Formulation and evaluation of mangiferin loaded transdermal patches for sustained release and improved bioavailability

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Abstract

In the present study the prime objective was to develop transdermal patches loaded with mangiferin in order to improve its bioavailability by sustaining the drug release. Transdermal patches were prepared using Hydroxy propyl methyl cellulose (HPMC K) as the hydrophilic matrix and eudragit (ER) as the lipophilic component. The pH levels of the patches ranged between 5. .31 ± 0.006 to 5.64 ± 0.015. The thickness of the transdermal patches ranged from 0.513 ± 0.004 mm to 0.693 ± 0.004 mm. The formulated transdermal patches displayed average weight between 191.33 ± 0.577 mg and 238.67 ± 2.032 mg. The moisture content of the formulated transdermal patches varied from 7.15 ± 0.058 % to 10.15 ± 0.158 %. The formulated transdermal patches displayed tensile strength values between 9.51 ± 0.006 kg/cm^2 and 10.46 ± 0.015 kg/cm^2, which were within the acceptable limits for transdermal patches. The drug content ranged from 93.5 ± 0.404 % to 97.3 ± 0.153 %. The *in vitro* drug release study depicted that the highest amount of drug was released from **T9** (86.01 ± 1.033 %) while the lowest was released from **T5** (55.27 ± 2.032 %) at the end of 24 hours of release study.

Keywords

Mangiferin, transdermal, drug delivery, eudragit, bioavailability

Introduction

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. In recent years, various drug delivery systems have been developed which provide sustained release therapy via a sub-dermal insert.[1] Systems have been disclosed which also provide drug delivery systems suitable for transdermal drug administration. Transdermal products for cardiovascular disease, Parkinson's disease, Alzheimer's disease, depression, anxiety, skin cancer, and post-menopausal bone loss are at various stages of formulation and development.[2] Many of the natural products have been known to possess the properties necessary to be effective in a transdermal drug delivery system. The properties include high potency, proper physic-chemical characteristics, good dermal penetration and lack of dermal irritation.

Mangiferin is a C-glycosyl compound consisting of 1,3,6,7-tetrahydroxyxanthen-9-one having a beta-D-glucosyl residue at the 6-position. It has a role as a hypoglycemic agent, an antioxidant, an anti-inflammatory agent and a plant metabolite.[3] It has been reported to be active against several disease conditions with lower side effects compared to synthetic drugs.[3] The transdermal delivery through patches has been widely investigated for improving the bioavailability of drugs.[4-7] In the present work an attempt was made to formulate transdermal patches containing mangiferin with objective to improve the bioavailability of the drug.

Material and Methods

Mangiferin (Yucca enterprises, Mumbai), hydroxypropyl methyl cellulose (HPMC) (Oxford Fine Chem, Mumbai), Eudragit (Oxford Fine Chem, Mumbai) were used as obtained for the study. The preformulation study of procured mangiferin was done to obtain the necessary information for ascertaining its use for formulation. The study included organoleptic characterization, melting point determination (open capillary), solubility (qualitative), FT-IR study for identity and compatibility[8] and calibration curve preparation in methanol[9].

Formulation of transdermal Patches

Mangiferin loaded transdermal patches were formulated utilizing the solvent casting method using a petridish of area 38.46 cm^2. Polymers were accurately weighed and dissolved in 10 mL of water-ethanol (1:1) solution, stirrer for 30 min on a magnetic stirrer and kept aside to form clear solution (Table 1).[10] Mangierin was accurately weighed and was dissolved in the above solution and mixed until clear solution was obtained.[11] PEG 400 (30% w/w of total polymer) was added to be used as plasticizer and olive oil (10% w/w of total polymer) was added as the permeation enhancer.[10] The resulted uniform solution was cast on the petri dish, which was 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.

Table 1. Formula for mangiferin loaded transdermal patches

Ingredients	Mangiferin	HPMC (mg)	ER (mg)	PEG 400 (%w/w)	Olive oil (%w/w)
T1	180	100	50	30	10
T2	180	125	75	30	10
T3	180	150	75	30	10
T4	180	125	75	30	10
T5	180	100	100	30	10
T6	180	125	75	30	10

T7	180	100	75	30	10
T8	180	125	75	30	10
T9	180	150	50	30	10
T10	180	125	75	30	10
T11	180	125	100	30	10
T12	180	125	50	30	10
T13	180	150	100	30	10

Evaluation of patches

Physical appearance

The formulated patches were evaluated for homogeneity, transparency, clarity, color, and smoothness.

Uniformity of weight test

The patches were subjected to mass variation by individually weighing each formulated patch and checking the weight of patch against the average weight of the formulated patches.

Thickness

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

Surface pH

The surface pH of the transdermal patches was measured using a calibrated pH meter. In a test tube, 1 mL of distilled water and a 1 cm^2 portion of transdermal patch was kept at room temperature (25 ± 2°C) for 2 h. The water from the test tube was decanted and the wet patch was used for surface pH analysis. The pH electrode was placed at three different places at the swollen part of the patch for calculating the average pH.

Folding endurance

Folding endurance was determined by repeatedly folding one patch from the same place till it cracked or broke.

Tensile Strength

The determination of tensile strength of the prepared patches was conducted using pulley apparatus fabricated in the laboratory. The initial patch length was identified using a scale. One side of the transdermal patch was attached to a weighing balance hook, and the other side was attached toa rope that crossed over the pulley and attached to

a weighing pan. In the pan, weight gradually increased until a crack or break appeared in the patch. Tensile strength was calculated by the total weight present in the pan.

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 h 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 257 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.

***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, 2, 4, 6, 8, 12 and 24 h) and analyzed the drug content by UV at 257 nm by appropriated dilution. 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 results of the preformulation study of mangiferin are reported in table 2.

Table 2. Observations of preformulation study of mangiferin

Test	Observation
Color	White
Odor	Odorless
Appearance	Crystalline powder
Solubility	Ethanol and methanol solutble
Melting point	158-159°C
Loss on drying	0.30%

Calibration curve of mangiferin was determined by plotting absorbance versus concentration (µg/ml) at 257 nm (Figure 1).

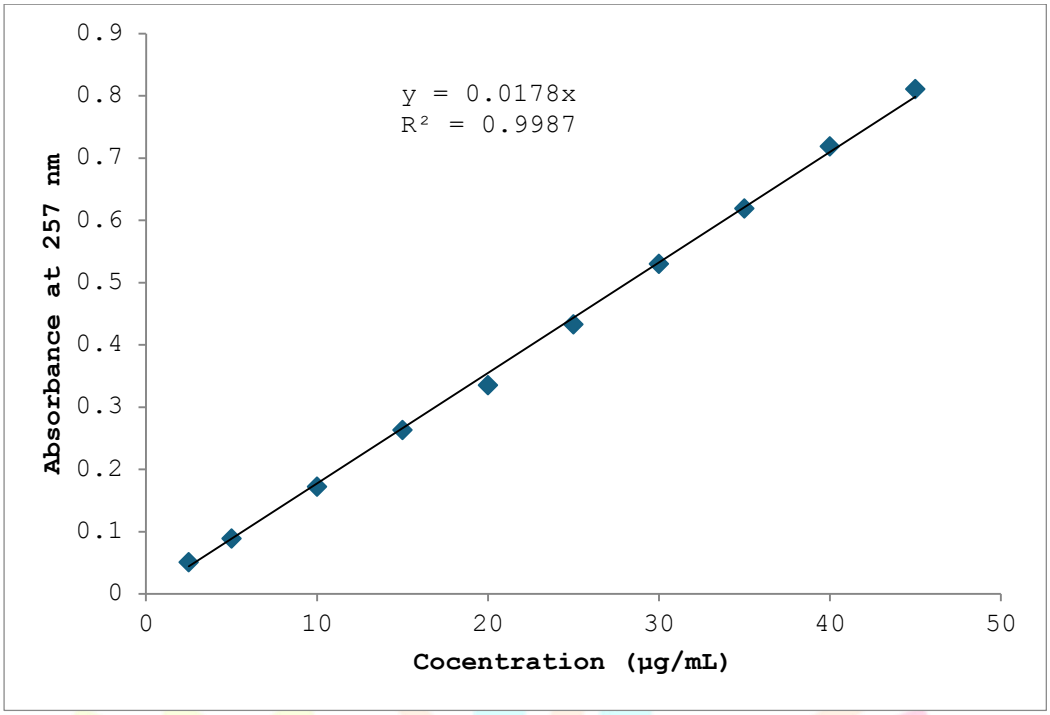

Figure 1. Calibration curve of mangiferin

Drug-polymer compatibility study

The FTIR spectra of the pure drug and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm^{-1}). Deletion of the peaks of the pure drug in the mixture spectra is usually taken as an indication of incompatibility of the drug and excipients. On comparison of the FTIR spectra of the drug and the mixture it was observed that no peak was deleted and only the intensities of the existing peaks changed which might be due to the coupling of absorption frequencies. This provides evidence of compatibility between the drug and the matrix forming polymers.

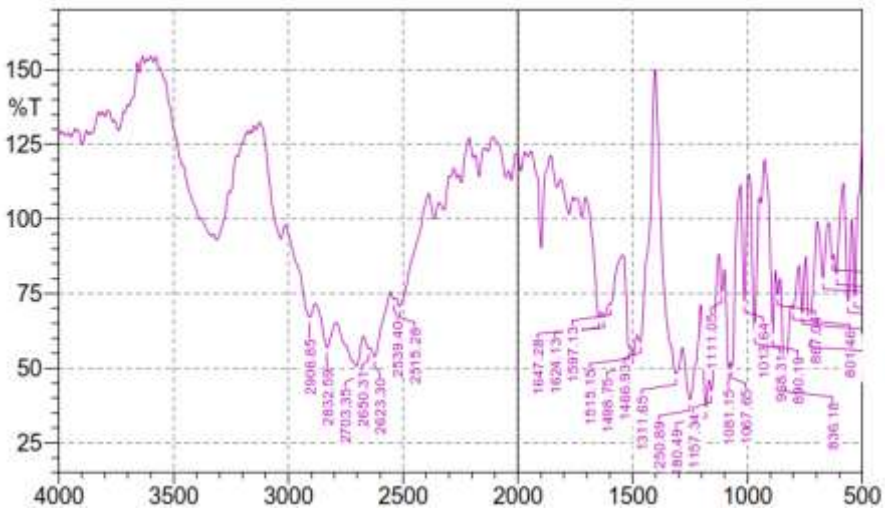

Figure 2. FTIR spectra of mangiferin

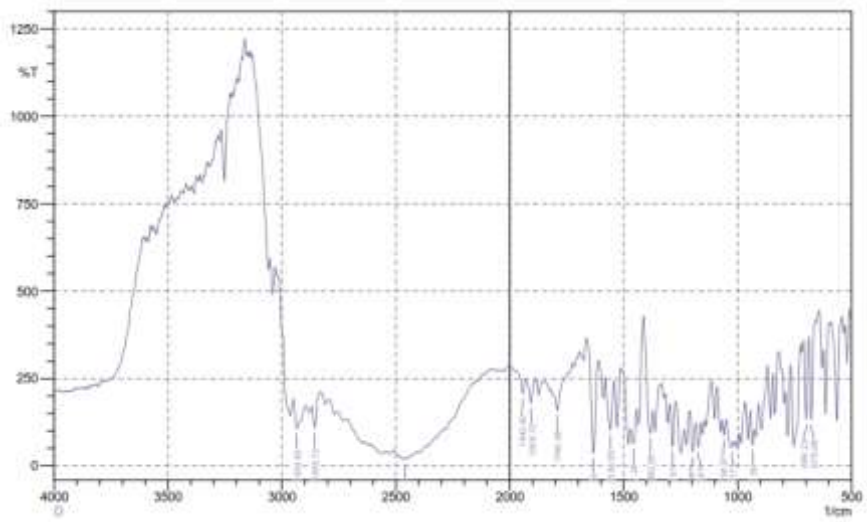

Figure 3. FTIR spectra of physical mixture (mangiferin, HPMC & ER)

Results of Evaluation of the patches

Transdermal patches containing mangiferin were prepared using Hydroxy propyl methyl cellulose (HPMC) as the hydrophilic matrix and eudragit (ER) as the lipophilic component. The elasticity of the patches was attained using oleic acid (30% polymeric weight) as the plasticizer and olive oil (10% polymer weight) was used as the permeation enhancer to assist permeation of drug into the dermis. Solvent casting method is the most widely used and the simplest method for formulation of transdermal patches. The use of inverted funnel allows for controlled evaporation of the solvents from the patch. All the prepared patches were subjected to visual inspection for examining the physical appearance. The physical appearance of the patches gave satisfactory results. All the prepared patches were found to be smooth, non-sticky, opaque, homogeneous, and flexible in nature.

Table 3. Characterization of mangiferin loaded transdermal patches

Formulation	Thickness (mm)	Average weight (mg)	Moisture loss (%)	Drug content (%)	Folding Endurance	Surface pH	Tensile Strength
T1	0.513 ± 0.004	191.33 ± 0.578	7.15 ± 0.158	93.5 ± 0.404	73.4 ± 0.578	5.31 ± 0.006	9.51 ± 0.006
T2	0.561 ± 0.004	221.33 ± 2.309	7.63 ± 0.058	94.6 ± 0.173	76.7 ± 0.578	5.35 ± 0.006	9.54 ± 0.016
T3	0.629 ± 0.003	238.67 ± 1.528	10.15 ± 0.158	97.3 ± 0.153	82.5 ± 1.033	5.51 ± 0.026	10.46 ± 0.015
T4	0.559 ± 0.004	218.67 ± 2.082	7.73 ± 0.058	95.7 ± 0.058	78.3 ± 1.033	5.64 ± 0.012	9.91 ± 0.021
T5	0.533 ± 0.003	193.67 ± 2.082	7.07 ± 0.058	94.9 ± 0.6	75.0 ± 0.578	5.41 ± 0.025	9.58 ± 0.013
T6	0.561 ± 0.003	220.15 ± 3.000	7.28 ± 0.058	95.3 ± 0.265	79.5 ± 0.578	5.53 ± 0.025	9.74 ± 0.113
T7	0.522 ± 0.004	193.33 ± 1.548	7.13 ± 0.100	94.1 ± 0.600	74.1 ± 0.578	5.54 ± 0.040	9.58 ± 0.01

T8	0.558 ± 0.004	226.67 ± 1.528	7.68 ± 0.058	95.1 ± 0.265	76.8 ± 0.578	5.61 ± 0.031	9.76 ± 0.021
T9	0.587 ± 0.003	236.33 ± 4.163	10.07 ± 0.058	97.3 ± 0.115	81.5 ± 0.578	5.54 ± 0.02	10.24 ± 0.025
T10	0.560 ± 0.003	217.33 ± 2.517	8.01 ± 0.058	95.1 ± 0.173	77.5 ± 1.458	5.58 ± 0.015	9.69 ± 0.029
T11	0.603 ± 0.002	216.67 ± 2.082	8.01 ± 0.058	95.6 ± 0.100	76.8 ± 0.578	5.53 ± 0.021	9.73 ± 0.025
T12	0.536 ± 0.003	219.33 ± 0.577	7.75 ± 0.058	95.2 ± 0.231	77.8 ± 1.033	5.57 ± 0.021	9.77 ± 0.035
T13	0.693 ± 0.004	235.33 ± 1.528	9.86 ± 0.1	97.1 ± 0.208	82.6 ± 1.033	5.63 ± 0.015	10.34 ± 0.035

As shown in the table the pH levels of the patches ranged between 5.31 ± 0.006 to 5.64 ± 0.015 suggesting their suitability of human use and possibly suggesting that no skin irritation would be produced on application of the patches. The thickness of the transdermal patches ranged from 0.513 ± 0.004 mm to 0.693 ± 0.004 mm. This difference in the thickness could be attributed to the nature and concentrations of polymers, i.e., an increase in the concentration of the hydrophilic polymer HPMC led to an increased thickness of the transdermal patch. The formulated transdermal patches displayed weight variations between 191.33 ± 0.577 mg and 238.67 ± 2.032 mg. It was revealed from the weight variation data that the increase in the concentration of HPMC resulted in an increased weight of patches. This might be due to the fact that HPMC possesses a greater affinity for water and greater moisture uptake, causing an increased patch weight. The HPMC polymer is more hygroscopic in nature in comparison to ER; it might cause water retention in the patches, thereby resulting in increased weight of patches.

The moisture content of the formulated transdermal patches varied from 7.15 ± 0.058 % to 10.15 ± 0.158 %. Once again, the formulations containing greater amounts of HPMC resulted in an increase in moisture content. As HPMC is hydrophilic and it can cause absorption, as well as retention, of water in transdermal patches. Folding endurance is of utmost importance for patches because greater folding endurance prevents patches from being easily broken or damaged, and patches are considered to meet good quality. All the formulated transdermal patches exhibited high folding endurance (>70 times). This reveals that all transdermal patches meet the standard patch requirements. Different concentrations of the polymers (HPMC and ER) did not considerably affect the folding endurance of the transdermal patches though higher HPMC content increased the folding endurance. PEG400 was used as a plasticizer for obtaining flexible patch formulation. The formulated transdermal patches displayed tensile strength values between 9.51 ± 0.006 kg/cm^2 and 10.46 ± 0.015 kg/cm^2, which were within the acceptable limits for transdermal patches. All the transdermal patch formulations exhibited uniform drug content and with a minimum variability within the batch. The drug content ranged from 93.5 ± 0.404 % to 97.3 ± 0.153 %. This drug content range is deemed suitable for transdermal application.

***In-vitro* release study**

The amount of drug that permeated or released from the transdermal patches was determined using Franz diffusion cell. The *in vitro* drug release study depicted that the highest amount of drug was released from **T9** (86.01 ± 1.033 %) while the lowest was released from **T5** (55.42 ± 2.032 %) at the end of 24 hours of release study. Faster drug release was observed from formulated patches containing greater amounts of the hydrophilic polymer, HPMC and lower amounts of the lipophilic polymer, ER. The study also depicted an increase in hydrophilic polymer that resulted in an increase in burst effect, as well as drug release in the formulation (Figure 4).

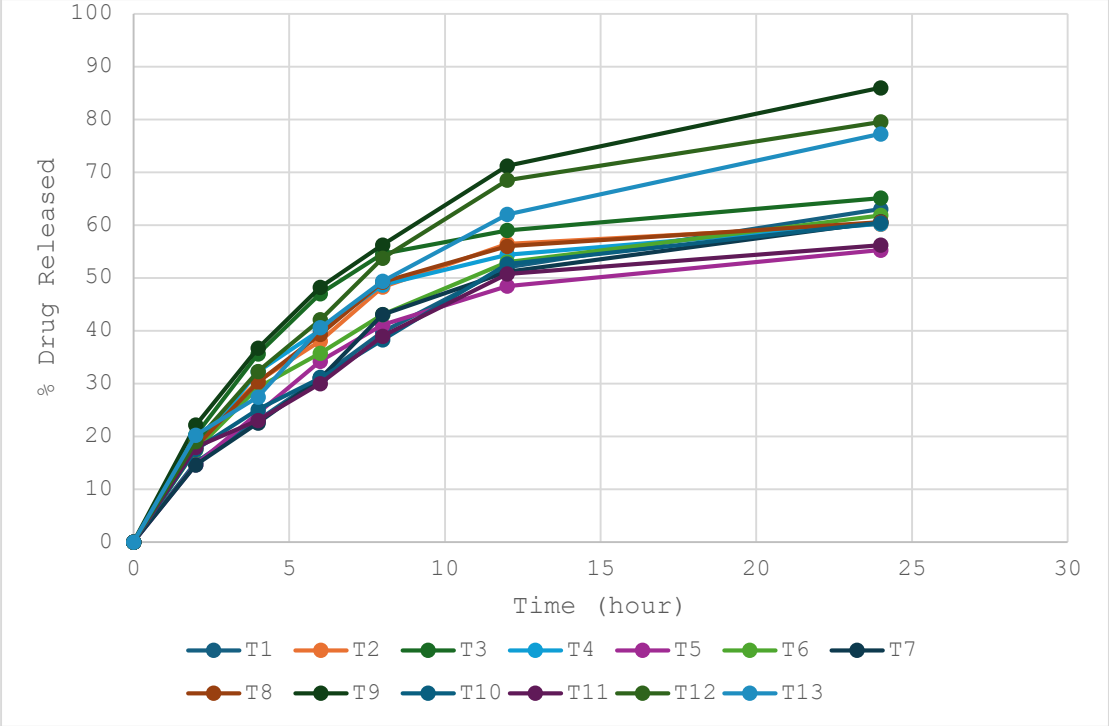

Figure 4. Release of mangiferin from transdermal patches (*in vitro*)

Conclusion

The primary objective of the present investigation was formulating transdermal patched loaded with mangiferin, for management of inflammation. The formulation was achieved using hydroxy propyl methylcellulose (HPMC) and eudragit (ER) as the polymeric release controlling matrix. The formulation was expected to overcome the problems of poor bioavailability, poor distribution and high metabolism associated with oral administration of mangiferin. The ability of the formulated transdermal patches to sustain the release of mangiferin for more than 24 hours was conclusive enough that the problems associated with the oral administration were taken care of. The formulation **T9** released the highest amount of drug and presented highest drug loading. Thus, is could be concluded that **T9** was the best formulation with sufficient strength and drug release that would be able to effectively manage inflammation throughout the day. The optimization study revealed that higher amount of hydrophilic polymer and lower amounts of lipophilic polymers was beneficial for maximum release of mangiferin from the patches in 24 h.

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