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Original Article

Design Development and Evaluation of Transdermal Drug Delivery System of Antipyretic Agent

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ABSTRACT

Transdermal drug delivery system (TDDS) was planned to release the drug in appropriate manner and to improve patient compliance. Present study describes the alternative route for systematic delivery of drug into the body system which enhances the rate of absorption and increases the bioavailability of the drug into systemic circulation by reducing the gastic irritation. The purpose of the present investigation was to design and formulate TDDS of Paracetamol with various polymers such as hydroxyl methyl cellulose (HPMC), Xanthan gum etc along with to check the effect of penetration enhancers like dimethyl sulphoxide (DMSO) Oleic acid, Linseed oil on release of drug from patch system. Formulations were developed by solvent casting technique. to evaluate their characterastics such as Physical appearance, thickness, weight variations, drug content uniformity, folding endurance, tensile strength moisture content, moisture loss, flatness, surface pH, etc. In vitro drug release studies and stability study were also carried out. In vitro drug release study was also carried out by using PBS pH 7.4 and the samples were analyzed UV-spectrophotometrically at 249 nm. Formulations showed good uniformity of drug content; there was no any kind of effect on moisture loss test. Formulation F10 shows the release of drug 98.29% at the end of 7 h and was considered as a optimized formulation. A result of short-term stability study indicated the formulations were remained stable both physically and chemically. Hence, aforesaid study accomplishes goal such as decrease frequency of administration, less dosing, improved patient compliance and reduced systemic toxicity.

Key words: Paracetamol patch, penetration enhancer, physical characterization, drug release study, stability study

1. INTRODUCTION

Transdermal drug delivery is an enthusiastic and demanding area. During the last few years, drug delivery technology has been changing into the fashion in which they are required to elicit pharmacological action by the utilization of old drug molecules. The development of such a type of novel drug delivery system not only enhances the performance of the

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drug in terms of therapeutic effectiveness and safeness but also increase the patient compliance. The concept of providing drug through the underlying skin is gaining huge significance due to its several benefits. Numerous important advantages of transdermal drug delivery are a limitation of hepatic first pass metabolism, enhancement of therapeutic effectiveness, prolonged duration of action of potent drugs with short plasma half-life. So transdermal drug delivery has been investigated in order to avoid hepatic first pass effect improving drugs bioavailability or to decrease the dosing frequency required for oral treatment [1]. In present days pharmaceutical industries are been able to make the transdermal drug delivery system, transdermally drug application has been well known since ancient times. Several ancient cultures used ointments, pastes, medicated plasters, and complex inductions in the treatment of various symptoms or diseases associated with skin. It is the delivery of drugs across epidermis so as to achieve the systemic effects. The success of transdermal patches lies in their commercialization. The transdermal patch offers the delivery of drug at controlled manner by employing an appropriate combination of hydrophilic and lipophilic polymers. Delivering medicine via the skin is seen as an attractive choice of route, because of an oral route is having some drawbacks like first pass metabolism, poor bioavailability, and tendency that produce high and low rapid blood level spike and it requires frequent dosing which is not convenient and cost prohibitive.

The transdermal drug delivery market, worth $12.7 billion dollars in 2005, is expected to reach $32 billion [2]. The skin is the largest organ in the body; it protects against the influx of toxins and the efflux of water and is largely impermeable to the penetration of foreign molecules. Human skin consists of three main layers: the epidermis, dermis, and hypodermis [3]. The epidermis, in particular the stratum corneum, acts as the major barrier to drug absorption. The stratum corneum contains only 20% of water and is a highly lipophilic membrane; it is 10–20 µm thick depending on its state of hydration [4]. The thickness of the epidermis varies from 0.06 mm on eyelids to 0.8 mm on the soles of the feet.

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 develop effective transdermal system ultimately involves ensuring adequate drug permeability through the stratum corneum (SC) [5]. Transdermal route of administration is unsuitable for drugs that irritate or sensitize the skin. A transdermal patch is a medicated adhesive patch that is placed on skin to deliver a specific dose of medication through the skin and into the bloodstream. Due an advantage of being non invasive, high potency, better permeability through skin and non irritation for better compliance, avoiding the fluctuation in drug level, ability to deliver drug more selectively to a specific site and it provides suitability for self administration [6].

Transdermal delivery systems (TDS) were introduced onto the US market in the late 1970s [7]. Transdermal drug delivery system provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. TDDS is the system in which the delivery of the active ingredients of the drug occurs by means of skin. Transdermal drugs are self-contained, discrete dosage form. Most of the drugs do not reaches the targeted area in the body with adequate concentration so as to elicit therapeutic response because many of them are prematurely excreted or inactivated in conventional drug delivery system. TDDS reduces the dosing frequencies of drug by delivering the drugs directly into the intended site of action that's why less amount of dose of drug is required [8].

The penetration enhancers are used to penetrate the drug into systemic circulation via skin. The site of action of the chemical skin penetration enhancer is located in stratum corneum and those that influence diffusion across the stratum corneum [9] such as dimethyl sulphoxide, alcohols, DMSO, oleic acid, linseed oil etc. The transdermal drug delivery system gained the popularity over the fast decades the major pathway of drug molecules through stratum corneum of impact human skin is by diffusing through lipid envelops of the skin cell [10].

The paracetamol is potent antipyretic analgesic drug. The mechanism of action of paracetamol is not completely understood. The main mechanism proposed is the inhibition of cyclooxygenase (COX), and recent findings suggest that it is highly selective for COX-2 .Because of its selectivity for COX-2 it does not significantly inhibit the production of the pro-clotting thromboxanes. While it has analgesic and antipyretic properties [11] comparable to those of aspirin or other NSAIDs, its peripheral anti-inflammatory activity is usually limited by several factors, one of which is the high level of peroxides present in inflammatory lesions. However, in some circumstances, even peripheral anti-inflammatory activity comparable to NSAIDs can be observed.

From the aforesaid mentioned drawbacks and benefits of transdermal delivery of drugs we consider the project title entitled design, development and evaluation of transdermal patch of Paracetamol by using two different polymers they are as hydroxy propyl methyl cellulose, xanthan gum. These two polymers are widely used and accepted for pharmaceutical formulations because of non irritancy low cost and easily suitable for patch. The present investigation also checks the effect of penetration enhancer on release of drug.

2. MATERIALS AND METHODS

Materials

Paracetamol drug was obtained as a gift sample from Mankind Pharma Mumbai, India. Hydroxy propyl Methyl Cellulose was received as a gift from Alex Pharmaceutical

Pvt.Ltd, Sanand,. All the other excipients and chemicals wee puchased from local supplier such as Xanthan Gum (Loba chemicals, Mumbai), Polyethylene glycol-400 (Rankem chemicals Mumbai India) Dimethyl Sulphoxide (DMSO),Oleic acid (Loba chemicals,Pvt. Ltd Mumbai India), Linseed Oil (Merck Pvt. Ltd., Mumbai, India). Doubled distilled water was used throughout study and all other chemicals used were analytical grade.

Methods

Preformulation Study

It is necessary that certain fundamental properties of drug molecule and other derived properties of drug powder are determined. Preformulation testing is the first step in the rational development of any dosage forms of a drug substance. It also, defined, as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients in order to formulate stable, safe and effective 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. The overall objective of Preformulation testing is to generate information needed to define the nature of the drug substance and useful to the formulator that provide a framework for the drug combination with pharmaceutical excipients in the dosage form in developing stable and bioavailable dosage forms that can be mass produced.

Confirmation of drug test was carried out by Solubility study FTIR, Melting point determination by capillary method and DSC.

Solubility study:

Solubility of Paracetamol in water, Methanol, PBS pH 7.4 and 6.8 was determined. Excess amount of paracetamol powder was added in conical flask containing 10 ml of phosphate buffer solution. The solution was briefly sonicated and agitated at 32 °C on water bath shaker at 300 rev. / min for 24 hours until equilibration. Aliquot was withdrawn and then filtrated through 0.45µm millipore filter and then diluted with solvent. The samples were analyzed by UV-spectrophotometer to determine the concentration of drug at λmax 249 nm of Paracetamol [12].

Drug-Excipients compatibility Studies [13]

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

A) Infrared Spectroscopy:

FTIR spectra of plane drug Paracetamoland the mixture of polymers were taken to study the interaction between them. A mixture of with HPMC- E5 and Xanthan gumwere mixed separately with IR grade KBr in the ratio of 100:1 and compressed using motorized pellet press at 15 tones pressure.

B) Differential Scanning calorimetry (DSC):

Firstly, melting point of drug was determine by capillary method then confirmed by DSC. Drug-excipients compatibility study was also performed by Differential Scanning calorimetry.

Formulation of transdermal patch:

The transdermal patch was prepared by solvent casting technique employing mercury as a substrate using glass petri plate having diameter of 7.2 cm^2. The polymer hydroxyl propyl methyl cellulose E5 and xanthan gum were used with different concentration. The polymers were accurately weighed and dissolved in 10 ml of distilled water and methanol in the ratio of (8:2) solvent. The solution was then kept on magnetic stirrer and adequate amount of penetration enhancers were added in each batch in beaker containing polymeric solution. Dimethyl Sulphoxide, oleic acid and linseed oil were used as penetration enhancer with different concentration in all formulations. The polymeric solution was kept on magnetic stirrer for 2 hrs at the rate of 100 rpm. PEG-400 used as plasticizer so as to stop the breakdown of patch. The drug was incorporated while mixing the penetration enhancer. After stirring the solution it was poured in the petri plate containing mercury as substrate. Then the solution kept in hot air oven for 3-4 hrs at temp 30-40^{0}C for drying the patch and it was then easily removed from the petriplate and patch used for further evaluations [14].

Table 1: Composition of Transdermal Patches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Paracetamol(mg)	100	100	100	100	100	100	100	100	100	100	100	100
Xanthan gum(mg)	100	100	100	150	150	150	-	-	-	-	-	-
HPMC E5(mg)	-	-	-	-	-	-	300	300	300	400	400	400
PEG-400(%)	15	15	15	15	15	15	15	15	15	15	15	15
DMSO(%)	2	-	-	4	-	-	2	-	-	4	-	-
Oleic acid(%)	-	2	-	-	4	-	-	2	-	-	4	-
Linseed oil(%)	-	-	2	-	-	4	-	-	2	-	-	4
Methanol(ml)	2	2	2	2	2	2	2	2	2	2	2	2
DW(ml)	8	8	8	8	8	8	8	8	8	8	8	8

Evaluation of Transdermal Patches:

Physico-Chemical Evaluation

Physical appearance

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.

Surface pH

Surface pH of the patches was determined by using pH meter. The patches were allowed to swell by keeping them in contact with double distilled water for 1 hour in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 minute [14].

Thickness of the patch

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

Weight Uniformity

Weight variation should be studied 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 was calculated [16].

Folding endurance

Folding endurance was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times, which is considered satisfactory patch properties. The number of times patch could be folded at the same place without breaking gives the value of folding endurance. This test was done on all the batches for three times and average values were calculated [17].

Flatness

Three longitudinal strips were cut out from each film: one from the center, one from the left side, and one from the right side. The length of each strip was measured and the variation in length because of non uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness [18]

$$\text{Constriction}\,(\%) = \frac{\text{Final length of Patch} - \text{Initial length of Patch}}{\text{Final length of Patch}} \times 100$$

Percentage moisture absorption

Percentage moisture absorption test was carried out to check physical stability or integrity of the films maintained at high humidity. Tree films were taken out from each flm, weighed and placed in a desiccator maintained with high humidity at about 75% RH. After three days, the films were taken out and reweighed:[19]

$$\text{Percentage Moisture absorbed} = \frac{Final\ weight - Initial\ weight}{Initial\ \ weight} \times 100$$

Percentage moisture loss

The percentage moisture loss was determined to check the integrity of the flm at dry condition. Films were weighed and kept in a desiccator containing anhydrous calcium chloride. After three days, the films were taken out and reweighed. The percentage moisture loss was calculated using the following formula [19];

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

Drug content uniformity

The patches at (2x2cm^2), were cut and added to a beaker containing 100ml ofPhosphate 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 millilitre of above resulting solution was withdrawn, after suitable 10 ml dilution with Phosphate buffered solution of pH 7.4 and analyzedUV-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 [20].

***In vitro* drug release**

Franz diffusion cell was used for in-vitro drug release studies. It consists of donor and receptor compartment, donor compartment for introduction of formulation and receptor compartment for collecting drug samples. The receptor compartment was filled with PBS pH 7.4 and then it was agitated by using magnetic stirrer by placing small magnetic bead. Dialysis membrane was placed over it and prepared patch was placed in center position of dialysis membrane. The donor cell was preset using clips. The arrangement was placed on magnetic stirrer and temperature was maintained at 35 ±1^{o}C. Samples were withdrawn periodically at different time intervals over the 7 h and samples were analyzed for drug content. Receptor phase was replaced with an equal volume of PBS at each time of interval and % drug released measured by UV-spectrophotometer ay λ-max 249 nm [21].

Stability study

Stability studies were carried out on formulation F10, according to ICH guidelines by storing replicates of patches (packaged in aluminium foil) in a humidity chamber, with a relative humidity of 75± 5% and a temperature of 40±0.5 °C [21]. At different time intervals the samples were withdrawn at 0, 15, 45 and 90 days and the period for their degradation of the patch were checked. Samples were also analyzed for physical apperance and drug content.

3. RESULT AND DISCUSSION

In the present study, transdermal patches of paraceamol were prepared using various polymers such as HPMC E5 and xanthan gum. Melting point of Paracetamol was measured; and found to be in the range of 168-1720C..The drug was confirmed by using different tests these are tabulated (2) as follows. The solubility study of paracetamol was assessed in different solvent system viz., distilled water, pH 7.4 buffer solutions, pH 6.8 buffer solutions, Methanol. The solubility is shown in table 2.

Table 2: Preformulation data and Solubility Study for Paracetamol Drug

Description	White crystalline powder	**Medium**	**Solubility (mg/ml)**
Melting point	168-172°C	Distilled water	0.13±0.01
λmax	249nm	6.8 pH buffer	4.35±0.02
Partition coefficient (log P)	0.51	7.4pH buffer	5.52±0.02
pH	5.5-6.5	Methanol	8.13±0.06
PKa	9.38	------	

It was confirmed with the reported melting point of paracetamol. It was also confirmed by differential scanning calorimetry at scanning rate of 10ºC/min and it exhibits a sharp melting endothermic peak at temperature of 169.8ºC given in figure1.

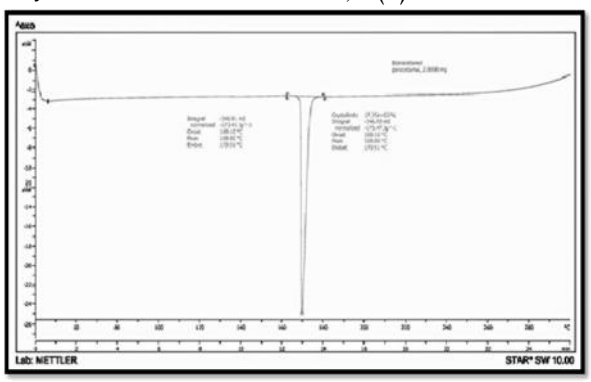

Fig 1: DSC Thermogram of Paracetamol Drug

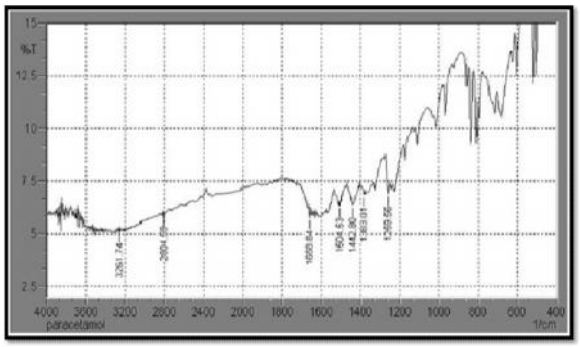

Fig 2: IR spectrum of paracetamol

Drug polymer compatibility study of pure drug, drug-polymer physical mixtures were analyzed by IR spectroscopy and Differential Scanning calorimetry

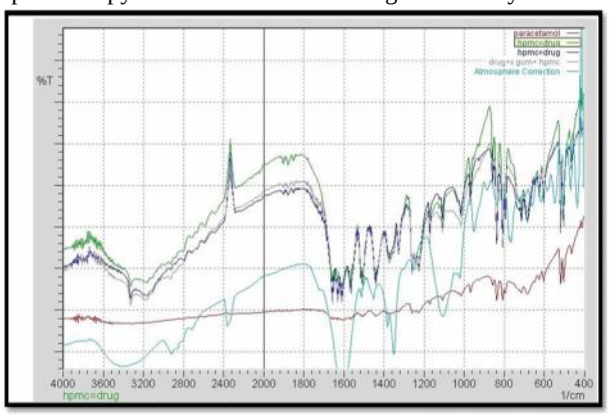

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Fig 3: Overlay spectra of Physical Mixture including Drug

The prepared formulations transdermal patches were found to be clear, transparent and smooth. Thicknessesof drug-loaded patches were measured with the help of screw guage. Film thickness was found in the range 0.126±0.12 to 0.172±0.21 mm. It means that the concentration of polymer showed significant change in the thickness of the film. The concentration of plasticizer also alter the change in the thickness of patch.The mean values are shown in the table 3.

The weight of the patch was found to be in the range of 9.46±0.11 to 13.68±0.7 gm. Uniformity of the patches shows the good distribution of the excipients. As the Increasing polymer concentration weight of patch also Increases. Each reading is an average of three determinations; their values are shown in table 3. The results obtained after flatness study no any formulation had the difference in the patch lengths before and after their cuts, thus representing 100% flatness. It also specifies 0% constriction in the patches and thus they could retain a smooth surface when applied to skin leading to intimate contact and therefore which results in better drug permeation.

Drug content of all the developed formulation was found to be in the range of 94.11 % to 99.28%. It was clear that the drug was uniformly distributed throughout the developed formulations as shown in table 3. The folding endurance of the patch was found to be in the range of 65 to 88. 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 F10 and lowest for F12 as shown in table 3. The concentration of polymer and Plasticizer shows higher effect on tensile strength of patch. When the concentration of HPMC-E5 increases accordingly then the tensile strength also increases. As per the formula mentioned, the plasticizer showed effect on tensile strength.

Table 3: Physico-chemical evaluations data of Paracetamol transdermal patches

Formulation code	Drug content (%)	Thickness (mm) (AM±SD)	Weight (mg) (AM±SD)	pH	Folding endurance	% Moisture absorbed (AM±SD)	% Moisture Lost (AM±SD)
F1	94.23	0.126±0.12	9.46±0.11	5.8	70	2.31±0.25	1.20±0.12
F2	95.62	0.132±0.13	10.12±1.2	5.9	72	3.88±0.19	1.34±0.54
F3	95.16	0.129±1.1	10.65±0.2	5.8	65	2.25±0.14	1.41±0.21
F4	94.11	0.146±0.14	12.54±0.4	5.8	68	2.91±0.36	1.25±0.61
F5	95.63	0.140±0.15	11.35±0.5	5.7	70	2.84±1.06	1.37±0.12
F6	97.46	0.153±0.11	12.45±0.3	5.6	71	3.94±1.23	1.18±1.04
F7	96.15	0.139±0.2	11.35±0.1	5.6	86	3.90±0.21	4.37±0.14
F8	98.44	0.146±0.14	12.43±0.6	5.8	71	4.88±0.48	3.12±1.21
F9	97.62	0.159±0.12	12.35±1.5	5.9	74	4.95±0.12	3.18±0.81
F10	99.28	0.156±0.1	13.27±0.1	5.8	88	4.45±0.17	2.24±0.24
F11	97.28	0.172±0.21	13.68±0.7	5.7	76	6.47±1.34	4.11±0.36
F12	98.24	0.164±0.24	13.54±0.6	5.4	88	6.05±1.26	4.31±1.37

Moisture content was found to be in the range of 2.84±1.06 to 6.47±1.34%. Percentage moisture content was calculated from the weight differences relative to the final weight. Results of moisture content study are shown in table 3. Moisture content was found to be increasing with increasing concentration of hydrophilic polymer. 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 the Patch to take up water is an intrinsic parameter of the polymeric system in consideration to the release of drug. Moisture absorption of the patch was found to be in the range of 1.18 ±1.04 to 4.31 ±1.37%. The percentage of moisture absorption was calculated as the difference between final and initial weight with respect to initial weight. The Patches were exposed to relative humidity of 75% (Saturated solution of sodium chloride) at

room temperature. The results of moisture absorption studies are shown in table 3 Low moisture absorption protects the patch from microbial contamination and bulkiness.

In vitro drug release study:

The in vitro diffusion studies of 12 formulations are given in the table hence, F10 formulation shows maximum release rate as compared to others. The in-vitro drug release profile is an important tool that predicts in advance how a drug will diffuse and targeted to the site. The results of in-vitro permeation studies of paracetamol from transdermal patches are shown in table 4. In the present study, HPMC E5 and xanthan gum polymers are used to prepared patches. Formulation F10 exhibited 98.29% of drug release upto 7 hr of diffusion. The cumulative amount of drug released from formulations containing HPMC and Dimethyl Sulphoxide showed release of drug at faster rate than Oleic acid and Linseed oil. Hence we can say that not only polymeric concentrations are resposible for release of drug at different time but also penetration enhancer also played importment role in release pattern of drug.

Table 4: % Cumulative drug release study of prepared formulation

	% Cumulative drug release (Mean ± S.D.)					
Time(h)	**F1**	**F2**	**F3**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0
0.5	11.45±1.2	10.25±0.14	11.45±0.52	11.25±1.02	10.56±0.12	10.68±1.2
1	38.24±0.26	32.16±0.56	29.45±0.42	22.68±0.21	24.89±0.6	28.54±1.3
2	49.65±1.34	46.28±0.11	48.26±1.21	36.45±0.64	34.25±1.2	36.45±0.21
3	66.43±0.15	59.69±1.23	64.85±1.3	51.26±0.12	49.73±0.25	48.76±0.4
4	78.12±1.6	74.59±1.41	79.24±0.4	64.53±1.2	62.35±0.16	59.45±0.12
5	96.78±1.4	92.46±1.62	96.34±0.6	81.52±0.3	79.52±0.14	74.46±0.11
6				98.29±0.4	92.64±0.12	93.47±0.42

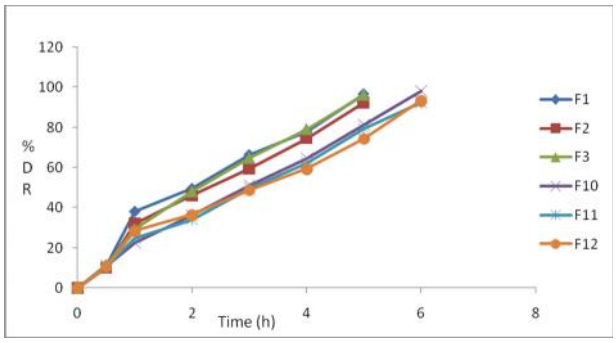

Fig 4: In vitro diffusion study of some formulation

Accelerated Stability studies were carried out for optimized formulation at 40°C temperature in a humidity chamber having 75 % RH & were carried outas per the ICH guidelines. Results are shown in table 5. No major differences was found between evaluated parameters before and after ageing/storing and all were found to be in acceptable limits. Based on the results of initial characterization batch F10 were thought to be the superior formulation and hence further subjected to accelerated stability study for 90 days.

Table 5: Stability Study on Optimized Formulation F10

Evaluation parameters	**Before stability Storage**	**After 15days storage**	**After 45 days storage**	**After 90 days Storage**
Drug content (%)	99.28%	98.71%	98.44%	97.23%
Percent drug dissolve in 7.4pH phosphate buffer	91.44%	91.569%	88.849%	90.667%
Weight variation	13.27±0.1	13.19±0.06	13.16±0.09	13.13±0.08
Drug release (%)	98.29%	97.38%	97.69%	96.37%

4. CONCLUSION

In conclusion, the study demonstrated that the formulated transdermal patch as a drug delivery system promising the approach, which can be utilized in near future for improving therapeutic efficacy of Paracetamol. There was no drug polymer interaction observed in FTIR and DSC. Among all the patches F10 showed better drug release over the time period of 7 h. Hence it can be conclude the HPMC E5 400 mg and the 15% plasticizer PEG-400 and DMSO 0.4 ml of penetration enhancer may be suitable for development of transdermal drug delivery of Paracetamol. The use of polymer such as Hydroxy propyl methyl cellulose, xanthan gum and PEG-400 as plasticizer for optimized batch and water/methanol as a solvent showed better drug release profile at the end of 7 hours. There was no significant decrease in drug release and drug content rate of formulation F10 over the period of 3months. Inclusion of Paracetamol also improve therapeutic efficacy of formulation Hence, in future such type of drug delivery system may utilize for the child patient and old ages which can't able to take drug orally to treat the fever and pain.

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