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FORMULATION CHARECTERISATION AND IN VITRO EVALUATION OF TRANSDERMAL PATCHES OF KETOPROFEN WITH DIFFERENT POLYMER CONCENTRATION

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ABSTRACT

Transdermal drug delivery system is a new era of pharmaceutical dosage forms along with various features to provide successful drug delivery. Transdermal drug delivery system establishes itself as an integral part of novel drug delivery system. In the present study, an attempt was made to design and evaluate transdermal patches of Ketoprofen, in order to overcome first pass metabolism in GIT, drug deactivation by lever and better patient complaints and to reduce adverse effect and frequency of administration. Each of the proposed transdermal patches is composed of using different polymers, anticipating rapping drug permeation and drug release. Controlled released transdermal preparation of Ketoprofen prepared to give sustained effect as compared to conventional multiple oral dose. The patches were prepared by solvent evaporation method using polymers such as ethyl cellulose and polyvinyl pyrrolydine. The prepared patches were evaluated for thickness, weight variation, folding indurance, surface PH, tensile strength, percentage flatness, swellability, percentage moisture update, drug content uniformity, invitro permeation, in vitro drug release. In vitro drug release studies were perfomed by using USP type second apparatus (paddle method) at 50 rpm in 900 ml of 7.4 phosphate refer for 8 hour at 37+_ 0.5^{o}C. In vitro permeation studies were franz diffusion cell apparatus with 7.4 phosphate buffer for 10 hours. Transdermal drug delivery had become an appealing and patience acceptance technology as it is minimize and avoids the limitations while comparing with conventional as well as parenteral route of drug administration such as peak and valley phenomenon i.e. exhibit fluctuation in plasma drug concentration level, pain and inconvenience of injections and the limited controlled release options of both. A transdermal patch is defined as medicated adhesive patch which is placed above the skin to

deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the blood stream.

INTRODUCTION

A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. The basic components of any transdermal delivery system include the drug dissolved or dispersed in a reservoir or inert polymer matrix; an outer backing film of paper, plastic, or foil, and a pressure-sensitive adhesive that anchors the patch to the skin. The adhesive is covered by a release liner which needs to be peeled off before applying the patch to the skin. Drugs administered via skin patches include scopolamine, nicotine, estrogen, nitroglycerin and lidocaine Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives,and eliminates pulsed entry into systemic circulation which often causes undesirable side effects.

Advantages of Transdermal Patches

- They facilitate more predictable drug absorption due to avoidance of GI tract variables such as pH, motility transit time, food, and enzyme activity.
- Suitable for patients who are unconscious or suffering from vomiting and diarrhea.
- They avoid the first-pass metabolism in the gastrointestinal tract and avoid drug deactivation by liver enzymes.
- The activity of drugs having short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
- They provide extended therapy with a single application, improving compliance over the dosage forms requiring more frequent dose administration.
- Avoiding the inconvenience of parenteral therapy.
- Drug therapy may be terminated rapidly by removal of the drug delivery system from the surface of the skin.
- Drug levels can be maintained in systemic circulation, within therapeutic window.
- Improved patient compliance and acceptability of drug therapy.

Disadvantages of Transdermal Patches

- The limitations of transdermal drug delivery are mainly associated with barrier function of skin, so it is limited to potent drug molecules.

- Skin irritation or contact dermatitis due to drug, excipients and enhancers is another limitation.

FACTORS THAT INFLUENCE TRANSDERMAL DELIVERY

1. Biological parameters
2. Physicochemical parameters

Biological parameters

a) Skin Condition

The skin is a tough barrier to penetration, but only if it is intact. Vesicants such as acid, alkalis injure barrier cells and there by promote penetration. In disease characterized by defective stratum cornium, percutenious absorption increases.

b) Blood flow

Theoretically, changes in peripheral circulation, or blood flow through the dermis, could affect percutaneous absorption. Thus an increased blood flow could reduce time for which a penetrant remain in the dermis and also raise the concentration gradient across the skin.

c) Regional skin sites

Variation in cutaneous permeability around the body depends on the thickness and the nature of stratum corneum and the density of skin appendages. However rate of absorption at identical skin sites in different healthy volunteers varies.

d) Skin metabolism

It has been recently reviewed the role which the skin plays in metabolism of drugs and steroidal hormones. The topical bioavailability should account for not only skin permeation but also cutaneous drug metabolism.

e) Species differences

Mammalian skin differs widely in characteristics such as horny layer thickness, sweat gland and hair follicle densities, and pelt condition, the capillary blood supply and the sweating ability from species to species, so affect the permeation.

Physicochemical parameters

a) Hydration of skin

When water saturates the skin; tissue swells, softens and wrinkles and its permeability increases markedly. In fact, hydration of stratum corneum is one of important factor in increasing the penetration rate of most substances that permeate the skin.

b) Temperature

The penetration rate of material through the human skin can change tenfold for large temperature variation, as the diffusion coefficient decreases as the temperature falls. Occlusive vehicles increase skin temperature by few degrees, but any consequent increased permeability is small compared to effect of hydration.

c) Diffusion coefficient

The diffusional speed of molecule depends mainly on state of matter in the medium. In gases and air, diffusion coefficients are large because the void space available to the molecules is large as compared to their size.

d) Drug concentration

The drug permeation usually follows the ficks law. The flux of solute is proportional to the concentration gradient across the entire barrier phase.

e) Partition Coefficient

Partition coefficient is important in establishing the flux of the drug through the Stratum corneum. The balanced partition coefficient is required for drug permeation.

f) Molecular size

Absorption is apparently inversely related to molecular weight. Small molecule penetrates faster than large once.

MATERIALS AND METHODS

Ketoprofen are the selected drug used for the study purchased from the yarrow chem products, Mumbai india.

IDENTIFICATION OF DRUG

Preparation of stock solution

An accurately weighed quantity of 100mg ketoprofen was transferred to 100mlvolumetric flask and diluted using phosphate buffer of pH 7.4 and make up to the volume. From this 5ml was transferred to 10ml volumetric flask and diluted to the mark. Determination of λ max.

By appropriate dilutions of standard solutions, ketoprofen was scanned in the range of 200-400nm to determine the wavelength of maximum absorbance for the drug. Ketoprofen show absorption maxima at 254nm38.

CURVE PREPARATION OF STANDARD CALIBERATION OF KETOPROFEN

Preparation of standard solution

Weighed accurately 100mg of pure Ketoprofen. It was transferred to 100ml volumetric flask. Then it was dissolved in phosphate buffer of PH 7.4 and made up to the volume to 100ml.This resulted solution had the concentration of 1mg/ml (1000µg/ml) which was labeled as "stock solution".

Preparation of standard calibration curve of ketoprofen

From the above stock solution, aliquots of 4, 6,8,10 and 12ml were transferred to 100ml volumetric flask and diluted with PH 7.4 phosphate buffer. This absorption of solution was measured at 254nm using UV Spectrophotometer. A calibration curve was plotted by concentration of X axis and absorbance on Y axis.

FTIR

The IR spectra of physical mixture suggested that there was no interaction between the drug and polymer because principal peaks of both the drug and the drug-polymer mixture were Nearly similar to that of pure substances. A few peaks were merged in the spectrum of the formulation and this might be due to physical but not chemical interaction between the drug and polymer. These results indicated that ketoprofen in ketoprofen transdermal patch might be present in the form of amorphous state. The FTIR spectra suggested that the major bands of drug were intact and there was no evidence of interaction and it showed that drug and polymers are compatible with each other.

Procedure for FTIR

Integrity of the drug in the formulation was checked by talking an IR spectrum of he selected formulation along with the drug and other excipients. The spectra were taken by using Shimadzu IR Prestige-21 Spectrometer were compared with standard spectra. In this study palletisation of potassium bromide (KBr) was employed. Before forming the pellet of potassium bromide, it was completely dried at 1000C for one hour and after drying it was thoroughly mixed with the sample in the ratio of 1 part of sample and 100 parts of KBr. The mixture was compressed to form a disc using dies. This disc was placed in the sample chamber and a spectrum was obtained through the software program which is further subjected to interpretation.

FORMULATION DEVELOPMENT

Composition of Transdermal Patch

INGREDIENTS	F1	F2	F3	F4	F5	F6
Ketoprofen Polymers	20	20	20	20	20	20
(EC:PVP)	500:00	475:25	465:35	450:50	350:150	300:200
DibutylPthalate	1.5	1.5	1.5	1.5	1.5	1.5
DMSO	0.5	0.5	0.5	0.5	0.5	0.5
Chloroform(Casting)	5	5	5	5	5	5

EVALUATION OF TRANSDERMAL PATCH

Physical appearance

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

Thickness

The thickness of the patch was assessed by using screw gauge at three different points of the patch. From each formulation ten randomly selected patches were used. The average value for thickness of a single patch was determined49.

Weight Variation

Twenty different patches from individual batches were weighed individually using digital balance and the average weight was calculated. The individual weight should not deviate significantly from the average weight.

Folding Endurance

This was determined by repeatedly folding the patches until it shows any crack or brake. The number of times the patch could be folded without breaking/cracking gave the value of folding endurance.

Surface pH

The patches were kept in contact with 0.5 ml of phosphate buffer saline for 1h. The surface pH was measured by means of pH paper placed on the surface of the swollen patch. The mean of two readings was recorded.

Tensile Strength

The tensile strength of the patches was determined by using a tensile strength instrument. Average reading of three patches was taken as the tensile strength. The transdermal patch was fixed to the assembly, the weights required to break the patch was noted, and simultaneously elongation was measured with the help of a pointer mounted on the assembly and calculated the tensile strength of the patch using the following formula

$$T.\ S. = \text{break force}/\ a.b\ (1+\Delta L/L)$$

Where a, b and L are width, thickness and length of the patch respectively. ΔL is the elongation of patch at break point.[50-52]

$$\text{Break force} = \text{Weight required to break the patch}$$

Percentage Flatness

Longitudinal strips were cut out from the prepared medicated patches and the lengths of each strip were measured and then the variation in the lengths due design and in-vitro evaluation of Ketoprofen transdermal patches containing EC and PVP K-30 to the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.[53]

$$\text{Constriction}\ (\%) = (I1-I2)/I1 \times 100$$

Where I1= initial length of each strip; I2= final length

Swellability

The drug loaded patch was weighed. It was kept in petridish and 50 ml of phosphate buffer pH 7.4. Solution was added after 10 min. The patch was removed, wiped with tissue paper and weighed up to 1 hr, until a constant weigh was observed. The difference in the weight

gives the weight increase due to absorption of water and swelling the patch. The percentage swelling was calculated using the following equation % S = (Xt –X0/X0) ×100

Where, Xt is the weight of the swollen patch after time t and X0 the original patch weight at Zero time 54.

Percentage Moisture Uptake

The weighed films were kept in a desiccators at room temperature for 24 hours and then exposed to 84% relative humidity using a saturated solution of potassium chloride. Finally, the films were weighed and the percent moisture uptake was calculated using the formula55-57.

Percentage moisture uptake = [Final weight -Initial weight/Initial weight] ×100 100

Percentage Moisture Content

The prepared films were weighed individually and kept in a desiccators containing fused calcium chloride at room temperature for 24 hours. The films were again weighed and the percentage moisture content was calculated using the formula.[58-59]

Percentage moisture content = [Initial weight -Final weight/Final weight] × 100

Skin irritation of Ketoprofen

Photo allergic dermatitis that occurs as a result of topical Ketoprofen use presents acutely with oedema and papulovesincles on area of skin exposed to both the drug and to the sunlight. The listen are often pruritic and although this may initially appear only on the sun exposed areas. But may present to involve other sites as well due to the systemic nature of the cell mediated immune response. Other factors may also contribute to the spread of dermatitis including transfer of topical drug by hands or clothing to other body sites.

RESULTS AND DISCUSSION

Organoleptic Properties

Sl. No	Test	Specifications of IP	Results
1	Character	White, odourless, non-hygroscopic, fine to granular powder.	White, odourless, non-hygroscopic, fine to granular powder.
2	Solubility	Soluble in ethanol, chloroform, acetone, ether and benzene.	Soluble in ethanol, chloroform, acetone, ether and benzene.
3	IR spectra	The potassium bromide disc contain drug was prepared to record the spectrum by using FTIR Spectrometer	The spectrum showed the prominent peak of Ketoprofen
4	Melting point	90-95^{0}C	93^{o}C

Physical Evaluation

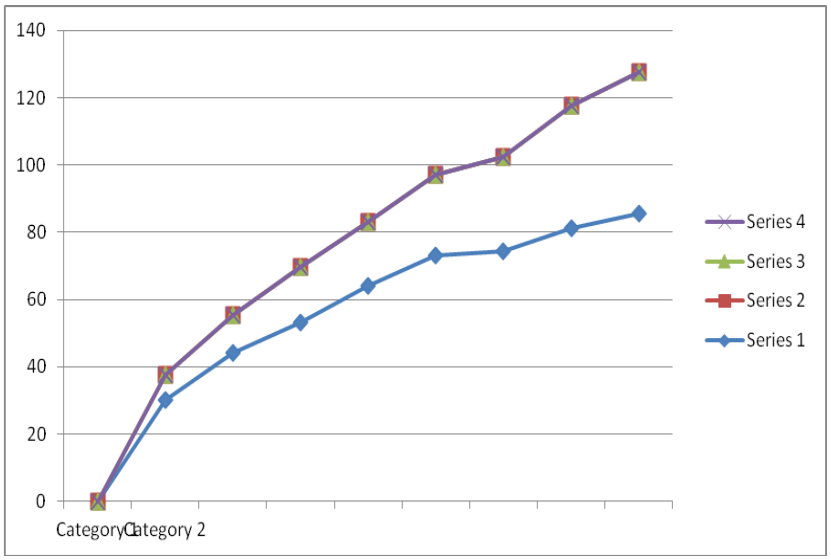
Sl. No	Formulation	Weight Variation(mg)	Thickness (nm)	Folding Endurance	Tensile Strength (g/mm^2)	Percentage Flatness (%)	Surface pH
1	F1	430	0.053	48	18.76	92.67	6.7
2	F2	420	0.041	51	16.36	92.54	6.7
3	F3	420	0.045	47	17.89	92.26	6.6
4	F4	420	0.057	48	21.67	90.33	6.7
5	F5	430	0.059	50	15.98	92.76	6.6
6	F6	430	0.078	51	19.85	92.56	6.7

Physical Evaluation of Patches

Post formulation studies of the formulated batches are shown in the table. From the physical evaluation of all the batches formulated, it was concluded that the patches of all the batches had desirable physical properties. Thickness varies from 0.04 – 0.07nm. Folding endurance varies from 47-51. Percentage flatness varies from 90 – 92.6%, which indicates that all the batches had sufficient mechanical strength to withstand mechanical abrasion. Surface pH varies from 6.6 -6.7, which indicates the electrolytic balance. All the batches of formulation passes the weight variation test as per the limits prescribes in IP.

Comparison of release drug from F6 formulation and marketed Ketoprofen

Rate of release from different formulation are given in graph and table. It may be observed that release of drug occurred fast initially then after some time release become slower. From graph it was observed that cumulative release of ketoprofen was more than other marketed product.



RESULTS OF STABILITY STUDY

Physical Evaluation Colour Odour Taste	White-off white Odouless Bitter taste	No changes No changes No changes
Relative humidity	25^0C+- 2^0C60%RH	40C+_2^0C75% RH (Accelerated stability study)
Uniformity drug content	97.36%	No changes
Diffusion study	92.29 (%drug release in 8hr)	92.32%

Different batches of transdermal Ketoprofen gel with different penetration enhances were selected for stability study which was conducted at accelerated climate condition. In accelerated stability study of three months, minimum three point including initial time and final time were analyzed by using Uv visible spectrophotometer, The condition for accelerated study were compressed temperature 40+_2^0C and relative humidity 75+_5% RH for three month in stability chamber. FTIR studies showed that there were no marked incompatibility between the drug and polymers. The results of thickness and tensile strength revealed that all the six formulation F1 to F6 showed good mechanical strength and compiled with pharmacopoeia specifications. Stability testing provide evidence on how the quality of a drug substance or products varies over a given time period and under the influence of environmental factors including temperature humidity and light. The studies are designed to include testing of attributes susceptible to change during storage and are likely to influence, quality, safety and efficiency. Testing primarily covers physical chemical and microbiological attributes. For accelerated storage condition test frequency is recommended to be a minimum of three time points, including the initial and final time points for a six months study. A drug substance should be evaluated under the storage condition that test its thermal stability and its sensitivity to moisture.

CONCLUSION

Different batches of transdermal Ketoprofen gel with different penetration enhances were selected for stability study which was conducted at accelerated climate condition.

In accelerated stability study of six months, minimum three point including initial time and final time were analyzed by using Uv visible spectrophotometer, The condition for

accelerated study were compressed temperature 40±20c and relative humidity 75±5% RH for three month in stability chamber.

In vitro drug permeation showed significantly improved permeation through the skin. The in vitro permeation rate of drug through patch increased when the concentration of hydrophilic polymer was increased.

In vitro drug release from F1 to F6 patches showed improved drug dissolution.

Optimized formulation F6 showed a drug permeation of 92.29% and drug release of 97.75%. The kinetic study showed that the optimized formulation F6 followed First order kinetics.

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