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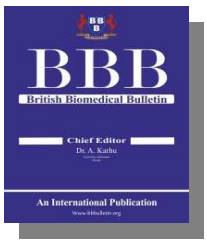

Original

Effectiveness of Sodium CMC as a Polymer for the Development of Transdermal Patches Containing Paracetamol IP in Paediatric Category

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A B S T R A C T

Paracetamol IP traditionally considered as a NSAID, is an effective analgesic and antipyretic drug available as over the counter without prescription. Paracetamol IP is used widely in all age groups and it has intensely bitter taste which makes it difficult to administer in children. The current study is an attempt to develop transdermal patches of Paracetamol IP for paediatric patients by solvent evaporation method (with slight modifications) using a hydrophilic polymer, Na CMC in combination with polyvinyl pyrrolidone and glycerin as plasticizer. To improve the effective permeation of Paracetamol IP through skin, permeation enhancers such as 5% of oleic acid, menthol and ethanol are incorporated. All the developed transdermal patches showed desired properties of an ideal TDDS and followed ideal zero order kinetics. Formulation containing 5% menthol as permeation enhancer showed higher release rates.

Introduction

Transdermal drug delivery systems [TDDS] are self contained, discrete dosage forms which when applied to intact skin deliver the drug through skin at controlled rate into systemic circulation[1]. TDDS have advantages such as improved patient compliance, ability of site targeting, non-invasiveness and avoid first pass effect. TDDS are superior in terms of safety and convenience. Hence it is most preferred drug delivery system over oral and invasive conventional drug delivery systems[2]. A transdermal drug delivery device which may be of an active or a passive design, which provides an alternative route for administering medicaments. Transdermal delivery not only provides controlled and constant administration of the drug, but also allows continuous input of drugs with short biological half-life and eliminates pulsed entry into systemic circulations, which may result in undesirable side effects[3].

Transdermal drug delivery systems may depend on following factors[4].

(a) Physicochemical properties of drug and polymers used.

(b) Pharmaceutical or formulation factors.

(c) Physiological factors.

Generally there are four types of transdermal drug delivery systems,

- Membrane permeation controlled systems.
- Matrix diffusion controlled system.
- Adhesive dispersion type system.
- Micro reservoir type or micro sealed dissolution controlled systems.

Membrane permeation controlled systems

In this system, the drug reservoir is totally encapsulated in a shallow compartment moulded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane e.g. Ethylene vinyl acetate with defined drug permeability (Fig No.1). The drug molecules are permitted to release only through the rate-controlling membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid-polymer matrix or suspended in a viscous liquid medium to form a paste like suspension. A thin layer of adhesive polymer is applied to the external surface of the rate-controlling membrane to achieve an intimate contact of the transdermal system and the skin surface[5].

Matrix diffusion-controlled system

In this approach, the drug reservoir is prepared by homogenously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness. This drug reservoir containing polymer disc is then pasted on to an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing. The adhesive polymer is then spread along the circumference to form a strip of adhesive rim around the medicated disc[5] (Fig No.2).

Adhesive dispersion type system

This is a simplified form of the membrane permeation controlled system. The drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive by solvent casting or hot melt onto a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the top of the drug reservoir layer, thin layers of non-medicated, rate-controlling adhesive polymer of a specific permeability are applied to produce an adhesive diffusion-controlled delivery system[5] (Fig No.3).

Micro reservoir type or micro sealed dissolution controlled systems

Here, the drug reservoir is formed by first suspending the drug solids in an

aqueous solution of a water soluble liquid polymer and then dispersing the drug suspension homogenously in a lipophilic polymer by high shear mechanical force to form a large number of micro reservoirs. These are un-leachable microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by the addition of cross linking agent like gluteraldehyde which produces a medicated polymer disc with a constant surface area and a fixed thickness. A transdermal therapeutic system is produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim and then it is spread on to the occlusive base plate with adhesive foam pad[5] (Fig No.4).

Basic components of TDDS are as follows

- Polymer matrix /Drug reservoir.
- Drug Permeation enhancers.
- Pressure sensitive adhesive (PSA).
- Backing laminates.
- Release liner.
- Other excipients like plasticizers and solvents.

Polymers are the backbone of a transdermal drug delivery system (TDDS). TDDS are fabricated as multilayered polymeric laminates in which a drug reservoir or a drug-polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and / or rate-controlling membrane[6].

Polymers are used in transdermal delivery systems in various ways, such as

- Matrix formers.
- Rate-controlling membranes.
- Pressure-sensitive adhesives (PSA).
- Backing layers.
- Release liners.

Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the systems such as penetration enhancers and pressure sensitive adhesives (PSAs). They should provide consistent and effective delivery of a drug throughout the product's intended shelf-life or delivery period and should have approved safety profile, e.g. acrylic acid polymers, ethyl cellulose, polyvinyl-pyrrolidone, hydroxy propyl methyl cellulose, organogels etc where as silicone rubber, polyurethane etc are used as rate controlling membranes[6].

Drug should posses the right physicochemical and pharmacokinetic properties. Transdermal patches may be useful to deliver drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic index, drugs with short half-life which causes non-compliance due to frequent dosing and can useful to deliver drugs which produces severe gastrointestinal side effects[4]. To increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug, penetration enhancers may be incorporated into the formulation. The enhancement in absorption of oil soluble drugs is apparently due to the partial leaching of the epidermal lipids by the chemical enhancers, resulting in the improvement of the skin conditions for trans epidermal and trans follicular penetration. The miscibility and solution properties of the enhancers used could be responsible for the enhanced transdermal permeation of water soluble drugs[4].

Various categories of penetration enhancers used in TDDS, as follows[4]

- Terpenes / essential oils
  E.g. cineol, menthol etc
- Pyrrolidones
  E.g. N-methyl-2-pyrrolidone
- Fatty acids and esters
  E.g. oleic acid, linoleic acid etc
- Sulfoxides
  E.g. dimethyl sulfoxide (DMSO)
- Alcohols, glycols and glycerides

E.g. ethanol, propylene glycol etc

- Miscellaneous enhancers like cyclodextrins, enzymes , phospholipids.

Pressure sensitive adhesives (PSA) maintain an intimate contact between patch and the skin surface. It should adhere with not more than applied finger pressure is aggressively and permanently tacky, exert a strong holding force. The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. PSA should be physico-chemically and biologically compatible and should not alter the drug release. The PSA can be positioned on the face of the device (as in case of reservoir system) or in the back of the device with peripheral extension (as in case of matrix system) [4].

Backing layer provides support to the patch. It should be chemical resistant and excipient compatible since the prolonged contact between the backing layer (BL) and the excipients may cause the additives to leach out or may lead to diffusion of excipients, drug or penetration enhancer through the layer. They should have low moisture-vapour transmission rate, optimal elasticity, flexibility and tensile strength, e.g. of some backing materials are an aluminium vapour coated layer, a plastic film (polyethylene, polyvinylchloride, polyester) and a heat seal layer[4].

Release liner prevents loss of the drug that has migrated into the adhesive layer as well as the contamination during storage and it is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. PVC) and a release coating layer made up of silicon or teflon. Other materials used for release liner includes polyester foil and metalized laminate[4]. Solvents such as chloroform, ethanol, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir[4]. Due to toxicity issues for paediatrics, acetone, diluted acetic acid and ethanol may be suitable solvents. In addition, plasticizers such as dibutylphthalate, triethyl citrate, polyethylene glycol, propylene glycol and glycerine are added to provide plasticity to the transdermal patch. Polyethylene glycol and glycerine are commonly used in paediatric patches due to better safety profile[4,7].

Paracetamol IP was selected as the drug for this investigation since it is the most commonly prescribed drug in the paediatric category in India. This molecule is available as tablet or syrup/suspension in the market. One of the major draw back of the molecule is its severe bitter taste which makes it most difficult formulation to consume under paediatric category. In spite of using different taste masking agents the effort seems to be unsuccessful. The suspension/syrups are still tried at highest level in paediatric patients in 125mg and 250mg dosing. These products do contain some of the additives which are proved to be harmful for paediatric category. Hence in this investigation an effort was made to develop the transdermal patch of the most widely prescribed paediatric drug to make it safer and successful in regular use.

Materials and Methods

Paracetamol IP was procured from Balaji chemicals, Gujarat. Sodium CMC Polyvinyl pyrrolidone and Glycerin was bought from Loba Chemi Pvt. Ltd Mumbai. All other chemicals and reagents were supplied from Spectrum Reagents and Chemicals Pvt. Ltd. Chemicals and reagents used were of laboratory grade.

Preparation of transdermal patches of Paracetamol IP

The transdermal patches containing Paracetamol IP were prepared by solvent casting method with required modification[8-

[10]. The specified ratios of polymer solutions were prepared by dissolving required amount of polymers (sodium CMC, HPMC) in 1% acetic acid and stirred by using a mechanical stirrer at 100 rpm for 2hrs. Polyvinyl % of the dry weight of polymer) was added to the above polymer solution and continued the stirring at the same rpm for 1hrs and the resulting polymer solution was plasticized using glycerin (6% of total volume). 10 ml of the above solution was added with calculated amount of Paracetamol IP and specified quantity of permeation enhancers (5% ethanol, 5% oleic acid or 5% menthol). This solution was sonicated for 15 min and kept overnight to remove air bubbles and poured in to a glass mould having a surface area of 34 cm^2. It was dried in room temperature and the dried film were removed and wrapped in aluminium foil and kept in desiccator for further evaluations.

Physical evaluations

All the patches were visually inspected for colour, transparency and smoothness[11,12].

Measurement of thickness (μm)

Thickness of patches was measured using screw gauge with a least count of 0.01 mm at five different spots of the patches and average was taken[11,12].

Weight variation

Ten patches of $1cm^2$ were weighed individually and average was taken. Weight variation of the individual sample from the average was calculated[11,12].

Tensile strength (Kg/cm^2) [11,12]

The instrument used to measure the tensile strength was specially designed in Pharmaceutics laboratory for this project work (Fig No.5). A film of 2.5 cm length was attached to one side hook of the balance and the other side hook was attached to plate fixed up to the pan as shown in figure (Fig No.5).Weights were added to the pan to measure the tensile strength.

Folding endurance

Strip of prepared patch (2X 2cm) was folded repeatedly at the same place till it broke. The number of times the patch could be folded at the same place without breaking is equal to the value of folding endurance[11,12].

% Moisture content

The patches were weighed individually and kept in desiccators containing silica at room temperature for 24hrs. Individual patches were reweighed until they showed a constant weight. The percentage of moisture content was calculated from the difference in weight[11,12].

% Moisture content = Initial weight-Final weight/Final weight.

Estimation of drug content

Prepared patch having an area of 4 cm^2 was dissolved in 50 ml PBS of pH 7.4 and shaken continuously for 24hrs. The solution was sonicated for 15 min. The resulting solution was filtered, made up to 100 ml with PBS of pH 7.4 and further diluted with same and the drug content was estimated by UV spectrophotometer at wavelength of 243 nm[11,12].

In vitro drug release study

The *In vitro* diffusion study of Paracetamol IP from prepared transdermal patches was studied using modified Franz diffusion cell and cellophane membrane. Patches of known weight and dimension were placed on cellophane membrane which was then fixed on to diffusion cell. The diffusion cell was made in contact with PBS of pH 7.4 which was used as receptor

medium for this investigation. The temperature at receptor compartment was maintained at 37±1°C and it was stirred at 100rpm using a magnetic bead stirrer. The system was maintained for 24hrs.5ml sample was withdrawn at every 2 hrs interval for 24 hrs and fresh PBS of pH 7.4 was replaced in equal volume. Withdrawn samples were diluted using PBS of pH 7.4 and Paracetamol IP content was estimated using UV spectrometer at wavelength 242nm[12].

Stability study

Patches (2 x 2 cm2) were wrapped individually in aluminium foil and maintained at oven temperature (45±2ºC) room temperature (30±2ºC) and refrigerated temperature (4±2ºC) for a period of 45 days. Changes in physical appearance and drug content for the stored patches were evaluated.

Results and Discussions

The patches were prepared using Sodium CMC polymer. The drug and polymer were at fixed concentration. The formulations were varied in the basis of permeation enhancers incorporated. Composition of developed formulations were summarised in Table No.1.

The prepared patches were subjected to visual inspection for analyzing its physical appearance in terms of colour and clarity. The visual inspection gave satisfactory results. All the developed patches were white in colour and free of any air entrapments as well as foreign bodies. In spite of the application of heat during the development of the formulations, colour of developed patches were almost same as that of polymers incorporated, which proves that, there is no undesirable reactions has occurred during the process. The physical evaluations indicated that the prepared patches were smooth, flexible and having desirable physical characteristics.

Thickness of all formulations was range between 57 to 59 µm (Table No.2 & Fig No.6). Low deviation value in film thickness measurements ensured uniformity of patches prepared by solvent evaporation technique. Data for patch thickness were matching within the desired range of thickness identified through review of literatures for transdermal patches which varies according to the polymers used[11,13-17].

The data obtained from weight variation analysis of all the formulations showed that there was no significant difference in the weight of individual patch from the average value and the variations were within the acceptable limit ((Table No.3 & Fig No.6). Thus the results show the uniformity of contents in prepared patches. Tensile strength was measured by using an instrument designed and developed exclusively for the project. From the obtained data it was clear that all formulations had sufficient tensile strength, the variations were within acceptable limit (Table No.2).

From the results ((Table No.2), among the formulations, F2 was having highest % moisture content compared to other two (F1 & F3). F2 contains 5% menthol as permeation enhancer which is also hygroscopic in nature. From the extensive review of literatures[25, 41] it was evident that presence of menthol may enhance the moisture absorption of hydrophilic polymers due to its hygroscopic nature. The percentage drug loaded in the Patches was found to be within the range of 93 to 96 % (Table No.3 % Fig No.6) .Since all the formulations have the same polymer concentrations drug entrapped was more or less same in all the patches. Maximum % drug content was reported with formulations F1&F2.The obtained values confirmed the high entrapment efficiency of the sodium CMC [11,13-17].

Irrespective of polymers used, all the patches showed good folding endurance, the values obtained were above 300 in all of the developed patches revealed that the prepared films were having the capacity to withstand the mechanical pressure along with good flexibility (Table No.3 & Fig No.6). Effect of glycerin in flexibility of films as a plasticizer was not closely investigated in this study but it was evident from the literatures [17, 18]. Thus the excellent flexibility of the prepared films was may be due to the presence of glycerin in optimized concentration.

The effective permeation of Paracetamol IP through the skin is very difficult due to its intrinsically poor permeability. Hence permeation enhancers were incorporated into each formulation. F1 contains 5% ethanol as permeation enhancer but the release rate was approximately 70%. Ethanol is a good permeation enhancer, but its concentration incorporated into paediatric formulations were limited by regulatory agencies due to the increased chance of toxicity[19]. The concentration used here may not be sufficient for producing desirable impact.

After the good initial burst release, the formulation F2 showed a controlled release profile up to a period of 24 hour (Table No.4). At the end of 24 - hour diffusion study, the % drug diffused from F2 was 95.7, at the same period of study, F1 and F3 had 69.5% and 83.8% drug diffused. These three formulations (F1, F2 & F3) contained same percentage of polymer (sodium CMC & PVP) and plasticizer (glycerin) but permeation enhancers were different, 5% ethanol, 5% menthol & 5% oleic acid in respectively. Improved drug release was observed in F2 compared to F1 & F3 (Table No.4 & Fig No.7). The permeation enhancer present in F2 was 5% menthol which has a superiority in its skin permeation enhancement effect with respect to others (5% ethanol & 5% oleic acid) and it is clearly justified by literatures[7,17,20-22]. Menthol preferentially distributes into the intercellular spaces of stratum corneum and possibly causes the reversible disruption of lipid domains, thus enhancing the permeation of drugs[23].

Stability studies were used to determine the shelf life and storage condition of a product. All the developed formulations (F1-F3) were subjected to accelerated stability studies for a period of 45 days. Accelerated stability studies were performed in accordance with ICH guidelines with necessary modifications. There was no significant change observed in colour, and thickness of all the developed formulations at the end of study period (45 days) irrespective of the temperature difference (Table No.5). The folding endurance value was reduced for all formulations at higher temperature, which may be due to degradation of polymer[20, 24]. After the completion of study period (45 days) formulation F1 had 95.5 % of drug content reported at room temperature, with a minor decrease during the storage at refrigeration temperature of 4 ± 2^0C (Table No.5). The % drug content for F2, and F3 were 95.7% to 92.4% respectively in room temperature. But when these formulations were exposed to higher temperature, all the formulations experienced a drop in % drug content in a range of 10% to 20% approximately. The data obtained after estimating the % drug content may prove the significance of selecting optimized storage condition for these developed formulations. Based on the result, developed transdermal patches may be more stable between temperature ranges of $0\text{-}30^0$C, whereas higher temperature may cause deleterious effect on patches. The drop in % drug content for the patches during oven condition may be because of the possible degradation of polymer structure and polymer matrix at higher temperature[20,24]. Based on the data obtained after the stability studies, it was clearly proved that the Sodium CMC used

may be able to develop a stable transdermal patches containing Paracetamol IP.

Conclusion

Based on results obtained from our investigation data, it may be concluded that Na CMC as a polymer may be suitable to develop stable transdermal patches to deliver Paracetamol IP for paediatric patients. Design and development of such TDDS may be highly beneficial for delivering drugs for a period of 24hrs duration. Apart from this, common drawbacks associated with conventional dosage forms of Paracetamol IP may be absent in case of transdermal patches. Since TDDS has to by pass the tough skin barrier, it may recommendable to incorporate a suitable permeation enhancer. Based on our investigations it was evident that 5% menthol may be a suitable permeation enhancer to be incorporated in to TDDS developed from Sodium CMC to deliver Paracetamol IP. Unlike other agents, menthol may be considered as safer permeation enhancer for paediatric patients. The transdermal patches of Paracetamol IP developed from Sodium CMC is expected to provide better patient compliance especially in paediatric segment. Further clinical investigations may be recommended for transdermal patches of Paracetamol IP to substantially prove its safety and effectiveness as a good alternative for existing oral & rectal formulations.

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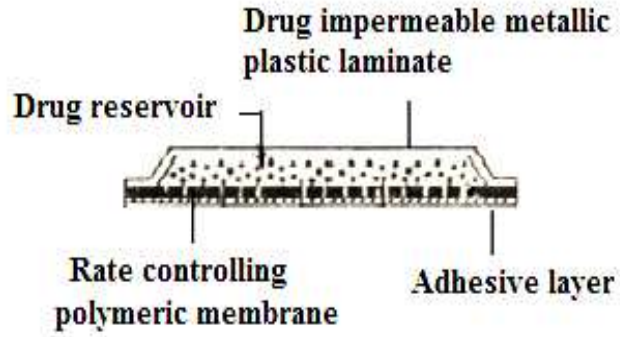

Figure 1. Membrane permeation controlled systems

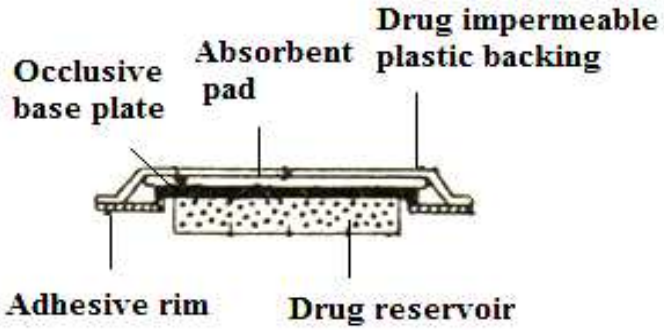

Figure 2. Matrix diffusion-controlled system

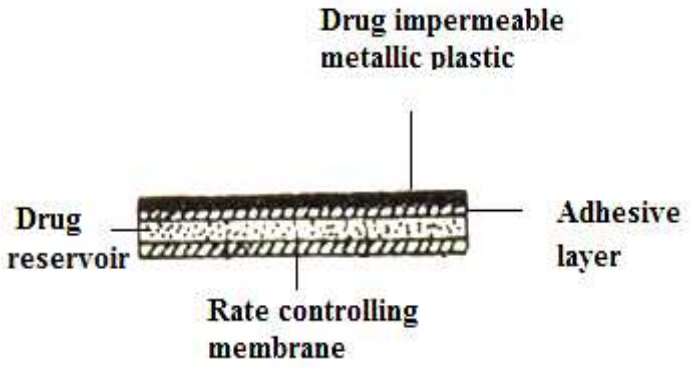

Figure 3. Adhesive dispersion type system

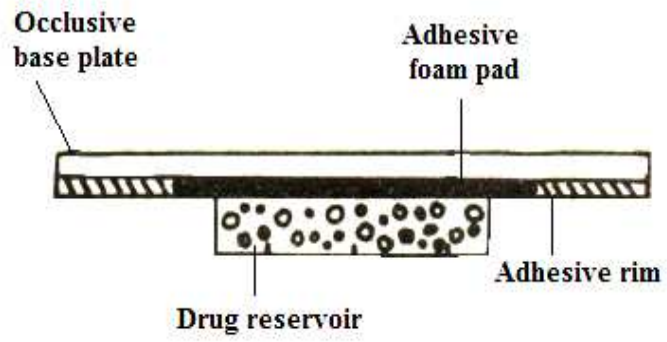

Figure 4. Micro reservoir dissolution controlled transdermal drug delivery systems

Figure 5. Tensile strength apparatus

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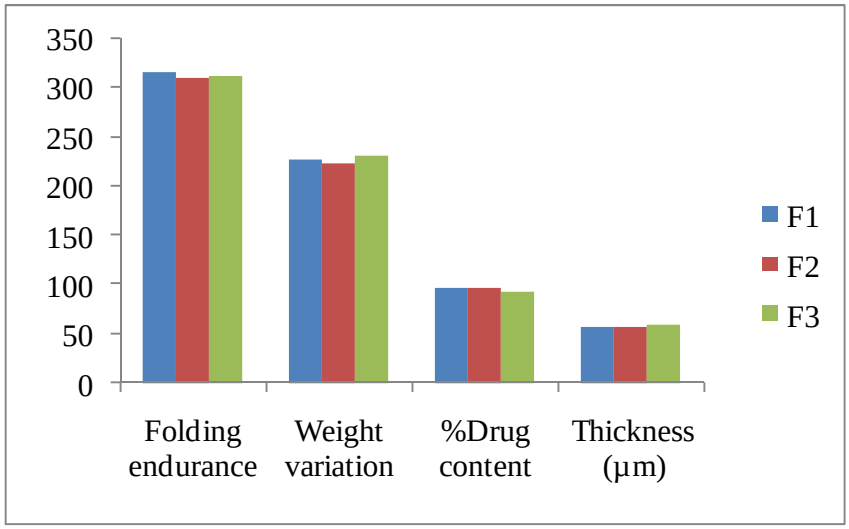

Figure 6. Physical evaluations of developed patches

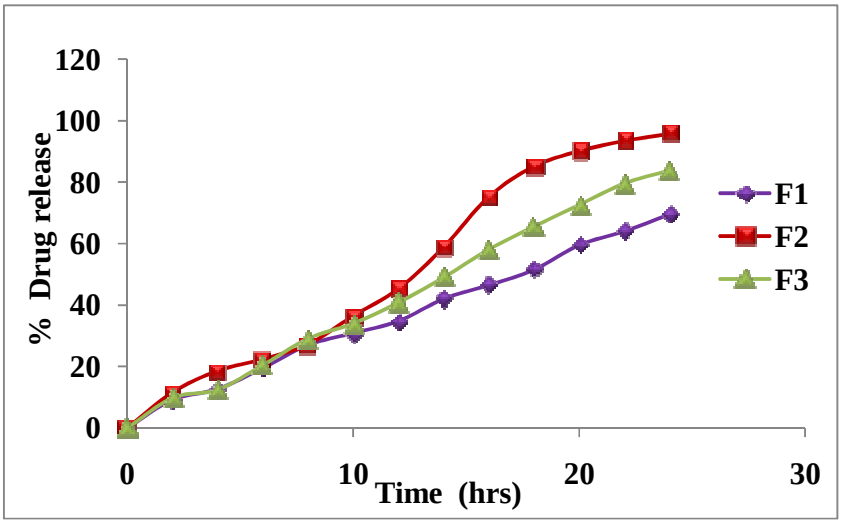

Figure 7. Comparison of *in vitro* drug release profile of transdermal patches F1-F3

Table 1. Formulation of transdermal patches of paracetamol IP

Contents	Formulation code		
	F_1	F_2	F_3
Paracetamol IP	15	15	15
Sodium CMC (%w/v)	3%	3%	3%
PVP (%w/w)	30 %	30%	30%
Glycerin (%w/v of total volume)	6%	6%	6%
Ethanol (%v/v)	5%	.....	.....
Menthol (%w/v)	.....	5%	.....
Oleic Acid (%v/v)	.....	.....	5%

Table 2. Physical characterization of developed formulations

Formulation	% Moisture content	Tensile strength (Kg/cm^2)	Thickness (µm)
F1	2.52±0.02	2.57±0.02	58±0.02
F2	3.06±0.03	2.58±0.01	57±0.04
F3	2.49±0.05	2.60±0.04	59±0.02

Table 3. Physical characterization of developed formulations

Formulation	Weight variation	Folding endurance	%Drug content
F1	227.9±0.84	317±0.70	96
F2	224.2±0.82	311±1.46	96
F3	231.6±0.96	312±0.85	93

Table 4. *In vitro* drug release data for the developed formulations

% Drug release													
Time (hrs)	0	2	4	6	8	10	12	14	16	18	20	22	24
F1	0	9.2	12.7	19.5	27.0	30.9	34.8	42.0	46.5	51.5	59.5	64.0	69.5
F2	0	11.6	18.6	22.4	27.2	36.5	45.3	58.8	75.2	85.1	90.1	93.4	95.7
F3	0	9.8	12.5	20.5	29.1	34.0	40.8	49.0	58.1	65.6	72.6	79.6	83.8

Table 5. Stability studies data for developed formulationsF1-F3

Formulation code	Physical appearance			% Drug content		
	4±2°C	30±2°C	45±2°C	4±2°C	30±2°C	45±2°C
F1	++	+	+++	95.4	95.5	76.8
F2	+	+	+++	95.6	95.7	75.5
F3	++	++	+++	92.1	92.4	73.4