Research Article

A WAY TO INCREASE EFFECTIVENESS OF PARACETAMOL DRUG THROUGH TRANSDERMAL PATCH

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ABSTRACT

Millions of people around the world suffers from the fever, effective treatment is essential by formulating Transdermal patch. Paracetamol IP traditionally considered as a NSAID, is an effective analgesic and antipyretic fully sold without prescription. The conventional formulations containing high dose as well as required to take the medication frequently so increase the risk factor associated with drug. The present study is an attempt to develop suitable matrix type patch of Paracetamol using blends of Xanthan Gum and HPMC K₄M with polyethylene glycol (PEG-400) as a plasticizer. To get better effect permeation enhancers such as Linseed oil and oleic acid was also incorporated and their optimum concentration was determined. Prepared formulations were evaluated for compatibility, drug content, moisture loss and absorption, thickness, weight variation, adhesion, folding endurance etc. In vitro permeation study was performed by using Franz diffusion cell. Formulations were found to be uniform in physicochemical parameter with a fewer variations and there was no significant interaction between drug and polymer used. Formulation of HPMC K₄M along with Linseed oil showed faster release of drug from developed formulations. Based on the observation, No burst effect but HPMC K₄M are better for faster release with linseed oil and xanthan gum for prolonged release for the development of patch. Stability studies indicated the formulations were remained stable both physically and chemically. All developed formulations showed desired properties of an ideal TDDS and followed zero order rate profile. Thus, the study achieved targets by reduction in frequency of administration and systemic toxicity.

Keywords: Paracetamol IP; Transdermal patch; Permeation enhancer; evaluation; stability study.

INTRODUCTION

In the past two decades, transdermal drug delivery has moved from a clinical reality to the point where it represents a viable diagnostic tool for non-invasive diagnosis. The first challenge is to effective transdermal system ultimately involves ensuring adequate drug permeability through the Stratum corneum (SC).¹ Now-a-days pharmaceutical industries are been able to formulate the transdermal drug delivery system. The idea of using skin for delivery of drug is since ancient time. Several ancient cultures used ointments, pastes, medicated plasters, and complex inductions in the treatment of various symptoms or disease. The prospective of using undamaged skin as the route of drug administration has been known for several years. Historically, the medicated plaster can be viewed as the first development of transdermal drug delivery; this medicated plaster became very popular in Japan as over the-counter pharmaceutical dosage form.² Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin.³ In recent times, development of transdermal delivery system started in 1970s, and in 1979, the first transdermal film of scopolamine was approved by USFDA for the treatment of motion sickness and later on nitroglycerine patch was marketed for the management of angina pectoris.⁴ Henceforth, numbers of drugs categories such as NSAID, antiemetic etc have been successfully delivered

through transdermal route. The drug applied topically is uniformly distributed following by absorption, first into the systemic circulation and then transported to the targeted tissue, which can be relatively remote from the site of drug application to achieve its therapeutic action.⁵

Transdermal drug delivery systems (TDDS) can be defined as self-contained discrete dosage forms which, when applied to the intact skin, delivers the drug(s) through the skin at a controlled rate to the systemic circulation. A Transdermal Drug Delivery (TDD) System is a polymeric drug delivery system, which contains drug either in a reservoir with a rate-controlling membrane or dispersed in a polymer matrix. Drug is released from these devices through the skin and is taken up by the systemic circulation via blood capillaries. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. TDDS offers several advantages such as reduces the dosing frequency, easy termination of therapy, improves bioavailability, provides constant blood level in the plasma and suitable for unconscious patients.⁶ The realization of transdermal delivery system in pharma market is evident as currently more than 35 transdermal drug delivery products are approved in the USA for wide variety of pathophysiological conditions including hypertension, angina pectoris, motion sickness, female menopause, male hypogonadism and approx. 40% of drugs are under investigations to validate the feasibility for transdermal drug delivery.^{7,8} A large number of fatty acids and their esters have been used as permeation enhancers. Oleic acid has been shown to be effective as a permeation enhancer for

many drugs, for example increasing the flux of salicylic acid 28-fold and 5-fluorouracil flux 56-fold, through human skin membranes *in-vitro*.^{9,10} It has also been used for ketoprofen¹¹, flurbiprofen¹², 5-FU, zidovudine¹³ etc. Paracetamol is a widely used over-the-counter analgesic (pain reliever) and antipyretic (fever reducer). It is a very bitter drug; hence it was choice for selection of drug.

MATERIALS AND METHOD

Paracetamol was received as a gift sample from Biocon, Bangalore. India. Hydroxy propyl methyl cellulose K4M (HPMC) and Xanthan Gum was received as a gift sample from Alex Pharmaceutical Pvt. Ltd, anand, India. Polyethylene glycol 400 was purchased from (Rankem chemicals Mumbai India), Dibutylphalate (Loba chemicals, Pvt. Ltd Mumbai India), Linseed oil, Oleic acid was purchased from (Loba chemicals, Pvt. Ltd Mumbai India). Other materials used in the study (chloroform, methanol, dichloromethane, etc.) were of analytical grade. Double distilled water was used throughout the study.

Preformulation Study

Preformulation testing is the first step in the rational development of dosage forms. Preformulation study is the process of optimizing the delivery of drug through the determination of physicochemical properties of new compound that could affect drug performance as a stable dosage form. Confirmation of drug study was carried out by FTIR, Melting point determination by capillary method and DSC.¹⁴

Infrared Spectroscopy

IR spectrum of drug was measured in the solid state by using potassium bromide. FTIR spectra of Paracetamol IP were obtained by using a FTIR spectrometer-8400. The samples were previously ground and mixed thoroughly with potassium bromide (KBr), an infrared transparent matrix at 1:1000 (sample: KBr) ratio, By compressing the powder mixture, under force of 15 tonnes for 5 min in a motorized pellet press. The obtained peaks were compared with the reference standard IR spectrum of the drug.¹⁴

Melting point determination by Capillary and by DSC method

Melting point determination was done by Thiel's tube method. Drug was filled into capillary tube and tied to the thermometer in a way that it remains dipping in liquid paraffin bath. Then note down the temperature at which drug started melting and complete melting was noted ^[15]. Melting point of drug was also confirmed by DSC, thermogram of Paracetamol IP was obtained, using DSC. Hermetically (Completely sealed) sealed drug in perforated aluminum pans and heated at constant rate of 10°C/min over the temperature ranges of 35-300°C.¹⁴

Drug-Excipients compatibility Studies

The drug-excipients compatibility study was carried out by using FTIR and DSC.

FTIR spectra of pure drug and the mixture of polymers were taken to study the interaction between them. A mixture of with HPMC-K4M and xanthan Gum were mixed separately with IR grade KBr in the ratio of 100:1 and compressed using motorized pellet press at 15 tones pressure [17]. Drug-excipients compatibility study was also performed by Differential Scanning calorimetry (DSC). Melting point of drug was also confirmed by DSC, thermogram of paracetamol was obtained, using DSC. Hermetically sealed drug and polymer in perforated aluminum pans and heated at constant rate of 100C/min over the temperature ranges of 35-3000C.

Formulation of Transdermal patch:

TDDS of Paracetamol drug was composed by different concentrations of Hydroxypropyl methyl cellulose K4M and xanthan gum by the solvent casting techniques. Polymer was dissolved in a 5ml solvent of containing (Dichloromethane/methanol) (4:1) ratio by, which is previously dissolved by putting the solution on magnetic stirrer (rpm 60/min). The drug was then added to the above polymeric solution along with PEG-400, as plasticizer, and penetration enhancer, which was the-roughly mixed on magnetic stirrer (Rpm 60/min) to form a homogeneous mixture. The volume was made up to 10-ml. Entrapped air bubbles were removed by applying ultra sonicator. The solution was poured on the mercury placed in a glass Petri dish of 36.29 cm² area and dried at room temperature for 24 hr. then cut into the required size to deliver the equivalent dose (2 × 2cm² per patch) of drug and then the samples were wrapped in a aluminum foil, kept in a desiccator until its use. ¹⁵

Table 1: Composition of different formulations containing Paracetamol IP

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Drug(mg)	100	100	100	100	100	100	100	100
HPMC K4M	150	150	250	250				
Xanthan Gum					200	200	300	300
PEG 400 (%w/v)	15	15	15	15	15	15	15	15
Linseed Oil	3	5			3	5		
Oleic Acid			3	5			3	5
DW(%)	100	100	100	100	100	100	100	100
(Dichlo-methane/methanol)	5	5	5	5	5	5	5	5

Evaluation of Transdermal Patches

Thickness Uniformity

The thickness of the patch was assessed by using Digimatic Micrometer (Mitutoyo, Japan) at different points of the patch, from each formulation three randomly selected and their average was calculated. The standard deviations of thickness were computed from the mean value.¹⁵

Weight variation

Weight variation study was carried out by individually weighing 3 randomly selected patches. Such determination should be performed for each formulation. Patches from each batch were weighed individually and the average weight and SD was calculated.¹⁶

Folding Endurance

The folding endurance was determined by repeatedly folding one patch at the same place till it broke. The number of times of Patch could be folded at the same place without breaking give

the value of the folding endurance. This test was done on all the batches.¹⁷

Drug Content Uniformity

The patches at (2x 2 cm²), were cut and added to a beaker containing 100ml of Phosphate buffered solution of pH 7.4. To check the uniformity of the drug in the patch, three patches were taken out from each batch. Each Patch was then placed in volumetric flask containing 100ml of Phosphate buffered solution of pH 7.4, and shaken to extract the drug from patch overnight period. One milliliter of above resulting solution was withdrawn, after suitable 10 ml dilution with Phosphate buffered solution of pH 7.4 and analyzed UV-spectrophotometrically at 249 nm using Phosphate buffered solution of pH 7.4. The mean and standard deviation of drug content of three randomly selected patches were calculated. The same procedure was adopted for all the batches and drug content was noted.¹⁵

Tensile Strength

Tensile strength of the Patch was determined with "Texture analyzer" testing machine. It consists of two load cell grips. The lower one is fixed and upper one is movable. The test strip of specific size (3 x 1 cm²) was fixed between these cell grips and force was gradually applied till the patch breaks. The tensile strength of the Patch was taken directly from the dial reading. The tensile strength was calculated by applying the following equation. Same procedure was repeated for three times and standard deviation was calculated from mean values.¹⁷

$$\text{Tensile strength} = \text{Load at failure} / \text{Area of Patch} \times 100$$

Percentage Moisture Loss Test

Percentage moisture loss was determined by keeping the Films (2 x 2 cm²) in a desiccator containing anhydrous calcium chloride. After 3 days, the Films were taken out, re-weighed and the percentage moisture loss was calculated using the following formula;¹⁵

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Percentage Moisture up take Test

Percentage moisture uptake was determined by keeping the Films (2 x 2 cm²) in a desiccator. A weighed film kept in desiccators at 40°C for 24h was taken out and exposed to saturated solution of potassium chloride in order to maintain 84% RH. After 24hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula;¹⁵

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

In Vitro drug release study

The *in vitro* diffusion studies were carried out to get an idea of permeation of drug through barrier from the transdermal system. *In vitro* diffusion study was carried out with the cellophane membrane (0.4μ) by using Franz diffusion cell. The cylinder consists of two chambers, the donor, and the receptor compartment. The donor compartment was open at the top and was exposed to atmosphere. The temperature was maintained at 32±0.5° C and receptor compartment was provided with sampling port. The diffusion medium used was phosphate buffer (pH 7.4). *In vitro* drug release study was performed by placing patch of known weight and dimension (2×2 cm²) into small beaker containing 10ml of PBS pH 7.4. The beaker was placed on magnetic stirrer at 30 rpm. At periodic interval, the samples were taken and the drug content was analyzed at 249 nm against

reference standard using PBS pH 7.4 as a blank on a UV-visible spectrophotometer (Shimadzu Inc., Japan).^{16,17}

Stability Study

Stability study was performed on optimized formulation, according to ICH guidelines by storing replicates of Patches (packaged in aluminium foil) in a humidity chamber, with a relative humidity a temperature of 40±0.5 °C 70±5 RH%. At periodic intervals, the samples were taken out at 0, 15, 45, and 90 days and the period for their degradation of the patch was checked. Samples were also analyzed for drug content.^{16,17}

RESULT AND DISCUSSION

Preformulation studies

Table 2: Preformulation data for Paracetamol IP

Description	white Solid powder
Melting point	167-170°C
λ max	249nm
Partition coefficient (log P)	0.46
pH	5.9
pKa	8.9

Melting point determination

Melting point of Paracetamol was measured; and found to be in the range of 167.89-169.63°C. It was confirmed with the reported melting point of paracetamol. It was also confirmed by differential scanning Calorimetry at scanning rate of 10°C/min it exhibits a sharp melting endothermic peak at temperature of 169.63°C as shown in figure.

Compatibility study was carried out by using FTIR and DSC by the use of drug & excipients. The Individual IR spectra of pure drug and polymer as well as the combination spectra of the drug and polymer were taken, which indicates that there were no interaction between drug added and polymers when compared with spectrum of paracetamol, as all functional group frequencies were present. The DSC thermogram of formulation showed identical peaks correspondingly, to pure drug there was no chemical interaction between drug and polymers.

Figure 1: DSC Thermogram of Paracetamol

Thickness of drug-loaded patches was measured with the help of screw gauge. Film thickness was found in the range 0.072 ± 0.0447 to 0.119 ± 0.0537. It means that the concentration of polymer does not show any significant change in the thickness of the film. The concentration of plasticizer did not alter the change in the thickness of patch indicate that they are uniform in thickness. The weight of the patch was found to be in the range of 0.0102 ± 0.04 to 0.0193±0.012 gm. Uniformity of the patches shows the good distribution of the excipients. As the Increasing polymeric concentration weight of patch also Increases. Each reading is an average of three determinations. The folding endurance of the patch was found to be in the range of 195 to

389. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. Folding endurance was found to be highest for F2 and lowest for F3 as shown in table. The change in the concentration of polymers and permeation enhancer did not show the difference in the folding endurance of patch. The value of folding endurance exhibited good physical and mechanical properties. For the uniform dispersion of drug in patch, the drug content study was performed. The content uniformity of drug was analyzed at 249 nm with a suitable blank. The results were expressed in $AM \pm SD$ and reported in table. The below mentioned values indicated that the drug was uniformly dispersed within the formulations. Good uniformity of drug content among the batches was observed with all formulations and ranged from $97.9 \pm 0.8 \%$ to $99.2 \pm 0.07 \%$. The results

indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability. The mechanical properties of patches were evaluated using a texture analyzer. The peak load and the area under load distance curve obtained from the texture profile were used to assess the tensile strength of the Patches. The tensile strengths of drug loaded Patches are in the order of $F8 > F7 > F4 > F3 > F6 > F5 > F2 > F1$. Each measurement was repeated three times. The concentration of polymer and plasticizer shows higher effect on tensile strength of patch. When the concentration of HPMC-K4M increases accordingly then the tensile strength also increases. As per above observations, the plasticizer shows effect on tensile strength.

Table 3: Physicochemical characterization of the patches

Batch	Thickness (mm) (AM $\pm$ SD)	Weight Variation (gm) (AM $\pm$ SD)	% Drug Content (AM $\pm$ SD)	Folding Endurance (AM $\pm$ SD)	Tensile Strength (kgcm $^{-2}$) (AM $\pm$ SD)
F1	0.019 $\pm$ 0.05	0.0163 $\pm$ 0.03	98.13 $\pm$ 0.84	195.33 $\pm$ 5.07	1.55 $\pm$ 0.35
F2	0.087 $\pm$ 0.03	0.0102 $\pm$ 0.04	99.26 $\pm$ 1.07	218.33 $\pm$ 3.05	1.15 $\pm$ 0.16
F3	0.093 $\pm$ 0.06	0.012 $\pm$ 0.03	98.57 $\pm$ 2.23	239.66 $\pm$ 1.02	2.41 $\pm$ 0.55
F4	0.072 $\pm$ 0.04	0.0158 $\pm$ 0.01	97.09 $\pm$ 0.80	250.00 $\pm$ 3.05	2.98 $\pm$ 0.15
F5	0.103 $\pm$ 0.06	0.0184 $\pm$ 0.02	99.82 $\pm$ 0.30	256.00 $\pm$ 6.07	1.89 $\pm$ 0.28
F6	0.090 $\pm$ 0.05	0.0193 $\pm$ 0.04	98.14 $\pm$ 1.56	215.96 $\pm$ 4.04	1.63 $\pm$ 0.39
F7	0.019 $\pm$ 0.03	0.0244 $\pm$ 0.05	99.20 $\pm$ 0.07	220.54 $\pm$ 1.04	2.62 $\pm$ 0.02
F8	0.075 $\pm$ 0.01	0.0265 $\pm$ 0.08	98.27 $\pm$ 0.01	202.61 $\pm$ 0.08	3.03 $\pm$ 0.12

Moisture content was found to be increasing with increasing concentration of polymer. The percentage moisture absorption was noted for all the formulations in triplicate. Percentage moisture absorption found to be in between 3.69 (0.13) to 7.31 (0.04). Formulation F4 showed high moisture absorption which may be attributed to a high concentration of HPMC. Polymers present in the above formulations are hydrophilic in nature and can be expected to absorb water. There was very high percentage moisture at the humid condition. However, there was few or no change in the integrity of the film at that condition which was observed by its physical appearance. Low moisture absorption protects the patch from microbial contamination and bulkiness. Moisture content in the patches were found to be low, low moisture content helps them to remain stable and from being completely dried and brittle. The capacity of Patch to take up water is an intrinsic parameter of the polymeric system in consideration to release of drug.

Figure 2: Percentage Moisture absorption

Cumulative in-vitro drug release study was performed in PBS pH 7.4. The drug release profile is an important tool that predicts in advance how a drug will diffuse and targeted. In the present study, an HPMC K4M and xanthan gum polymer was used to prepared patches. Formulation F7 exhibited $98.65 \pm 5.4 \%$ of drug release at the end of 12 h, while formulation F1 exhibits $89.4 \pm 3.3 \%$ of drug release upto 6 h only. The cumulative

amount of drug released from formulations containing high concentration of polymer shows extended release of drug which contains less concentration of permeation enhancer.

Figure 3: In-vitro drug release study of formulation F1-F8

In vitro drug release study indicated that the release of drug varied from the formulation batches according to concentration of polymers and permeation enhancer utilized. As prepared, the concentration of xanthan increases gradually the release of drug was decreased. The variation in permeation enhancer in different formulation shows effect on release of drug. Linseed oil incorporated patches shows better drug release as compared to the oleic acid formulation F1, F2, F4 & F6 shows faster release rate because formulation containing low concentration of HPMC and Linseed oil. F7 batch shows sustain drug release 98.65 ± 1.5 but as compared to that batch F5, higher cumulative $99.34 \pm 1.5 \%$ in vitro releases was observed. The drug release from the patch was ordered as $F1 > F2 > F6 > F5 > F4 > F3 > F8 > F7$. Accelerated Stability Studies Results are showed no major differences was found between evaluated parameters before and after ageing/storing and all were found to be in acceptable limits.

In conclusion, transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood levels for longer period resulting in a reduction of dosing frequency, improved bioavailability, and

decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and hence improved patient compliance. The formulated transdermal patch as a drug delivery system promising the approach, which is utilized for improving therapeutic efficacy of paracetamol in the treatment of Fever. The use of polymer such as HPMC and Xanthan Gum showed their effect on release profile. Plasticizer PEG-400, and Dichloromethane/methanol as solvent showed better-mechanical properties of patches as well as the permeation enhancer showed their effect on release of drug over the period of 12 hours. Hence, in future such type of drug delivery system may utilize for the management of fever and inflammation.

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