Evaluation of drug release kinetics from salbutamol sulphateTrasdermal patches using Hydroxy propyl methyl cellulose

Nidhi Saini[1*], Babita[2], Rakesh Kumar[3], Neelam Kumari[4,] Rakesh Kumar[5]

1. *Institute of Pharmaceutical Sciences, Kurukshetra University, India, Kurukshetra-136119*
nidhisaini1919@gmail.com
2. *Dept. of Pharmaceutical Sciences and Research, BMU, India, Rohtak-124021*
suhagbabita7@gmail.com
3. *Institute of Pharmaceutical Sciences, Kurukshetra University, India, Kurukshetra-136119*
rakeshkumar2750@gmail.com
4. *Jan Nayak CH. Devi lal Memorial College of Pharmacy, Sirsa, 125055*
dhanda.neelam302@gmail.com
5. *Dept. of Pharmacy, Annamalai Nagar, Chidambaram, Tamil Nadu 608002*
kaliramana.rakesh@gmail.com

Abstract

Aims: The objective of the present research work was to formulate transdermal patches of Salbutamol sulphate using **Hydroxy propyl methyl cellulose(HPMC)** as release controlling factor and to evaluate drug release mechanism from polymer (HPMC) as per various release kinetic models.

Study Design: The transdermal patches of Salbutamol sulphate were prepared by solvent evaporation technique using different ratios of Hydroxy propyl methyl cellulose (HPMC K15 M) [6% TO 10 %] and PVP K30 and Tulsi Oil as permeation enhancer. The prepared transdermal patches were evaluated on parameters like weight variation, thickness uniformity, moisture content, moisture uptake, folding endurance, tensile strength, drug content, in vitro dissolution studies, in vitro drug release, skin irritation test and stability studies and results were found in acceptable limits. Different kinetic models were used to evaluate release mechanisms and kinetics. Criteria for selecting the most appropriate model were based on linearity (coefficient of correlation). The optimized batch was further subjected to kinetic modelling R2 value of different model indicates that the drug release kinetic followed mixed first-order and higuchi kinetics.

Keywords: Transdermal patches, HPMC K15, PVP K30, and Salbutamol sulphate.

INTRODUCTION

Transdermal drug delivery systems (TDDS) are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. Typically, the Transdermal patches, stored in a pouch; at the time of use, the pouch is opened and patches applied to skin to releases the drug. The Transdermal patches, typically consists of a release liner (e.g., polyester), adhesive (e.g. polyisobutylene-based, acrylic, silicone-based), active pharmaceutical ingredient (i.e., drug), and backing (e.g., polyester). The system may also contain penetration enhancers, excipients, a rate-controlling membrane, and a protective film over the backing and over the release liner.

Adhesive properties of patches can be affected by the type and concentration of additives used, thickness of the adhesive, type and concentration of enhancers. Composition, thickness of the backing layer, residual solvent, type and concentration of the active pharmaceutical ingredient give an impact on patch properties[1].

Transdermal route get advantage over conventional drug delivery system because it lowers the risk of toxicity or inefficacy in the case of drugs with narrow therapeutic window by providing the constant blood levels in the plasma also improves patient compliance by improving dosage regimens in case of the drugs which have low bioavailability due to first-pass metabolism in the gastrointestinal tract and liver, and/or short biological half-lives to be administered at most, once a day. The problems of the gastrointestinal environment, such as chemical degradation of the drug and gastric irritation, are avoided and drug input can be easily terminated by removing the patch from the stratum corneum. This route is noninvasive alternative to subcutaneous, parenteral and intramuscular injections and suitable for patients who are unconscious or vomiting. Along with these advantages there are some limitations of transdermal route as there is possibility of local irritation, erythema, itching at the site of application and heavy drugs molecules (>500 Daltons) usually difficult to penetrate the stratum cornea. Also drugs with very low or high partition coefficient fail to

reach blood circulation through skin and the drug candidate must have some desirable physicochemical properties for penetration through stratum corneum.

Main objective of this work is to evaluate drug release data using various kinetic models and to determine the mechanism of drug release from the HPMC matrix.

Materials and method

Materials

HPMC K15 M, PVP K30, Propylene glycol, DMS and Methanol were obtained from HiMedia Laboratories Pvt. Ltd., Mumbai. Salbutamol Sulphate and Tulsi oil was obtained from the lab of Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra.

Method of preparation of monolithic transdermal system

The transdermal patches of pure Salbutamol sulphate drug were formulated according to factors combination chosen by experimental design[6,7], by solvent evaporating technique using different ratios of Hydoxy propyl methyl cellulose (HPMC K15 M) [6% TO 10 %] and PVP K30. 5 mg of pure Salbutamol sulphate was weighed and dispersed in 10 ml distilled water[8]. Weighed amount of HPMC K15 M and PVP K30 was added to each aqueous drug solution with continuous stirring to ensure uniform distribution. Weighed amount of permeation enhancer is added to the solution. Propylene glycol was used to protect the polymeric patches from brittleness upon storage. The dispersion was done using a magnetic stirrer providing constant stirring (500 rpm) at room temperature until clear solution is obtained. Polymeric solution (10ml) was poured onto a prepared cavity (circular dish of 57 mm² diameter & 8 mm depth) and dried at room temperature for 72 hr with an inverted funnel overhead to provide a uniform rate of evaporation. Formulated patches were put in a desiccator over anhydrous calcium chloride for 24 hr before the evaluation process to assure total hydration and to eliminate entrapped air. The patches were evaluated within one week from the date of casting.

Evaluation of patches

Transdermal Patches of all formulations were evaluated for uniformity of weight[2], thickness of the patch, moisture content**,** moisture uptake[3], tensile strength[3], drug content[4, 5], percentage of moisture content and percentage of moisture uptake. In vitro release study was performed using USP type 1 test apparatus at 50 rpm and dissolution medium used was phosphate buffer PH6.8,temperature was maintained at 37°C± 0.5°C. The drug release was evaluated by taking sample of 5 ml (which were replaced with fresh medium) at predetermined time intervals and absorbance was measured at 263nm after filtration and suitable dilution. The drug content was analyzed using Shimazdu UV Spectrophotometer.

Results and Discussion

The diffusion behavior of many polymers cannot be described adequately by concentration dependent form of fick's law with constant boundary conditions, especially when the penetrant causes extensive swelling of the polymer. Generally this is the case with so called glassy polymers which are said to exhibit anomalous or non fickian behavior. In rubbery polymers other hand, diffusion is generally fickian.

Data analysis:

Mechanism of Drug release:

Korsmeyer et al derived a simple relationship which described drug release from a polymeric system eq (1).to find out the mechanism of drug release

$Mt/Mg = Kt^n$.....eq.1

Where Mt/Mg is fraction of drug released at time t, K is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table 1

Alfrey,Gurnee,and Lloyd proposed a useful classification according to the relative rates of diffusion and polymer relaxation. Three classes are distinguished:

(i)Case I or fickian diffusion in which the rate of diffusion is much less than that of relaxation.

(ii) case II diffusion, the other extreme in which diffusion is very rapid compared with relaxational process.

(iii)Non-fickian or anomalous diffusion which occurs when the diffusion or relaxation rates are comparable.

Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion [(17)].

Evaluation characteristics of optimized patch

Batch Code	Weight Variation (mg)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture Content (w/w) (%)	Moisture uptake (w/w) (%)	Tensile strength (kg/cm^2)	Flatness (%)
T5	172±1.98	0.374± 0.031	239±3.42	99.00± 0.54	8.1±0.021	5.3±0.015	0.98±0.14	100.03

All other evaluation parameters like thickness, folding endurance, weight uniformity, drug content and moisture content, moisture uptake and tensile strength are suggestive of good characteristic properties of optimized batch.

In vitro dissolution studies

In present study for controlled release under investigation, which is transdermal patch comprising drug the release should follow 3 steps. First step penetration of the dissolution medium in the patch (hydration), second step swelling with subsequent dissolution or erosion of the matrix and third step is the transport of dissolved drug, either through hydrated patch or from eroded part of patch to the surrounding dissolution medium (18). The salbutamol released at first hour was 35.71±0.098%, second hour was 45.71±0.072%, third hour was 62.14±0.093%, fourth hour was 72.85±0.045%, fifth hour was 78.57±0.074%, sixth hour was 80.71±0.033%, seventh hour was 84.28±0.097%, eight hour was 87.85±0.048% and ninth hour was 92.14±0.089% respectively.

Table no 2

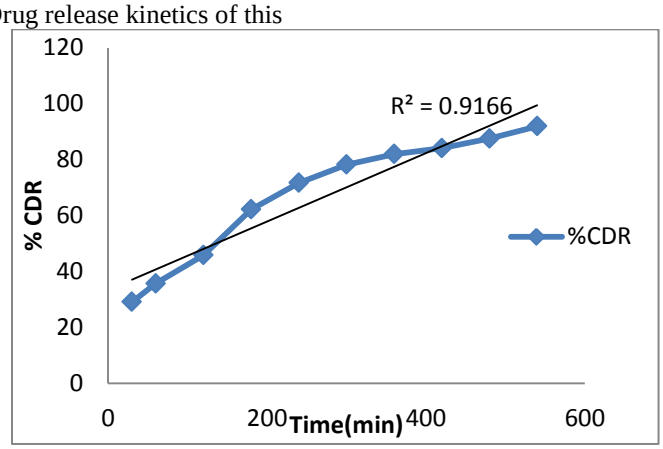
Formulation Code	**R^2**			
	Zero order	**First order**	**Higuchi Model**	**Korsmayer Peppas model**
Batch T5	0.916	0.99	0.976	0.967

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The following plots were made: *cumulative % drug release VS time* (zero order kinetic model); *log cumulative of % drug remaining to be released vs .time* (first order kinetic model); *cumulative % drug release vs square root of time (*Higuchi model); *log cumulative % drug release vs log time* (korsemeyer model) and R2 values obtained from different graphs were given in table 2.As shown in figure 2 3, 4, 5,6 plots were drawn. The regression value for the optimized batch is higher with 1st order and therefore the release kinetics followed 1st order. R^2 value is higher for First order and Higuchi. Hence, Salbutamol sulphate release from optimized bath followed is concentration and time dependent and penetration of drug from patches was governed by diffusion mechanism.

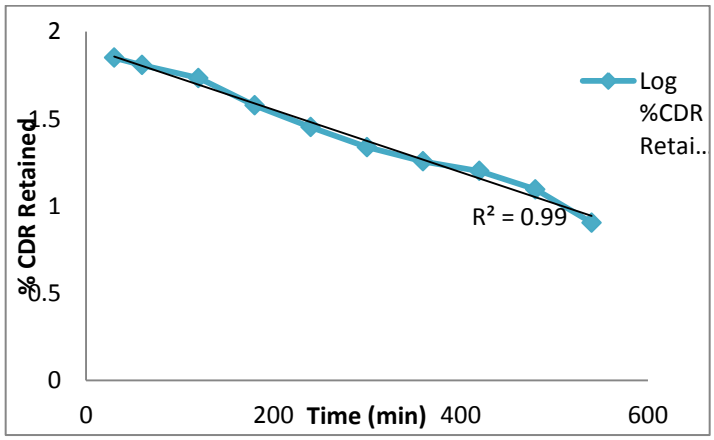
CONCLUSION

Salbutamol sulphate transdermal patches were prepared successfully using HPMC as film former and Tulsi Oil as

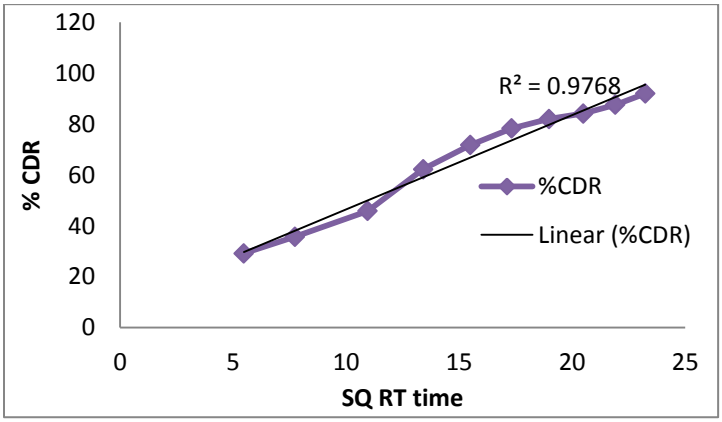
permeation enhancer. The regression value for the optimized batch is higher with 1st order and therefore the release kinetics followed 1st order. R^2 value is higher for First order and Higuchi. Hence, Salbutamol sulphate release from optimized bath followed is concentration and time dependent and penetration of drug from patches was governed by diffusion mechanism Drug release kinetics of this formulation corresponds best to Higuchi's model and First order. The value of exponent n obtained is less than 0.5, hence as per n value of Korsmeyer & Peppas can be predicted that drug release mechanism follows Fickian law of difusion.



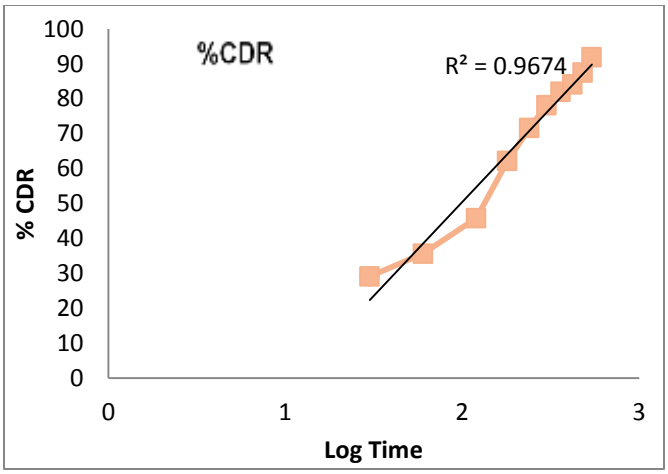
***In-vitro* release data of optimized formulation T5: Zero order kinetic**



***In-vitro* release data of optimized formulation: First order kinetics**



***In-vitro* release data of optimized formulation: Higuchi model**



***In-vitro* release data of formulation: Korsmeyer peppas model**

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