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Formulation and Characterization of transdermal patches loaded with Naringin

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ABSTRACT

A Transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream. The transdermal drug delivery system is one of novel drug delivery system which overcomes the conventional dosage form and offers controlled release of the drug into the patient. Naringin has poor bioavailability in the oral dosage form so the transdermal patch of Naringin increases the bioavailability of the drug with respect to the oral dosage form to reduce the inflammation with minimal drug content compliance to the patient. The aim of the study is to develop a transdermal patch loaded with Naringin for the purpose of inflammation. The formulation was achieved using Hydroxypropylmethylcellulose (HPMC) and ethylcellulose (EC) as the polymeric release controlling matrix for sustain release of the Naringin drug. The formulation development has been carried out through solvent evaporation method with an objective to deliver the drug in systemic circulation through skin at predetermined rate with minimal inter and intrapatient variation. Among the formulations developed(NGP1, NGP2, NGP3, NPG4) formulation NGP4 shows significant results, thus confirms the aim of study.

KEYWORDS: Naringin, Bioavailability, Inflammation, Sustain drug release, Transdermal delivery system, Solvent evaporation method

1. INTRODUCTION

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.1

1.1 NEW DRUG DELIVERY METHODS

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

- **Sustained release**

It is developed to maintain therapeutic blood or tissue levels of the drug for an extended period of time which is concentration dependent.

- **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.2

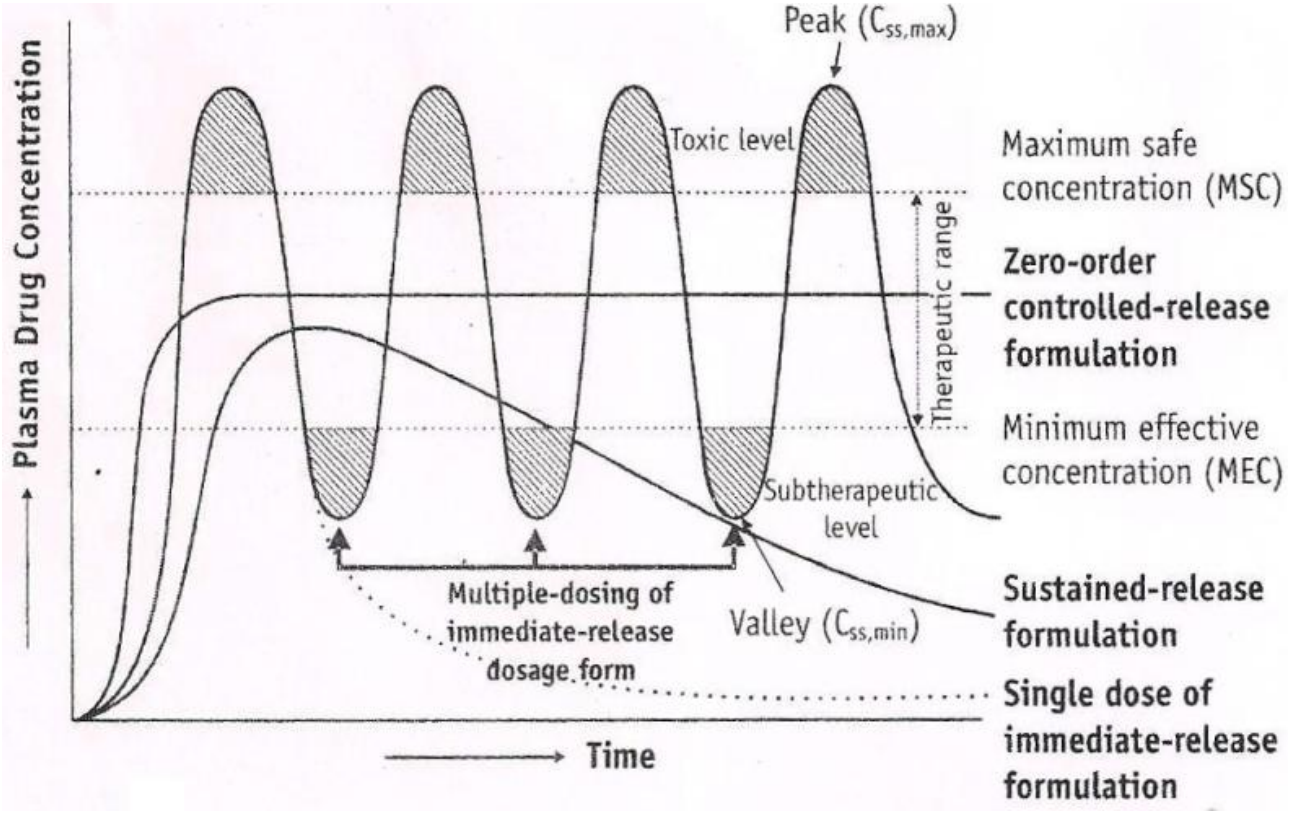

Figure 1.1 Illustrative plasma drug concentration-time profile for various delivery systems

In the proposed research work, we are planning to prepare transdermal patches of natural agent Naringin with the following objective.

• Transdermal patches loaded with Naringin will be prepared using polymers in varying concentration by solvent evaporation technique.

• The prepared transdermal patches will be evaluated for various parameters like weight variation, thickness, folding endurance, tensile strength, drug content, percentage of moisture content, in-vitro release study etc.

• The patch is expected to deliver Naringin at steady rate and for prolonged duration for management of inflammation.

• A lower transdermal dose of the drug would be required for achieving desired therapeutic action when compared to oral administration

2. PREFORMULATION STUDIES

Preformulation studies provide the necessary information of the drug for ascertaining its utilization with excipients for developing a particular formulation. They also fulfill the purpose of authenticating the drug using certain parameters.

2.1 Organoleptic properties

A small quantity of pure Naringin 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.

2.2 Solubility analysis

Solubility of Naringin was determined in water, methanol, ethanol, ethylacetate, n-butanol and petroleum ether. Solubility studies were performed by shaking small amount of naringin in test tubes containing the 1 mL of solvent and observing for undissolved particles (if any).

2.3 Melting point

The melting point of Naringin was determined by open capillary method. The pure drug was filled in a capillary tube sealed at one end and placed in the melting point apparatus. The capillary tube was heated gradually using electrically heated head of the apparatus and the temperature at which the melting starts and the temperature at which the total solid was in molten state was recorded.

2.4 Drug excipient compatibility studies by FT-IR

IR spectra of Naringin, and a physical mixture of Naringin and polymers and excipients were obtained using FT-IR. Spectra were recorded for pure drug, and physical mixture of drug and polymer.

2.5 Standard Curve of Naringin42

The maximum absorption of Naringin in ethanol was observed at 295 nm. The calibration curve was obtained using different concentrations of the drug at the above wave length.

2.5.1 Preparation of stock and standard solution

The stock solution was freshly prepared by dissolving 5 mg of Naringin in 50 ml of ethanol in a 10 ml volumetric flask and then made up the solution upto the mark using the same buffer for obtaining the solution of strength 100 µg/mL (stock I).

2.5.2 Preparation of various concentrations

5 mL stock solution was taken and volume made up to 50 mL by using ethanol to obtain 10 µg/ml. From this solution with draw 2, 4, 6, 8, 10 ml of solution in to the 10 ml volumetric flask and volume made up to 10 ml by using ethanol to get the solutions of 2, 4, 6, 8, 10 µg/ml.
The absorbance of each dilution was observed at 295 nm using UV spectrophotometeremploying ethanol as the reference blank and a calibration curve was plotted.

2.6 Results of Physical characterization of Naringin

The physical characterization of the drug was performed according to the reported procedure and the results obtained are presented Table 6.1 and 6.2.

Table 2.1 Physical Characteristics of Naringin

S No	Parameter	Observation
1	Physical appearance	Amorphous powder
2	Color	Pale Yellow
3	Odour	Odorless
4	Taste	Bitter
5	Melting Point	231-240°C

Table 2.2 Solubility of Naringin

Solvent	**Solubility**
Water	Soluble
Methanol	Soluble
Ethanol	Soluble
Ethyl acetate	Slightly Soluble
n-butanol	Slightly Soluble
Petroleum Ether	Poorly Soluble

Previous study has also revealed the solubility order of Naringin to be methanol > ethyl acetate > n-butanol > isopropanol > petroleum ether > hexane43.

2.7 Results of Drug-Polymer compatibility Study

The compatibility of Naringin with HPMC and Ethyl cellulose was studied using FT-IR spectrum of the pure drug as well as the physical mixture.

On comparison of the FTIR spectra of the drug (Figure 5.1) and the mixture (Figure 5.2) 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 an evidence of compatibility between the drug and the matrix forming polymers.

The FTIR spectrum of Naringin exhibited the stretching and bending vibrations due to OH (3340.56 cm-1), C=O (1699.89 cm-1), C=C (1603.53 cm-1) and C-O-C (1003.43 cm-1).

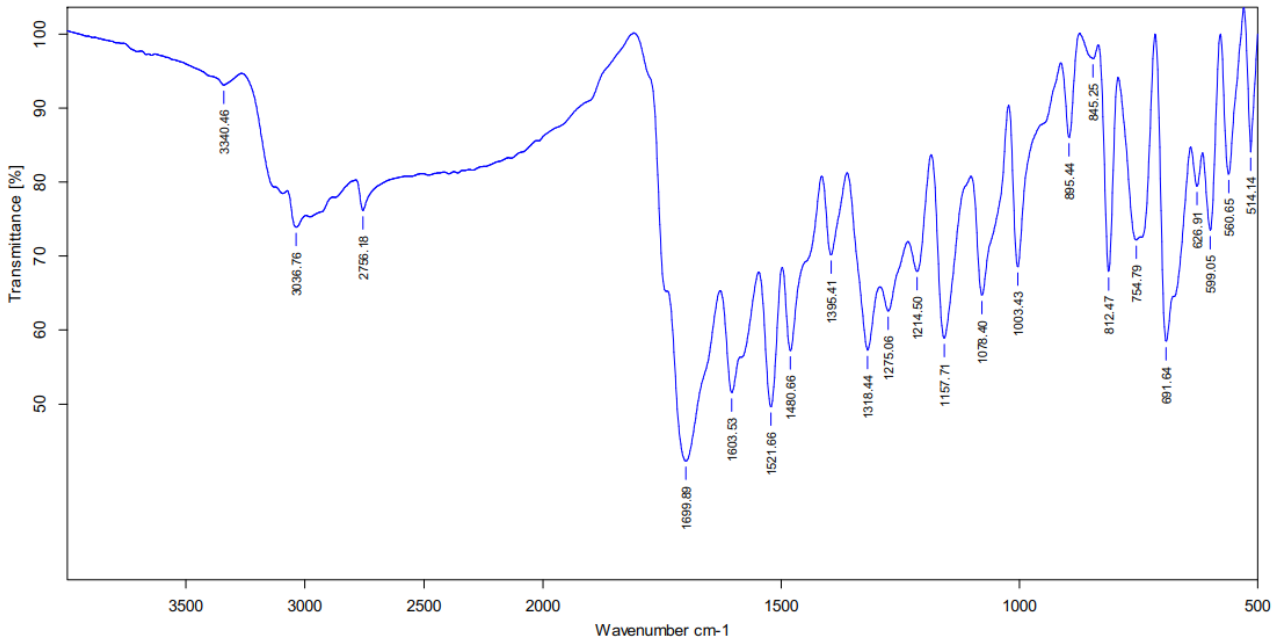

Figure 2.1 FTIR spectrum of Naringin

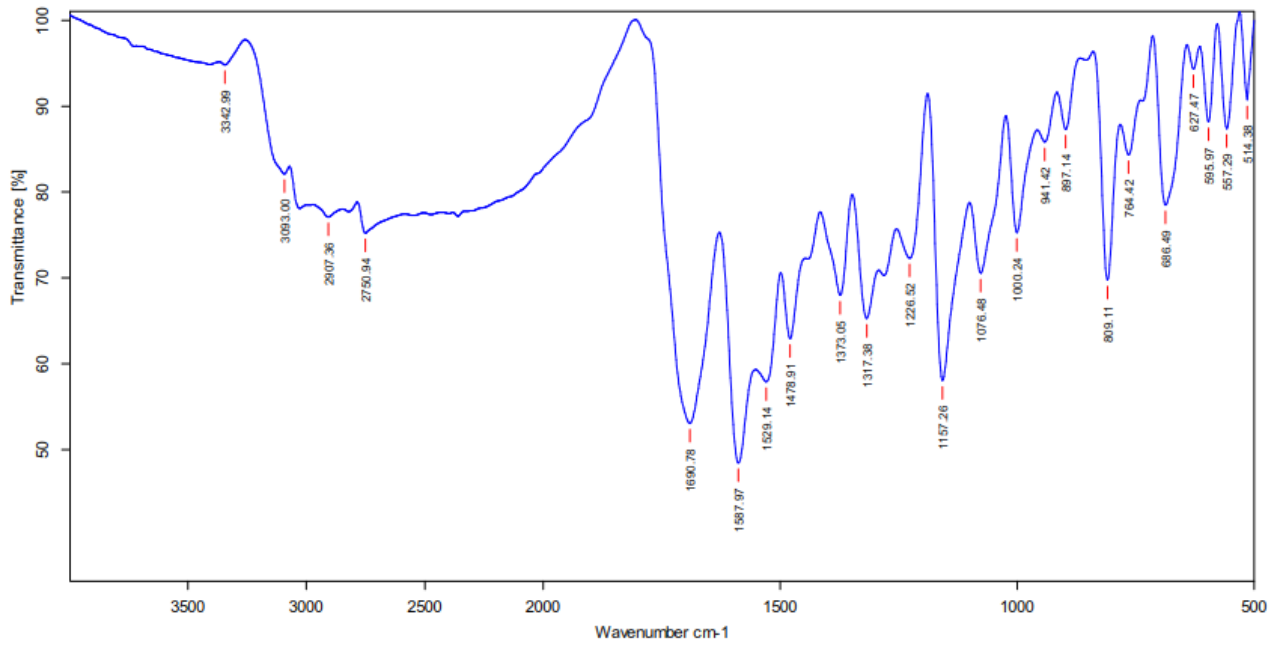

Figure 2.2 FTIR spectrum of physical mixture of drug and polymers

2.8 Calibration curve of Naringin

The Calibration curve of Naringin was constructed by plotting absorbance versus concentration (µg/ml) at 295 nm (Table 6.3, Figure 6.3).

Table 2.3 Calibration curve data of Naringin

Concentration (µg/mL)	Absorbance
0	0
2	0.115
4	0.210
6	0.334
8	0.459
10	0.573

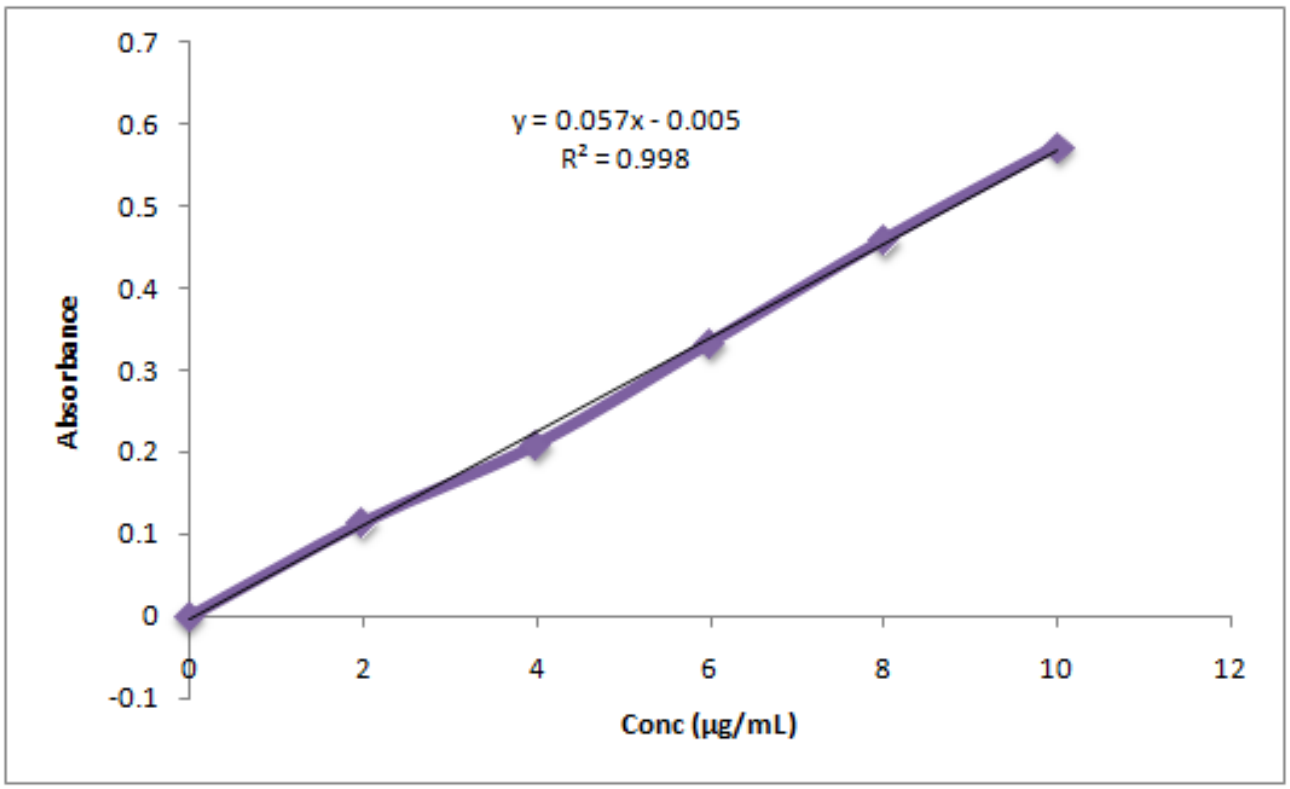

Figure 2.3 Calibration curve of Naringin in ethanol

The regression equation was used to calculate the concentration of Naringin in the formulation as well as in the release study.

3. MATERIAL AND METHODS

3.1 Background

The objective of the present work is to formulate transdermal patches loaded with Naringin. The method of preparation of transdermal patches, the evaluation of the patches and the results obtained are presented in the present chapter.

3.2 Formulation of transdermal Patches

Naringin loaded transdermal patches were formulated utilizing the solvent casting method using a petridish of area 38.46 cm2. 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 7.1). Narigin was accurately weighed and was dissolved in the above solution and mixed until clear solution was obtained. Polyethylene glycol 400 (30% w/w of total polymer) was added to be used as plasticizer and propylene glycol (15% w/w of total polymer) was added as the 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.

Table 3.1 Formula for Naringin loaded transdermal patches44

Ingredients	**NGP1**	**NGP2**	**NGP3**	**NGP4**
Naringin (mg)	180	180	180	180
HPMC (mg)	100	150	200	250
EC (mg)	100	100	100	100
PEG-400 (%w/w)	30	30	30	30
Propylene Glycol(%w/w)	15	15	15	15

Figure 3.1 Solvent evaporation using inverted funnel

Calculation of dose45

Area of petridish=	38.465 cm2
No. of films of 4 cm2 in whole plate=	9
Amount of drug in each film=	20 mg
Total amount of drug required=	180 mg
Label claim of films=	10 mg

3.3 Evaluation of Transdermal Patches46

3.3.1 Physical appearance

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

3.3.2 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. Measurement of

patch weight was carried out using a calibrated analytical balance. The determination was carried out for each formulation in triplicate.

3.3.3 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.

3.3.4 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 cm2 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.

3.3.5 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 represented the value of folding endurance.

3.3.6 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. The following equation was used for the calculation of force required for breaking or cracking of the transdermal patch:

$$Tensile\ Strength = F/[a * b\ (1 + L/I)]$$

where F is the force required to break the patch, a is the width of the patch, and b is the thickness of the patch (cm). L is the length of the patch (cm), and I is the elongation of the patch (cm) before breaking or cracking occurred.

The percent elongation of the formulated transdermal patches was evaluated using the following equation:

$$\% \, Elongation = (Lf - Li) / Li * 100$$

where Lf is the length of the patch before breaking, and Li is the initial length of the patch.

3.3.7 Drug content test

Three pieces of 4 cm2 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 295 nm using UV-Visible spectrophotometer and the drug content was calculated.

3.3.8 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

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

3.3.9 *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 cm2 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 295 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.

Figure 3.2 Franz diffusion cell assembly

4. RESULTS

Transdermal patches were prepared using Hydroxy propyl methyl cellulose (HPMC) as the hydrophilic matrix and ethyl cellulose (EC) as the lipophilic component. The elasticity of the patches was attained using PEG-400 (30% polymeric weight) as the plasticizer and propylene glycol (15% 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. The patches were prepared by varying the ratio of the hydrophilic and the lipohilic matrix. EC and HPMC were used in 4 different ratios (1:1, 1:2, 1:3, 1:4) to obtained the most optimized formulation

The evaluation of the patches was done for various physical parameters as per procedure and the results are reported .

All the prepared patches were subjected to visual inspection for examining thephysical 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 4.1 Characterization of Naringing loaded transdermal patches

Formulation	Thickness (mm)	Average weight (mg)	Moisture loss (%)	Drug content (%)	Folding Endurance	Surface pH	T S
NGP1	0.512 ± 0.0020	118.6 ± 2.88	7.26 ± 0.404	94.7 ± 0.6	68 ± 3.05	5.28 ± 0.005	9
NGP2	0.566 ± 0.0021	205.3 ± 2.51	7.6 ± 0.264	95.7 ± 0.26	72 ± 2.08	5.36 ± 0.01	9
NGP3	0.633 ± 0.0028	235.3 ± 2.08	10.2 ± 0.360	96.5 ± 0.34	77 ± 3.51	5.58 ± 0.005	1
NGP4	0.697 ± 0.0022	244 ± 2.64	11.93 ± 0.450	97.2 ± 0.15	79 ± 1.52	5.61 ± 0.011	1

Data are expressed as mean ±SD; n = 3

As shown in the table the pH levels of the patches ranged between 5.28 to 5.61 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 0.512 ±0.0020 mm to 0.697 ±0.0022 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.

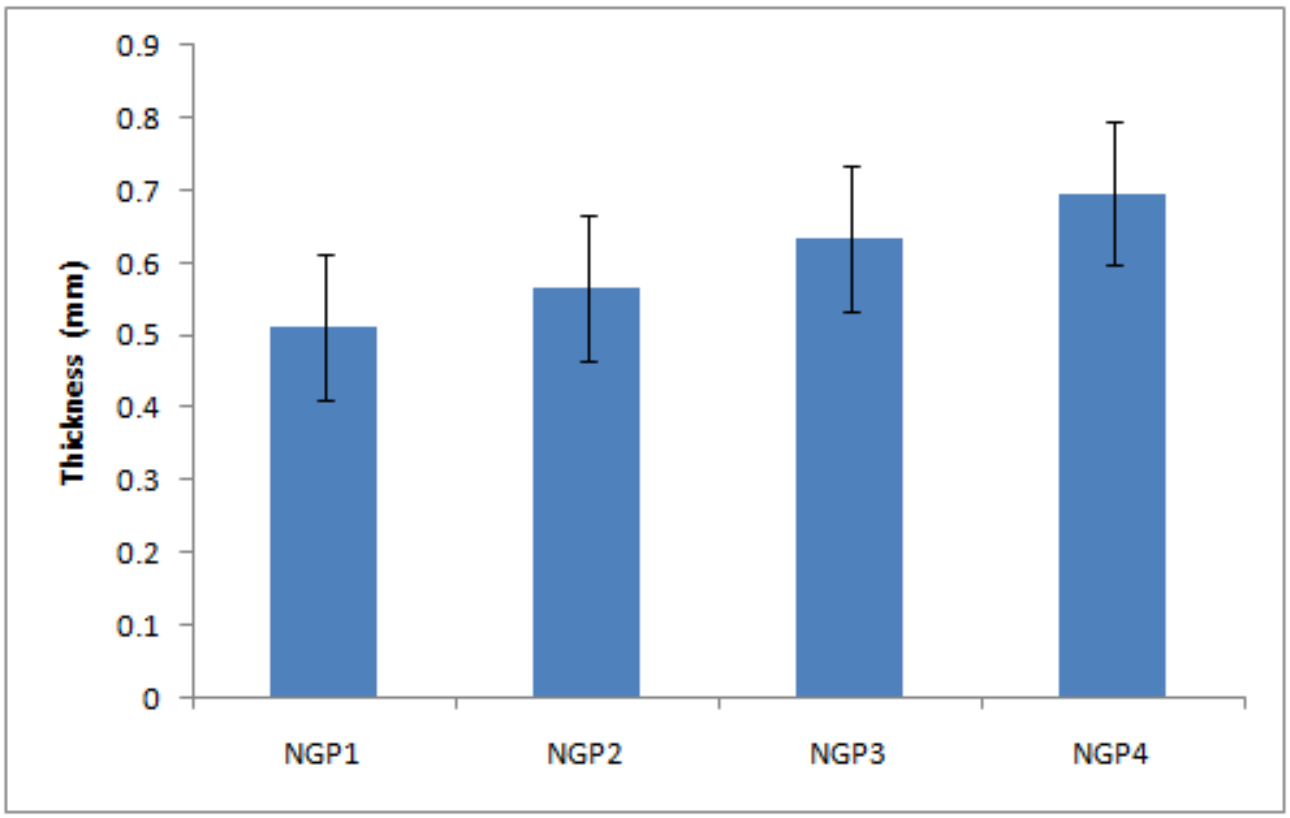

Figure 4.1 Variation in thickness of the transdermal patch formulations

The formulated transdermal patches displayed weight variations between 118.6 ±2.88mg and 244 ± 2.64 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 EC; it might cause water retention in thepatches, thereby resulting in increased weight of patches.

The moisture content of the formulated transdermal patches varied from 7.26 ±0.404% to 11.93 ± 0.450%. 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 .

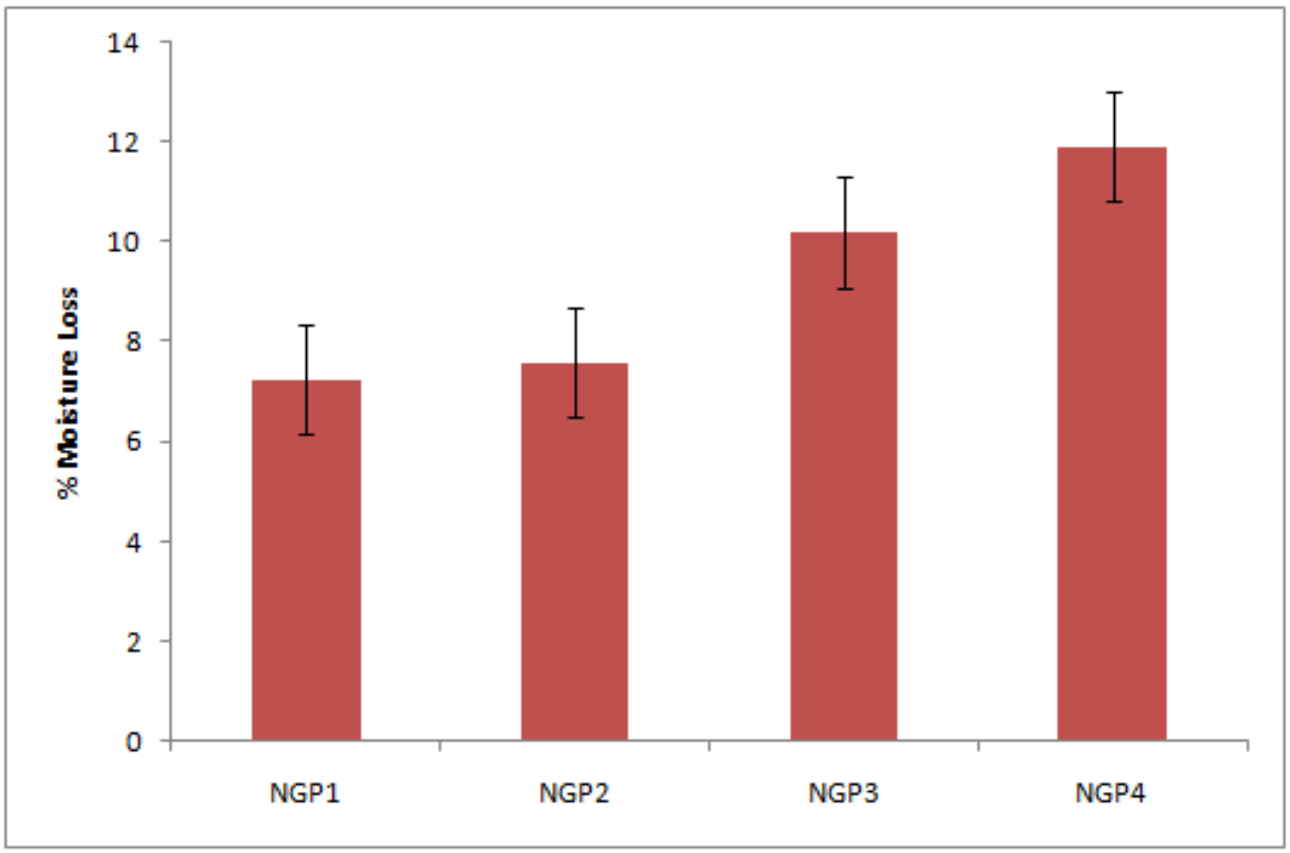

Figure 4.2 Variation in moisture content of the transdermal patch formulations

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 exhbitedhigh folding endurance (>60 times). This reveals that all transdermal patches meet the standard patch requirements. Different concentrations of the polymers (HPMC and EC) 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 9.61 ±0.052 kg/cm2 and 10.59 ±0.034 kg/cm2, 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 94.7 ±0.6% to 97.2 ±0.15%. This drug content range is deemed suitable for transdermal application.

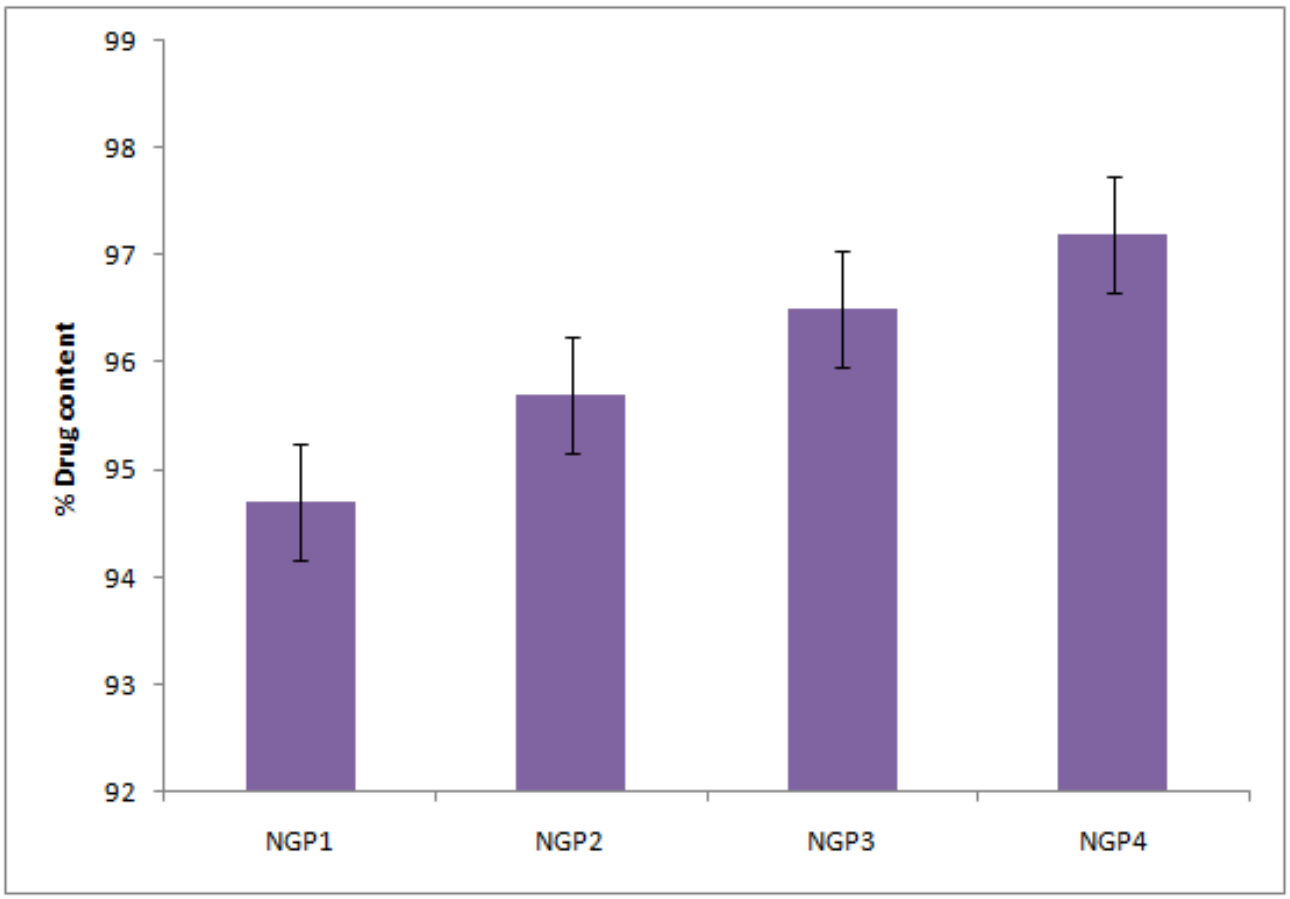

Figure 4.3 Drug content in the formulated transdermal patches

From the above figure it was very clear that increase in the concentration of HPMC caused an increase in drug loading in the patch which may be due to the fact that HPMC being a hydrophilic polymer had affinity for Naringin which is also having good water solubility. The retention of water by HPMC in turn led to the higher loading of Naringin.

7.5 Result of *in-vitro* permeation 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 NGP4 (87.96 ±1.145) while the lowest was released from NGP1 (64.06 ±1.793%) 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. 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.

Table 4.2 In vitro release of Naringin from transdermal patches

Formulation	Drug Release (%)						
	0	**2**	**4**	**6**	**8**	**12**	**24**
NGP1	0	19.21 ± 0.995	25.18 ± 1.342	33.73 ± 0.493	41.34 ± 0.773	51.56 ± 1.105	64.06 ± 1.793
NGP2	0	23.08 ± 2.718	31.62 ± 0.986	39.26 ± 3.011	49.47 ± 0.626	57.63 ± 0.040	72.44 ± 1.515
NGP3	0	27.54 ± 1.245	36.81 ± 1.042	48.23 ± 0.706	60.79 ± 1.194	70.28 ± 0.097	81.37 ± 0.436
NGP4	0	32.37 ± 0.566	39.05 ± 0.486	49.19 ± 0.385	61.58 ± 0.714	72.17 ± 0.652	87.96 ± 1.145

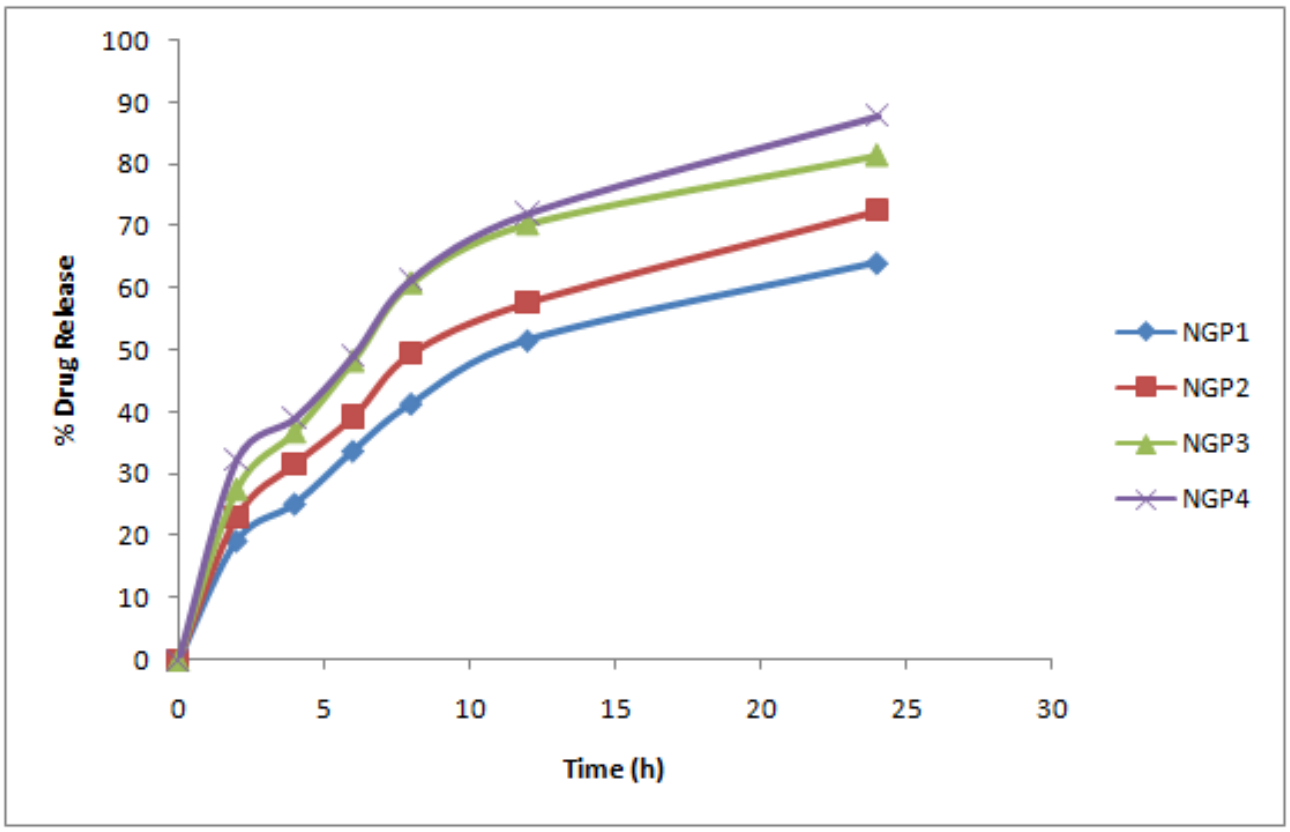

Figure 4.4 Release of naringin from transdermal patches (*in vitro*)

5. SUMMARY AND CONCLUSION

5.1 Summary

In the present study the prime objective was to develop transdermal patches loaded with Naringin in order to improve its bioavailability by sustaining the drug release. Transdermal patches were prepared using Hydroxy propyl methyl cellulose (HPMC) as the hydrophilic matrix and ethyl cellulose (EC) as the lipophilic component. The elasticity of the patches was attained using PEG-400 (30% polymeric weight) as the plasticizer and propylene glycol (15% polymer weight) was used as the permeation enhancer to assist permeation of drug into the dermis. The patches were prepared by varying the ratio of the hydrophilic and the lipohilic matrix. EC and HPMC were used in 4 different ratios (1:1, 1:2, 1:3, 1:4) to obtained the most optimized formulation

All the prepared patches were subjected to visual inspection for examining thephysical 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.

The pH levels of the patches ranged between 5.28 to 5.61 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 0.512 ±0.0020 mm to 0.697 ±0.0022 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 118.6 ±2.88mg and 244 ± 2.64 mg. It was revealed from the weight variation data that the increase in the concentration of HPMC resulted in an increased weight of patches.The moisture content of the formulated transdermal patches varied from 7.26 ±0.404% to 11.93 ±0.450%.

All the formulated transdermal patches exhbited high folding endurance (>60 times). This reveals that all transdermal patches meet the standard patch requirements. The formulated transdermal patches displayed tensile strength values between 9.61 ±0.052 kg/cm2 and 10.59 ±0.034 kg/cm2, 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 94.7 ±0.6% to 97.2 ±0.15%.

The *in vitro* drug release study depicted that the highest amount of drug was released from NGP4 (87.96 ±1.145) while the lowest was released from NGP1 (64.06 ±1.793%) at the end of 24 hours of release study.

5.2 Future Perspective

The results obtained from the study would be seconded by optimizing the formulation using various design approaches in order to obtain a highly optimized formula that might be able to sustain the release of naringin for even higher time duration so that the formulation once applied could be able to manage inflammation for several days.

5.3 Conclusion

The primary objective of the present investigation was formulating transdermal patched loaded with narinign, for management of inflammation. The formulation was achieved using Hydroxypropylmethylcellulose (HPMC) and ethylcellulose (EC) 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 naringin. The ability of the formulated transdermal patches to sustain the release of naringin for more than 24 hours was conclusive enough that the problems associated with the oral administration were taken care of. The formulation NGP4 released the highest amount of drug and presented highest drug loading. Thus is could be concluded that NGP4 was the best formulation with sufficient strength and drug release that would be able to effectively manage inflammation throughout the day.

REFERENCES

1. Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics- A treatise" 484-489.
2. Robinson J, Lee VHL. Controlled drug delivery-Fundamentals and applications. 2ndedition.
3. Basu B, Garala K, Bhalodia R, Joshi B, Mehta K. Solid lipid nanoparticles: A promising tool for drug delivery system. Journal of Pharmacy Research 2008; 3(1): 84 – 92.
4. Smola M, Vandamme T, Sokolowski A. Nanocarriers as pulmonary drug delivery systems to treat and to diagnose respiratory and non-respiratory diseases. International Journal of Nanomedicine 2008; 1-9.
5. Iman IS, Nadia AS, Ebtsam MA. Formulation and stability study of chlorpheniramine maleate transdermal patch. Asian J Pharm. 2010;70(4):455-460
6. Shah SS, Joshi R, Prabhakar P. Formulation and evaluation of transdermal patches of papaverine hydrochloride. Asian J Pharm. 2010;4(1):79:86

7. Ren C et-al. Design and in vivo evaluation of an indapamide transdermal patch. Int J Pharm. 2009;370:129-135

8. Shinde AJ, Shinde AL, More HN. Design and evaluation of transdermal drug delivery system of gliclazide. Asian J Pharm. 2010;4(2):121-129

9. Salimi A, Amirimoghadam S, Bagheri F. Preparation, Optimization and Evaluation of Naringenin- Loaded Microemulsion for Topical Application**.** Iranian Biomedical Journal. 2022 (Article in Press)

10. Dong Z, Wang R, Wang M, Meng Z, Wang X, Han M, Guo Y, Wang X. Preparation of Naringenin Nanosuspension and Its Antitussive and Expectorant Effects. Molecules. 2022, 27, 741.

11. Ishimoto K, Shimada Y, Ohno A, Otani S, Ago Y, Maeda S, Lin B, Nunomura K, Hino N, Suzuki M, Nakagawa S. Physicochemical and Biochemical Evaluation of Amorphous Solid Dispersion of Naringenin Prepared Using Hot-Melt Extrusion. Frontiers in Nutrition. 2022; 9: 850103.

12. Mohanty S, Badireenath Konkimalla V, Pal A, Sharma T, Si SC. Naringin as Sustained Delivery Nanoparticles Ameliorates the Anti-inflammatory Activity in a Freund's Complete Adjuvant-Induced Arthritis Model. ACS Omega. 2021; 6: 28630−28641

13. Bhia M, Motallebi M, Abadi B, Zarepour A, Pereira-Silva M, Saremnejad F, Cláudia Santos A, Zarrabi A, Melero A, Jafari SM, Shakibaei M. Naringenin Nano-Delivery Systems and Their Therapeutic Applications. Pharmaceutics. 2021; 13; 291.

14. Liu S, Dong J, Bian Q. Preparation of Naringenin Solution for *In Vivo* Application. *Journal of Visualized Experiments. 2021;* (174), e62736: doi:10.3791/62736.

15. Pawar AY, Jadhav KR, Naikwade K, Mahajan TP. Formulation & Evaluation of Naringin Nanoethosome by Cold Method. Journal of Pharmaceutical Research International. 2021; 33(42B): 139-152.

16. Kriplani P, Guarve K, Baghel US. Formulation optimization and characterization of transdermal film of curcumin by response surface methodology. Chinese Herbal Medicines. 2021; 13: 274-285.

17. Sharma JB, Bhatt S, Saini V, Kumar M. Pharmacokinetics and Pharmacodynamics of Curcumin-Loaded Solid Lipid Nanoparticles in the Management of Streptozotocin-Induced Diabetes Mellitus: Application of Central Composite Design. Assay and Drug Development Technologies 2021; 19(4): 262-279.

18. Jeevitha E, Sukumaran SK. Development and Evaluation of Naringenin Loaded Chitosan Nanoparticles for Improved Treatment of Neurotoxicity. Research Journal of Pharmacy and Technology. 2020; 13(1): 129-134

19. Zode RD, Barsagade PD, Giri NS, Umekar MJ, Raut NS. Nanoemulsion Based Transdermal Patch of Curcumin and Curcumin Analogue. International Journal of Pharmaceutical Sciences Review and Research. 2020; 62(2): 120-127

20. Gupta T, Singh J, Kaur S, Sandhu S, Singh G, Kaur IP. Enhancing Bioavailability and Stability of Curcumin Using Solid Lipid Nanoparticles (CLEN): A Covenant for Its Effectiveness. Frontiers in Bioengineering and Biotechnology 2020; 8: 879. doi: 10.3389/fbioe.2020.00879

21. Ban C, Jo M, Park YH, Kim JH, Han JY, Lee KW, Kewon DH, Choi YJ. Enhancing the oral bioavailability of curcumin using solid lipid nanoparticles. Food Chemistry 2020; 302: 125328. Doi: 10.1016/j.foodchem.2019.125328

22. Yang X, Almassri HNS, Zhang Q, Mia Y, Zhang D, Chen M, Wu X. Electrosprayed naringin-loaded microsphere/SAIB hybrid depots enhance boneformation in a mouse calvarial defect model. Drug Delivery. 2019; 26(1): 137-146

23. Malvajerd SS, Azadi A, Izadi Z, Kurd M, Dara T, Dibaei M, Zadeh MS, Javar HA, Hamidi M. Brain Delivery of Curcumin Using Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Preparation, Optimization, and Pharmacokinetic Evaluation. ACS Chemical Neuroscience 2019; 10: 728-739.

24. Ghosal K, Ghosh D, Das SK. Preparation and evaluation of naringin-loaded polycaprolactone microspheres based oral suspension using Box-Behnken design. Journal of Molecular Liquids. 2018; 256: 49-57

25. Wang W, Chen T, Xu H, Ren B, Cheng X, Qi R, Liu H, Wang Y, Yan L, Chen S, Yang Q, Chen C. Curcumin-Loaded Solid Lipid Nanoparticles Enhanced Anticancer Efficiency in Breast Cancer. Molecules 2018; 23: 1457. Doi: 10.3390/molecules23071578

26. Kriplani P, Guarve K, Baghel US. Optimization and characterization of transdermal film of curcumin containing natural oils as permeation enhancer by response surface methodology. Journal of Innovations in Pharmaceutical and Biological Sciences. 2018; 5(2): 1-15.

27. Kharia A, Gilhotra R, Singhai AK. Formulation and evaluation of transdermal patch for treatment of inflammation. Int J Pharm Sci Res. 2018; 10.13040/IJPSR.0975-8232.10(5).2375-84

28. Madderla S, Tripura Sundari P. Formulation and evaluation of curcumin loaded solid lipid nanoparticles by hot homogenization method by employing glyceryl monostearate. International Journal of Scientific Development and Research 2018; 3(12): 208-216.

29. Hindarto CK, Surini S, Saputri FC, Irawan C. In vivo evaluation of luteolin-loaded phytosome. The Pharma Innovation J. 2017;6(11):347-349

30. Setyawati DR, Surini S, Mardliyati E. Optimization of luteolin-loaded transfersome using response surface methodology. Int J Appl Pharmaceutics. 2017; http://dx.doi.org/10.22159/ijap.2017.v9s1.64_71

31. Jiang S, Zhu R, He X, Wang J, Wang M, Qian Y, Wang S. enhanced photocytotoxicity of curcumin delivered by solid lipid nanoparticles. International Journal of Nanomedicine 2017; 12: 167-178.

32. Ji H, Tang J, Li M, Ren J, Zheng N, Wu L. Curcumin-loaded solid lipid nanoparticles with Brij78 and TPGS improved in vivo oral bioavailability and in situ intestinal absorption of curcumin. Drug Delivery 2016; 23(2): 459-470.

33. Abidin L, Mujeeb M, Imam SS, Aqil M, Khurana D. Enhanced transdermal delivery of luteolin via non-ionic surfactant-based vesicle: quality evaluation and anti-arthritic assessment. Drug Del. 2016; 23(3):1069-1074

34. Khamora P, Trivedi N, Chandrawanshi H. Development and Evaluation of Transdermal Patch of Curcumin for Rheumatoid Arthritis. Panacea Journal of Pharmacy and Pharmaceutical Sciences. 2015; 3(4): 108-120

35. Sun J, Bi C, Chan HM, Sun S, Zhang Q, Zheng Y. Curcumin-loaded solid lipid nanoparticles have prolonged in vitro antitumour activity, cellular uptake and improved in vivo bioavailability. Colloids and Surfaces B: Biointerfaces 2013; 111: 367-375.

36. Chirio D, Gallarate M, Peira E, Battaglia L, Serpe L, Trotta M. Formulation of curcumin-loaded solid lipid nanoparticles produced by fatty acids coacervation technique. Journal of Microencapsulation 2011; 28(6): 537-548

37. Puhl AC, Fagundes M, dos Santos KC, Polikarpov I, das Graças MF, da Silva F et al. Preparation and characterization of polymeric nanoparticles loaded with the flavonoid luteolin, by using factorial design. Int J Drug Del. 2011;3:683-698

38. Saraswathi R, Krishnan PN, Dilip C, Shabir Ali TK. Formulation and evaluation of transdermal patches of curcumin. Der Pharmacia Lettre. 2010; 2(5): 117-126

39. Patel NA, Patel NJ, Patel RP. Design and Evaluation of Transdermal Drug Delivery System for Curcumin as an Anti-Inflammatory Drug. Drug Development and Industrial Pharmacy. 2009; 35: 234-239.

40. https://pubchem.ncbi.nlm.nih.gov/compound/Naringin; assessed on 07/01/2022

41. Ahirwar S, Kumar A, Sharma R. Formulation development and in vitro evaluation of oral dispersible tablets of Olanzapine by direct compression. Journal of Pharmacology and Biomedicine. 2021; 5(4): 304-311.

42. Cordenonsi LM, Sponchiado RM, Campanharo SC, Garcia CV, Raffin RP, Schapova EES. Study of Flavonoids presente in Pomelo (Citrus máxima) by DSC, UV-VIS, IR, 1H AND 13C NMR and MS. Drug Analytical Research. 2017; 01: 31-37.

43. Zhang L, Song L, Zhang P, Liu T, Zhou L, Yang G, Lin R, Zhang J. Solubilities of Naringin and Naringenin in Different Solvents and Dissociation Constants of Naringenin. Journal of Chemical Engineering and Data. 2015; 60(3): 932-940

44. Trivedi D, Goyal A. Formulation and evaluation of transdermal patches containing dexketoprofen trometamol. International Journal of Pharmaceutical Chemistry and Analysis. 2020;7(2): 87–97

45. Gavaskar B, Kumar S, Sharan G, Rao Y. Overview on fast dissolving films. Int J Pharmacy Pharm Sci.2010;2(3): 29-33.

46. Latif MS, Al-Harbi FF, Nawaz A, Rashid SA, Farid A, Mohaini MA, Alsalman AJ, Hawaj MAA, Alhashem YN. Formulation and Evaluation of Hydrophilic Polymer Based Methotrexate Patches: In Vitro and In Vivo Characterization. Polymers. 2022; 14: 1310.