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A REVIEW ON FORMULATION AND EVALUATION OF CURCUMIN LOADED TRANSDERMAL PATCHES

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ABSTRACT

An attempt was made to formulate and evaluate the curcumin transdermal drug delivery system. Preformulation studies on the drug curcumin were done which included description, solubility and compatibility studies. The transdermal patches were made which were of matrix diffusion control system. Solvent casting technique was used to prepare the transdermal patches. Three formulations were made with 20mg of curcumin and by using polymers namely hydoxy propyl methyl cellulose, ethyl cellulose at various ratios and the yield was noted. Curcumin was physically examined for color and odour. Solubility was determined in water, phosphate buffer pH -7.4, Ethanol, DMSO and Tetra hydro furan. Interaction of drug and polymer was confirmed by UV – Visible interaction and FTIR studies. Based on this further evaluation was carried out.Invitro drug diffusion stuy was also carried out using modified Franz diffusion cell. Transdermal patches were evaluated for the weight, thickness, percentage moisture uptake, percentage flatness, folding endurance, water vapor transmission rate, and in-vitro release studies.

KEYWORDS: Trandermal patches, curcumin, formulation, Evaluation.

INTRODUCTION

During the last two decades, significant advances have been made in the controlled release drug delivery of therapeutic agents. In the early stages of research on controlled release drug delivery, major emphasis was focused on the development of zero order release devices. Current technology has improved to such a level that delivery of some drugs at a constant rate for certain period of time ranging from days to years is not a major issue anymore.[1]

Transdermal patches deliver drugs at a constant rate for 24 hours or longer and the Norplant system releases progestin levonorgestel from silicon rubber tubular capsules for several years. The promise of zero order release is to maintain a constant drug concentration in blood for an extended period of time. The zero order release of a drug, however, does not necessarily result in a constant drug concentration in blood.

Most of the drugs introduced to clinical medicine exert their effects by interactive interference with cell and cell membrane related structure and function through concentration dependent reversible interactions at specific receptor site. To achieve and maintain the concentration of a administered drug within therapeutically effective range, it is often necessary to take drug dosage several times and this results in a fluctuating drug levels in plasma.

The fluctuations produced by the conventional drug delivery system can be overcome by using several approaches. They are.

TARGETED DELIVERY

It refers to the systemic administration of a drug-carrier with the goal of delivering the drug to predetermined target in therapeutic concentration, while restricting its access to non-target normal cellular linings, thus minimizing therapeutic index.

CONTROLLED RELEASE

Zero-order release constituted drug release from the dosage form that is independent of the amount of drug in the delivery system i.e. concentration independent and constant release time.

PROLONGED RELEASE

The release of the delivery system is attained for prolonged period of time i.e. for several weeks or even months.

MODULATED RELEASE

It implies use of a drug delivery device that releases the drug at a variable rate controlled by environmental conditions, biofeedback, sensor input or an external control device.

A typical plasma drug profile produced by various delivery systems has been shown in figure 1.1. The figure shows the differences between conventional drug delivery system and the

sustained/controlled drug delivery system. It could be concluded from the figure that fluctuations in the drug level is obtained in conventional delivery also the blood level reaches the toxic level. But as in the case of sustained drug delivery system, the sustained/controlled drug delivery system maintains the drug level below its toxic range also reducing the multiple – dosing.

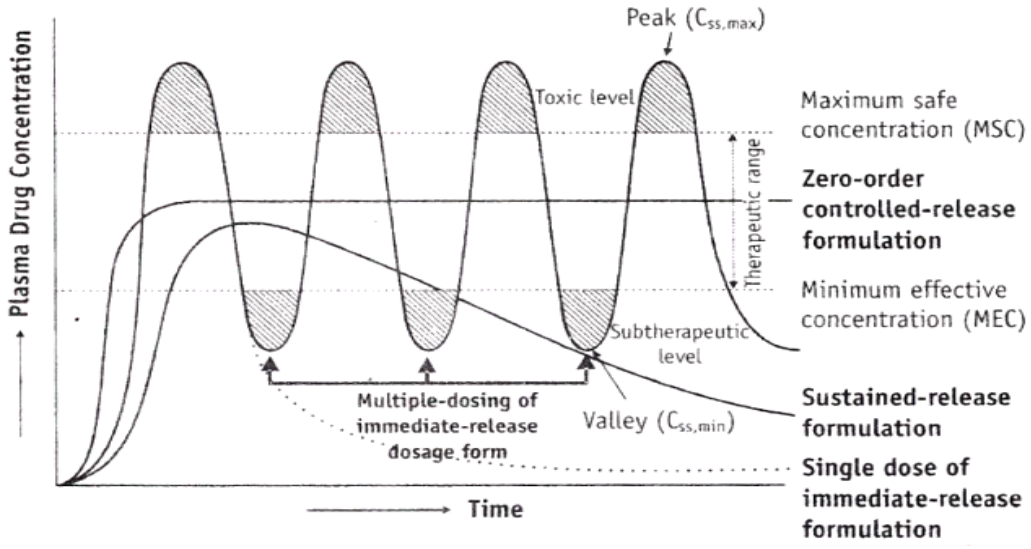


Figure 1: Illustrative plasma drug concentration-time profile for various delivery systems.

Nanoparticles

Nanoparticles are solid polymeric, submicronic colloidal system range between 5-300nm consisting of macromolecular substances that vary in size 10nm to 1000nm. The drug of interest is dissolved, entrapped adsorbed, attached or encapsulated into the nanoparticle matrix.

The following types of nanoparticle preparations have been used as carriers for drugs and diagnostic agents.

Lipid Nanoparticles

Lipid nanoparticles were invented by Muller and his coworkers in the early nineteenth century. In general, there are two types of lipid nanoparticles with a solid matrix, the solid lipid nanoparticles (SLNs) and the nanostructured lipid carriers (NLCs), which differ in their inner lipid structure.

SLNs consist of a solid lipid matrix that is solid at both room and body temperatures and that are prepared in a similar manner to an oil-in-water (o/w) emulsion, except that the oil phase of the emulsion is replaced by a solid lipid or a blend of solid lipids at room temperature.

NLCs matrices consist of a less ordered lipid matrix with imperfections due to the mixtures of solid and liquid lipids. There are three types of NLC: the imperfect type, the multiple type, and the amorphous type. The imperfect type is achieved by mixing solid lipids with small amounts of liquid lipids. If higher amounts of oil are mixed with the solid lipid, a different type of nanostructure is present. Here, the solubility of the oil molecules in the solid lipid is exceeded; this leads to phase separation and the formation of oily nanocompartments within the solid lipid matrix. Many drugs show a higher solubility in oils than in solid lipids so that they can be dissolved in the oil and still be protected from degradation by the surrounding solid lipids. This type of NLC is called the multiple type, and can be regarded as an analogue to w/o/w emulsions since it is an oil-in-solid lipid-in-water dispersion. Since drug expulsion is caused by continuing crystallization or transformation of the solid lipid, this can be minimized by the formation of a third type, the amorphous type. Here, the particles are solid but crystallization upon cooling is avoided by mixing special lipids (e.g., hydroxyoctacosanylhydroxy-stearate and isopropylmyristate).

Transdermal Delivery

Controlled release medication may be defined as the permeation-moderated transfer of an active material from a reservoir to a target surface to maintain a predetermined concentration or emission level for a specified period of time. Transdermal drug delivery system can be defined as the controlled release of drugs through intact skin. Controlled release technology has received increasing attention in the face of a growing awareness that substances are frequently toxic and sometimes ineffective when administered or applied by conventional means. The transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40 % of the drug delivery candidate products under clinical evaluation related to transdermal or dermal system.

A transdermal patch is a medicated adhesive patch placed on skin to deliver a time released dose of medication through the skin for treating topical or systematic illness. Since early 1990, this dosage form of transdermal therapeutic system has been available in the pharmaceutical market.[5] A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. A transdermal

drug delivery is a formulation or device that maintains the blood concentration of the drug within therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed minimum toxic dose.[6] Such a system offers variety of significant clinical benefits over other systems, such as tablet and injections. For example, it provides controlled release of the drug and produces a steady blood- level profile leading to reduced systemic side effects and, sometimes, improved efficacy over other dosage form. In addition transdermal dosage form is user-friendly, convenient, painless, and offers multi-day dosing, it generally leads to improved patient compliance.

Curcumin is capable of scavenging oxygen free radicals such as superoxide anions and hydroxyl radicals, which are the initiators of lipid per oxidation.The lipid per oxidation has a main role in the inflammation, in heart diseases, and in cancer.It was demonstrated that, curcumin protects (52%) hemoglobin from nitrate-induced oxidation to methemoglobin at 400 mM concentration. It has been suggested that the presence of a hydroxyphenyl group in compounds analogous to curcumin, especially in the 2-position, is supportive of the chemo protective activity through the ability to induce Phase II detoxification enzymes, so it has anticancer activity. Curcumin appear to reduce its anti-inflammatory activity by suppressing activation of NF-kB through inhibition of IkB kinase activity.

MATERIAL AND METHOD

Preformulation Studies

The following preformulation studies were carried out on the curcumin procured from the source. The preformulation studies were carried in order to confirm the purity and identity of the procured curcumin and also to study any possible interaction with the polymeric carrier to be used in the investigation.

Organoleptic characterization

A small quantity of pure curcumin powder was taken in a butter paper and viewed in well illuminated place to observe its color; the taste and odor were observed using tasting and smelling the drug.

Solubility

Solubility of curcumin was determined qualitatively in water, methanol and ethanol. Solubility studies were performed by shaking small amount of curcumin in test tubes containing the solvent and observing for undissolved particles (if any).

Melting Point determination

The melting point of curcumin was determined by open capillary method by filling the drug in a capillary tube sealed at one end and placing it in the melting point apparatus to observe the temperature at which melting occurs.

Drug excipient compatibility Study

IR spectra of drug and a physical mixture of drug and lipids were obtained using FT-IR spectrophotometer. The spectra were observed for physical and chemical incompatibility amongst the drug and the lipid under study.

Formulation of SLNs

Nano precipitation method was used for the preparation of the solid lipid nanoparticles. Various concentrations of lipids were used for formulation the SLNs (Table 4.1).

Table of Formula for preparation of SLNs.

Ingredients	SLNC1	SLNC2	SLNC3	SLNC4
Curcumin (mg)	200	200	200	200
Oleic acid (mmol)	0.1	0.12	0.14	0.16
Tween 80 (%)	5	5	5	5

The accurate quantity of oleic acid and curcumin were dissolved in a mixture of 18 mL ethyl acetate and 2 mL ethanol. A 5% solution of Tween 80 was prepared in distilled water and was used as the emulsifier solution. The drug containing organic solution was added drop wise to the emulsifier solution with stirring at 700 rpm at room temperature. The resultant turbid suspension of the nanoparticles was stirred for 5–10 min and the organic solvents were removed by vacuum evaporation followed by cooling of the dispersion to room temperature. The pH of the dispersion was adjusted to 1.2 by addition of 0.1 M hydrochloric acid solution to the precipitate the SLNs, and the precipitate was then collected by centrifuging at 12,000 rpm. The precipitate was re-dispersed in distilled water under sonication (13 mm probe, 35% amplitude and 2 min cycles) for 10 minutes.

Formulation of transdermal Patches

SLN loaded transdermal patches were formulated utilizing the solvent casting method using a petridish of area 44.15 cm^2. Polymers were accurately weighed and dissolved in 10 mL of water, methanol (1:1) solution and kept aside to form clear solution (table 5.2). The curcumin loaded SLN (SLNC-was dissolved in in the above solution and mixed until clear solution was

obtained. Polyethylene glycol 400 (30% w/w of total polymer) was used as plasticizer and propylene glycol (15% w/w of total polymer) was used as permeation enhancer. The resulted uniform solution was cast on the petri dish, whichwas lubricated with glycerin and dried at room temperature for 24 h. An inverted funnel was placed over the petridish to prevent fast evaporation of the solvent. After 24 h, the dried patches were taken out and stored in a desiccator for further studies.

Formula for SLN loaded transdermal patches

Ingredients	SLNP1	SLNP2	SLNP3	SLNP4
SLNC (mg)	45	45	45	45
HPMC (mg)	100	100	100	100
PVP K30 (mg)	0.1	1	1.5	2
PEG-400	30	30	30	30
Propylene Glycol	15	15	15	15

Evaluation of Transdermal Patches

Uniformity of weight test

The patches were subjected to mass variation by individually weighing randomly selected patches (44.15 cm^2). This determination was carried out for each formulation in triplicate.

Thickness

The thickness of each patch was measured by the use of vernier caliper at different positions of the patch and the average was calculated.

Folding endurance

Folding endurance was determined by repeatedly folding one patch from the same place till it cracked or broke. The number of times the film could be folded from the same place without breaking/ cracking gave the value of folding endurance.

Drug content test

Three pieces of 4 cm^2 were collected by cutting off zones from different parts of patch from each patch. These pieces were dissolved in 10 ml ethanol and were placed on vortex shaker for 1 hr to dissolve completely the patches. The resultant solutions were filtered through the whatman paper and then 0.1 ml solution was withdrawn into another volumetric flask (10 ml) and dilution was made up to 10 ml. The absorbance of this solution was observed at 421 nm using UV-Visible spectrophotometer and the drug content was calculated.

Percent moisture content

The prepared transdermal films were weighed individually and kept in desiccators containing fused calcium chloride at room temperature for the duration of 24 hours. After 24 hours, the films were re-weighed and the percentage moisture content was determined by the given formula.

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

In-vitro permeation study

In-vitro permeation studies of the transdermal patches were carried out by using Franz diffusion cell with a receptor compartment capacity of 30 ml. The formulated patch of surface area of 4 cm^2 was placed in between the dialysis membrane and the donor compartment and then dialysis membrane was mounted between the donor and receptor compartment of diffusion cell. The receptor compartment of diffusion cell was filled with phosphate buffer saline pH 7.4. The whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred magnetic beads at 50 rpm; the temperature was maintained at 37±0.5ºC. The 1 ml aliquots were withdrawal at different time intervals (0, 1, 2, 3, 4, 6 and 12 h) and analyzed the drug content by UV at 421 nm by appropriated dilution with ethanol. The receptor phase was replenished with an equal volume of phosphate buffer (37ºC) at each sample withdrawal, the cumulative amount of drug permeated per square centimeter of patches were plotted against time.

RESULTS AND DISCUSSION

The objective of the present work was to prepare solid lipid nanoparticles encapsulated with curcumin in order to improve the cellular permeability of curcumin and load these SLNs into transdermal patches for prolonged effect on topical application.

Preformulation Studies

Physical characteristics

The results of organoleptic characterization and melting point are presented in table 6.1 whereas the result of solubility analysis is presented in table 6.2.

Table 6.1: Organoleptic properties of Curcumin.

Test	Specification	Observation
Color	Orange- yellow needles	Pale Yellow
Odor	Characteristic	Characteristic
Taste	Bitter	Bitter
Melting Point	183°C	181-185°C

The melting point was determined using the open capillary method and is uncorrected for the variations due to atmospheric conditions.

Table 6.2: Solubility profile of curcumin.

Solvent	Solubility
Water	Insoluble
Methanol	Soluble
Ethanol	Freely soluble

FT-IR study

The FT-IR spectrum of curcumin (figure 6.1), and a physical mixture of curcumin and oleic acid (figure 6.3) were obtained and observed for any deletion of the peaks of the pure drug. The spectrum of curcumin exhibited peaks at 3341 cm^{-1} (OH stretching), 3056 cm^{-1} (CH aromatic stretching), 2923 cm^{-1} (CH_2 stretching), 1647 cm^{-1} (C=O stretching), 1574 cm^{-1} (C=C aromatic stretching), 1441 cm^{-1} (CH_2 bending), 1146 cm^{-1} (C-O stretching).

All the peaks were present in the physical mixture indicating a compatibility between the both the components.

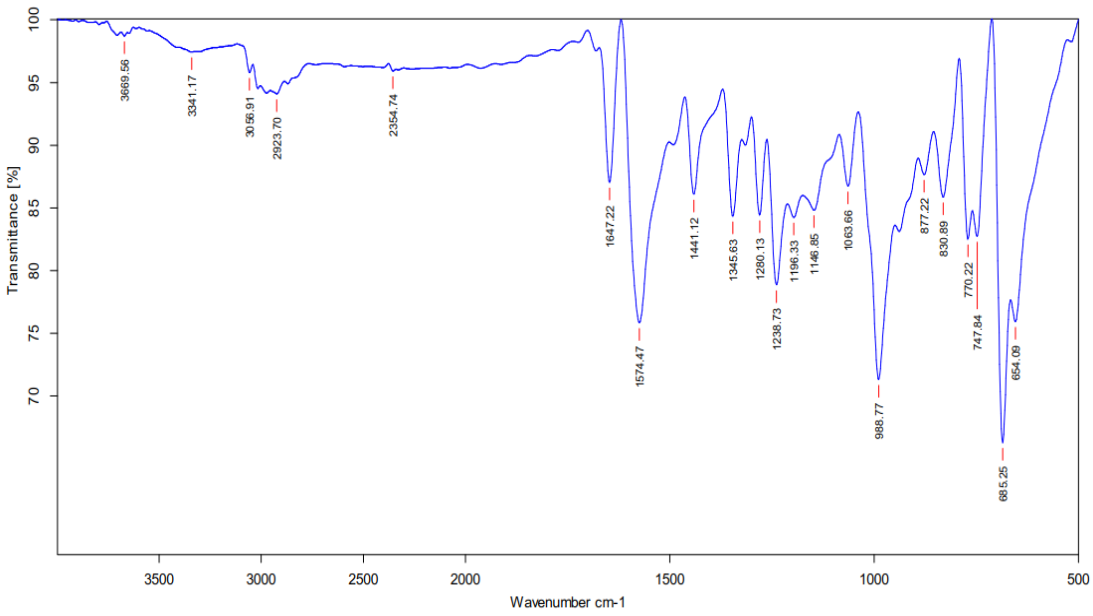


Figure 6: 1 FT-IR spectrum of Curcumin.

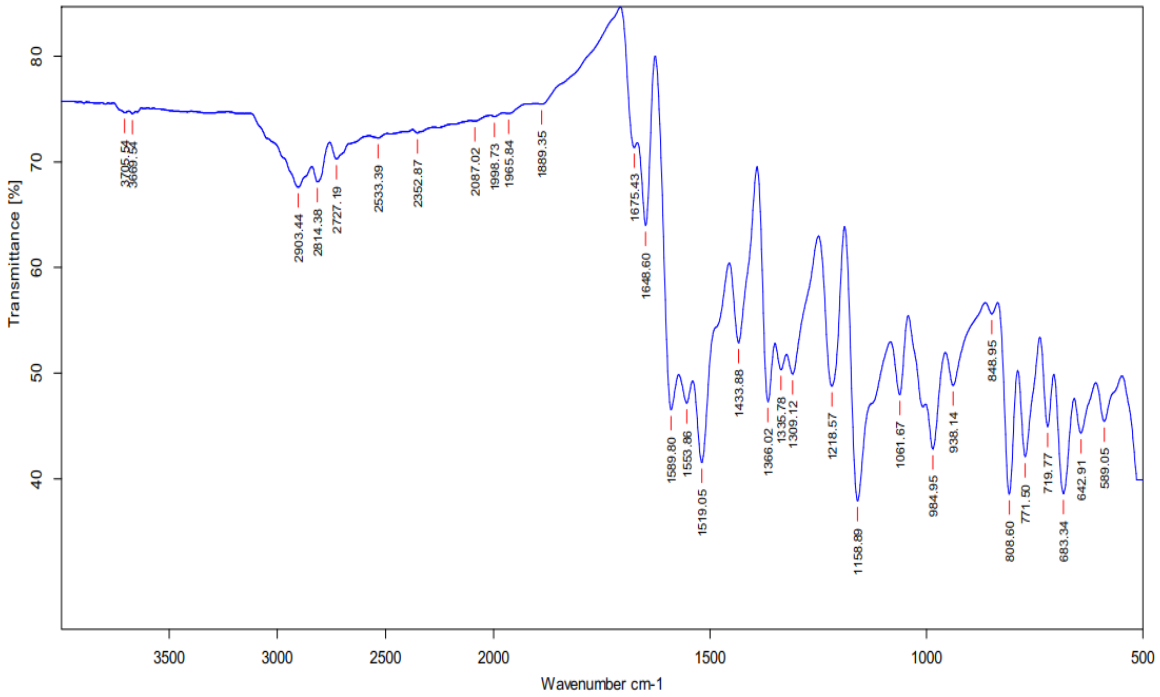


Figure 6: 2 FT-IR spectrum of physical mixture of oleic acid and curcumin.

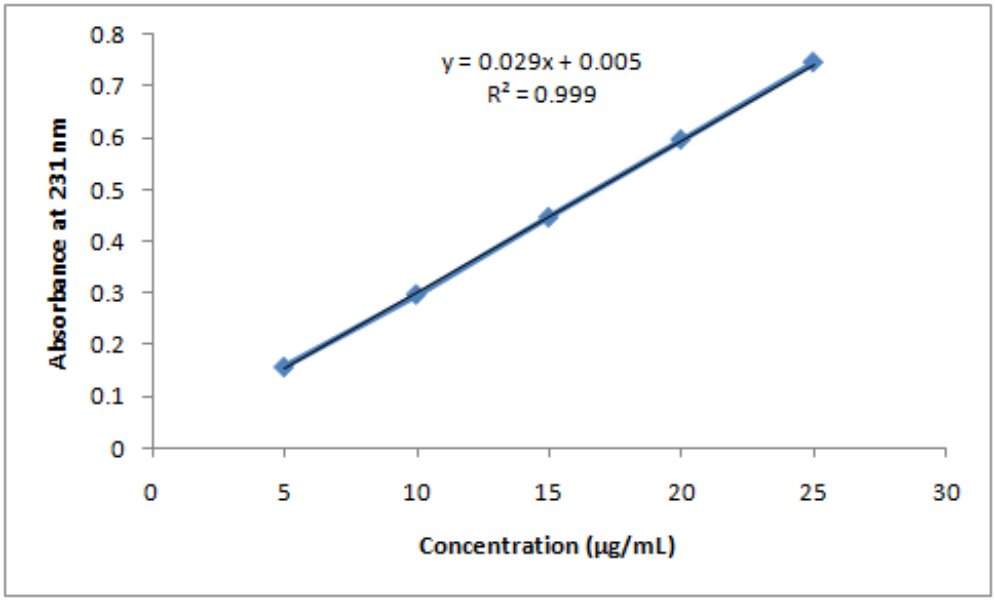
Calibration curve of cur cumin

The calibration curve of curcumin was prepared in methanol using UV-Visible spectrophotometer at 421 nm by plotting the absorbance against concentration (table 6.3, figure 6.3). The linearity equation was found to be Absorbance (y) = 0.029 concentration (x) +0.005 with a regression coefficient value of 0.999 (R^2). This equation was used to calculate the concentration of curcumin in various stages of the study.

Absorbance of cur cumin at 421 nm

Concentration (µg/mL)	Absorbance*
5	0.157 ± 0.000577
10	0.297 ± 0.001732
15	0.446 ± 0.002
20	0.596 ± 0.001528
25	0.745 ± 0.002517

*Average ± standard deviation; Average of three readings



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