % Moisture content (% MC), % Moisture absorption (% MA), Water vapour tTransmission rate (WVTR)

Data are shown in table 2 and 3.The least values of the % MA, % ML, % MC, WVTR in the patches containing Eudragit RS 100 can be explained on the basis of hydrophilicity, which is least in Eudragit RS 100 whereas PVPK30 and PEG 4000 are the hydrophilic polymer.

Folding endurance

Data are shown in table 2. The folding endurance was measuredmanually; films were folded 290 times and if the films shows any cracks it wastaken as the end point.The folding endurance represents the elasticity of the patches.

***In-vitro* release studies**

The % drug released profile from the patches are shown in figure 1 and 2.Transdermal drug delivery system based on chitosan formulated with PVP K30 showed a significantly higher steady state transdermal flux and those that was based on Eudragit RS 100 and PEG 4000 showed the least transdermal flux.These results may be attributed to the hydrophilic order of the polymers PVP K30. Chitosan are more hydrophilic as compared to Eudragit RS 100. Hydrophobic polymer have less affinity for water this results in decrease in thermodynamic activity of the drug in the film and decreased drug release. The drug release was found to increase on increasing the concentration of hydrophilic polymer in the polymer matrix. This is due to the facts that dissolution of the aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to a decrease in the mean diffusional path length of the drug molecules to release into the diffusion medium and hence to higher release rates[9].

***In-vitro* skin permeation studies**

In-vitro skin permeation studies and patches were performed using Keshary Chien type diffusion cell across freshly excised rat skin. Two Keshary Chien type diffusion cells were used in the present study. The % drug permeated profile from the patches are shown in Fig. 3 and 4. The maximum % drug was permeated in patches containing chitosan and PVPK30 and least drug was permeated in patches containing Eudragit RS 100 and PEG 4000. Initial rapid permeation was observed gradually approaching constant values for the rest of the time thus conforming to the controlled release behavior of the formulations. The burst effect would be beneficial since it would help to achieve the therapeutic plasma concentrations of the drug in minimum time and the constant release later on would then provide a sustained and controlled released of the drug. Burst effect might be due to the initial migration of the drug towards the surface of the matrix10.The cumulative amounts of drug permeated increased as the concentration of PVP K30 and PEG 4000 increased in the patches which may be due to the high solubility of these hydrophilic polymers that leads to accumulation of high amounts of drug on the skin Also the high solubility of the hydrophilic portion of the film leads to pore formation on the film surface and leads to higher release rates. Also PVP K 30 has antinucleating effect that converts crystalline drug into higher energy amorphous state with improved solubility.The effect of 20% propylene glycol on the permeation profile of aspirin from transdermal patches was investigated and shown in Fig. 5 and 6. The data revealed that incorporation of 20% propylene glycol led to a slight increase in permeation profile. This may be due to the role of propylene glycol as a cosolvent, which not only solubilizes aspirin but also can alter the the skin structure, thereby modifying the percutaneous absorption (Bendas *et al.* 1995 [11])

CONCLUSION

1. From *in-vitro* drug released studies it is concluded that by changing the ratio of polymers and solvents, release of aspirin can be controlled.
2. Transdermal patches of aspirin can avoid gastrointestinal side effect and also can avoid its first pass hepatic metabolism.
3. The added advantages of these films are that they possess good transparent nature. Transparent nature reveal that the incorporated drug had dispersed throughout matrix without any change in it,s characters.
4. Therefore it may be concluded that the transdermal patches are suitable system for the controlled release of Aspirin.
5. Further work is required to establish the utility of these transdermal patches through long-term pharmacokinetic studies on human subjects.

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