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Formulation and Performance Evaluation of Transdermal Patch of Luteolin Research

Tekeshwar Kumar Turkar, B.K.Dubey, Deepak Kumar Basedia
Technocrats Institutes of Technology- Pharmacy, Anand Nagar, BHEL, Bhopal, M.P.-462021, India.

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ABSTRACT
Luteolin (LUT) is a promising molecule with potential anti-arthritic activity. This investigation presents formulation and evaluation of niosomal trans gel for enhanced transdermal delivery of LUT. Different non-ionic surfactants and vesicle compositions were employed for preparation of niosomes. The vesicle size analysis showed that all vesicles were in the range from 534.58 to 810.22 nm which favoured efficient transdermal delivery. The entrapment of LUT in vesicle was found to be higher in all surfactant. The developed formulation was proved significantly superior in terms of amount of drug permeation with an enhancement ratio of 2.66 when compared to a control formulation. The in vivo bioactivity studies revealed that the prepared niotrans gel formulation of LUT was able to provide good anti-arthritic activity and the results were comparable to standard (diclofenac gel for anti-arthritic and analgesic). Finally, the results were confirmed through radiological analysis which proved that the prepared niosomal trans gel was effectively able to treat arthritis and results were comparable with the standard formulation.

I. 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. 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.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.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. It offers many important advantages over oral drug delivery, e.g., gastrointestinal and hepatic first pass metabolism, reduces variation in delivery rates, avoids interference due to presence of food, controls absorption rate, suitable for unconscious patients, and enables fast termination of drug delivery, if needed.

Types of Transdermal Patches
1. Single-layer drug – in-adhesive.
2. Multi-layer drug-in-adhesive.
3. Drug reservoir-in-adhesive.
4. Drug matrix-in-adhesive.

Benefits of transdermal drug delivery systems
1. Provides safe, convenient and pain less self administration systems for patients.
2. Beneficial for patients on polymedication.

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3. Provide constant rate of drug release.
4. Bypass metabolic problems like presystemic metabolism thereby improves therapeutic efficacy.
5. Decreases dosing frequency of the drug.
6. Very helpful in long term treatment regimes.

Basic components of transdermal systems

1. Polymer matrix.
2. Rate controlling membrane.
3. Adhesive.
4. Release liners.
5. Backing laminate.
6. Penetration enhancers
7. Drug.
8. Plasticizers and solvents.

II. METHODOLOGY AND MATERIAL

(1). Use of Chemical Enhancers:-

The enhancement of skin has been tested with water, surfactants, essential oils, dimethyl sulfoxide (DMSO), and alcohols. Barry and coworkers proposed the lipid-protein partitioning (LPP) theory to describe how enhancers affect skin permeability. By disrupting the intercellular bilayer lipid structure and interacting with intracellular proteins of the stratum corneum, chemical enhancers improve the partitioning of a drug, coenhancer, or cosolvent into the stratum corneum.

One of the safest and most widely used chemical enhancer to increase permeation is water. It is hypothesized that the increased hydration of the skin may lead to swelling and to the opening of the structure which can increase permeation. Other types of enhancers have shown increase in permeability by disordering the lipid structure of the stratum corneum. The diffusion coefficient of the drug is increased as microcavities are formed in the lipid bilayers. In other cases, enhancers can create permeable " pores" that provide less resistance for polar molecules. Penetration of chemical enhancers has also been found to interact with the keratin in the corneocytes. The surfactants interact and bind with keratin to disrupt the order within the corneocytes thereby diffusion coefficient. One of the major side effects of chemical enhancers is irritation to the skin at potent levels, which is not surprising since the chemicals disrupt organized lipid structures, cell membranes, and their components. The toxicity associated with many enhancers have limited their usefulness in clinical applications, however there has been a move towards investigating potential generally regarded as safe (GRAS) enhancers by the FDA, such as essential oils and terpenes.

(2). Iontophoresis

This method of transdermal drug delivery involves low level electric current applied either directly or indirectly to the skin in order to enhance its permeation. The electrical charge primarily drives drug molecules through the skin via sweat ducts since they provide less electrical resistance than the stratum corneum. The reason for the increased permeation can be attributed to one or all of the following: electrophoresis (for charged solutes), electro-osmosis (for uncharged solutes), and electropertubation (for both charged and uncharged solutes). Electrophoresis drives charge molecules across the skin by direct interaction with the applied electric field, therefore small highly charged particles are delivered more rapidly. In electroosmosis, the delivery of molecules occurs as they are dragged by the electrically induced solvent flow. The flow of the solvent is induced by the net flux of cations from the anode to the cathode. The electroosmotic flow of water is generated by the preferential movement of mobile cations in the cells (i.e. Na+) instead of fixed anions proteins in the skin.

Typically, a few milliamperes of current are applied to a small area of the skin, generating no pain beyond mild erythema. The Phoresor^{TM} was the first iontophoretic system approved by the FDA in the late 1970s as a therapeutic device. Currently, iontophoretic systems are approved for administering drugs into the body for specialized medical purposes, such as diagnosis of medical conditions and glucose monitoring. Despite the straight forward application, many parameters can affect the design of an iontophoretic device, including but not limited to electrode type, current intensity, pH of system, and competitive ion effect. Currently, there are many requirements for a successful iontophoretic device. For example, the device must: (1) be sufficiently high powered to provide desired delivery rate; (2) not produce any permanent harmful effects on skin permeability; (3) establish proportionality between flux and applied current/voltage; and (4) maintain constant current/voltage over time. In addition, iontophoresis is limited by the electric current that can be used on humans (regulated at 0.5mA/cm^2)

(3). Electroporation

This method of transdermal delivery is similar to iontophoresis, in which it uses electrical current to aid the delivery of drug molecules through the skin. In the case of electroporation,

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extremely high voltage pulses, rather than milliamperes of current, are used to induce skin perturbation. The high voltage creates transient pores which may account for the skin permeability. The increased skin permeability is related to the electroporation process, which is the formation of aqueous pathways across the lipid bilayer by a pulsed electric field. This technology can enhance the skin permeability to molecules of greater hydrophilicity and sizes compared to other methods.

High voltages (≥100 V) over short durations (milliseconds) are normally applied. The pulses can be administered painlessly using closely spaced electrodes to minimize the electric field in the nerve-free stratum corneum. With the application of high voltages, transdermal transport can be reduced to a few seconds opening opportunities for rapid-response delivery systems. Transdermal transport has been shown to increase by orders of magnitude with partial to full reversibility within minutes to hours. However, with the use of high voltage, there is a greater chance of cell damage if the pulses duration or intensity is too great. In addition, electroporation requires specialized and cumbersome equipment.

This method of transdermal drug delivery involves piercing the skin with very short needles. Solid microneedles (~50-100μm) encapsulated or coated with drug formulations for controlled or rapid release. Microneedles increase permeability and delivery of drugs transdermally by creating micron-scale pathways into the skin, driving drugs into the skin as coated cargo. Their effects are targeted in the stratum corneum, although they do pierce across the epidermis and into superficial dermis. Microneedles treatment have been reported to be painless by volunteers and generally well tolerated. This technique has great promise because they appear to be capable of delivering a broad range of drugs. A notable limitation is the diffusion rate of large compounds through micron-scale pathways. When rapid delivery is required, it may be necessary use an additional force to drive the drugs into the skin.

III. RESULT AND DISCUSSION:

(1). Preformulation Studies:-

Preformulation studies were carried out for luteolin for determination of its physical and chemical properties and also to confirm the specifications of the sample.

(4).Microneedles:-

(1.1). Physical Characterization:-

The results of the physical characterization of the pure drug are reported in Table:1.1

S.No.	Test	Observation
1.	Color	Yellow
2.	Taste	Tasteless
3.	Odor	Odorless
4.	State	Amorphous Powder

Table : 1.1 Physical characteristics of Luteolin

The available literature and data confirm the physical characteristics of the drug.

(1.2). Solubility profile of drug:-

The solubility of the pure drug was determined in various solvents and the result is reported in Table 1.2.

S. No.	Solvent	Solubility
1	Water	Partially soluble
2	Methanol	Soluble
3	Ethanol	Soluble
4	Dimethyl formamide	Freely Soluble
5	DMSO	Freely soluble

Table 1.2: Solubility of Luteolin

(1.3). Melting Point:-

The melting point was determined using open capillary method and the result is reported in table 1.3. It was found to be equivalent to already reported results.

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Test	Specification	Observation
Luteolin	325°C	327-330°C

Table 1.3: Melting Point of Luteolin

(1.4). Partition Coefficient:-

The partition coefficient study was performed and the log P value was found to be **2.5**. The literature reveals the experimental log P value of 2.53 for the drug.

(1.5). Calibration Curves of Luteolin:-

The coefficient of correlation obtains from the standard plot show the linearity of the analytical method. The correlation values of more than 0.99 are evident of the applicability of the analytical method. The calibration curve was constructed using water-methanol-acetic acid mixture as the mobile phase and diluent. The calibration curve is presented in Figure 5.1 along with the equation for regression and the data for calibration curve is presented in Table 5.4. The total run time was performed for 6 minutes and luteolin was found to be eluted out in 1.3 minutes. The chromatogram is presented in figure 5.2.

EVALUATION OF TRANSDERMAL PATCHES

(1). Physiochemical Parameters of Transdermal Patches:-

The evaluation of the patch was performed as per the procedures presented in the experimental section and the result is reported in Table 5.5.

S No	Concentration (µg/mL)	Peak Area
1	20	4591092
2	40	9262163
3	60	13573276
4	80	18064368
5	100	22955460

Table 5.4: Calibration data for luteolin

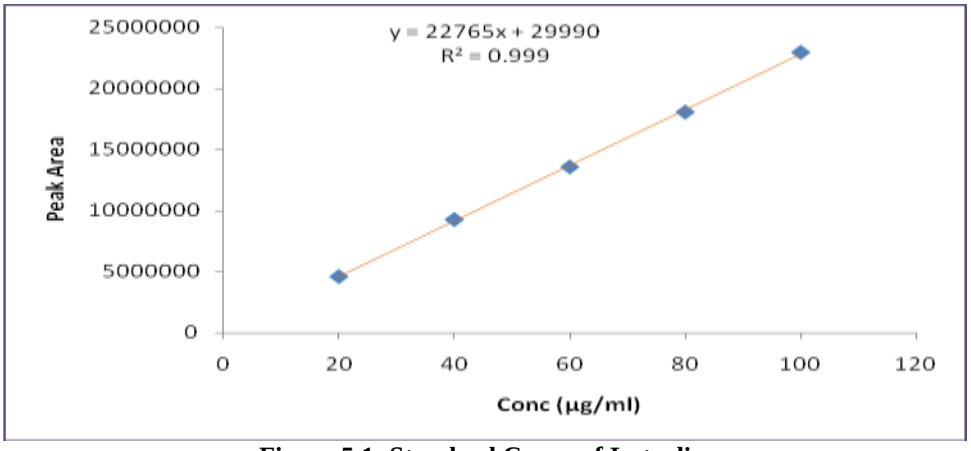

Figure 5.1: Standard Curve of Luteolin

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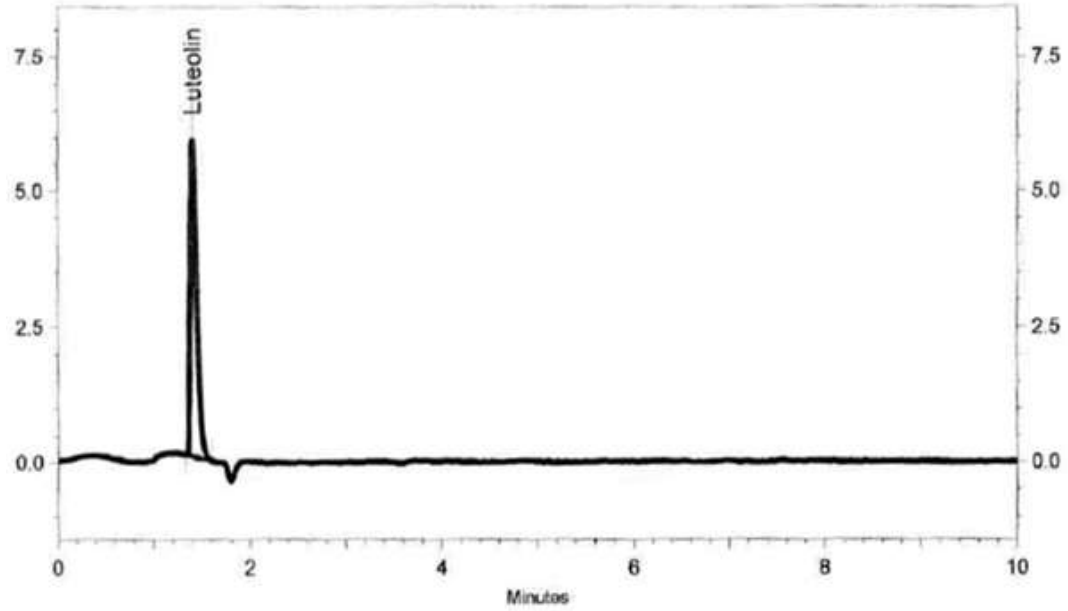

Figure 5.2 HPLC Chromatogram of Luteolin

Table 5.5: Physiochemical Parameters of Transdermal Patches

Formulation Code	Weight Variation (mean±SD)	Thickness (mm±SD)	Folding Endurance	Drug Content (% ±SD)	% Moisture content
LTP1	0.921±0.072	0.026±0.004	128	91.11±1.62	3.07±0.08
LTP2	1.016±0.081	0.024±0.003	135	94.27±3.25	2.36±0.62
LTP3	0.981±0.086	0.033±0.003	97	92.72±4.18	2.07±0.21
LTP4	0.936±0.036	0.021±0.002	124	95.13±6.21	1.91±0.19
LTP5	0.977±0.061	0.023±0.005	136	88.17±2.01	2.01±0.17
LTP6	0.969±0.051	0.024±0.003	115	90.57±4.58	1.90±0.22
LTP7	0.899±0.073	0.020±0.004	181	94.87±4.24	3.02±0.08
LTP8	0.899±0.024	0.027±0.002	153	92.35±6.63	1.84±0.31
LTP9	1.017±0.057	0.037±0.006	162	91.69±6.18	1.95±0.06

(2). In vitro drug release study:-

The drug release was found to increase with the increase of hydrophilic polymer in the matrix owing to the fact that gelatinous pores are formed in the matrix on dissolution of the aqueous soluble fraction of the formulations. The formation of these pores results in decrease in the mean diffusional path length travelled by the drug molecule and hence a higher release rate. Release studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance. The diffusion kinetics of the drug was analyzed by graphical method for Zero order, First order, Higuchi and Peppas equation. The R^2value (Table 5.7) of fitting model indicates that the drug release kinetics of formulations.

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Time (h)	% cumulative drug release								
	LTP1	LTP2	LTP3	LTP4	LTP5	LTP6	LTP7	LTP8	LTP9
0	0	0	0	0	0	0	0	0	0
1	9.08±0.33	6.87±0.33	5.39±0.66	8.78±0.33	6.93±0.11	6.21±0.66	11.09±0.33	9.54±0.66	7.36±0.11
2	19.36±0.33	16.08±0.66	14.29±0.33	19.54±0.66	14.66±0.11	16.46±0.33	25.97±0.66	21.61±0.33	17.43±0.33
4	27.18±0.66	21.88±0.33	21.77±0.33	28.49±0.66	23.97±0.33	21.12±0.11	35.68±0.66	31.33±0.66	24.52±0.66
6	32.84±0.66	28.62±0.11	26.86±0.11	34.02±0.33	27.71±0.66	25.73±0.11	38.83±0.33	34.85±0.33	30.94±0.33
8	38.33±0.33	33.49±0.33	31.07±0.66	39.32±0.11	32.09±0.66	30.03±0.33	45.59±0.11	41.41±0.11	36.38±0.11
10	45.71±0.66	38.52±0.11	36.64±0.66	43.04±0.11	38.25±0.66	35.28±0.11	48.84±0.33	45.79±0.33	41.81±0.11
12	49.53±0.11	44.51±0.11	43.25±0.66	47.66±0.33	42.91±0.33	41.07±0.33	53.51±0.66	51.53±0.33	48.12±0.66

Table 5.6: In vitro drug release from transdermal patches

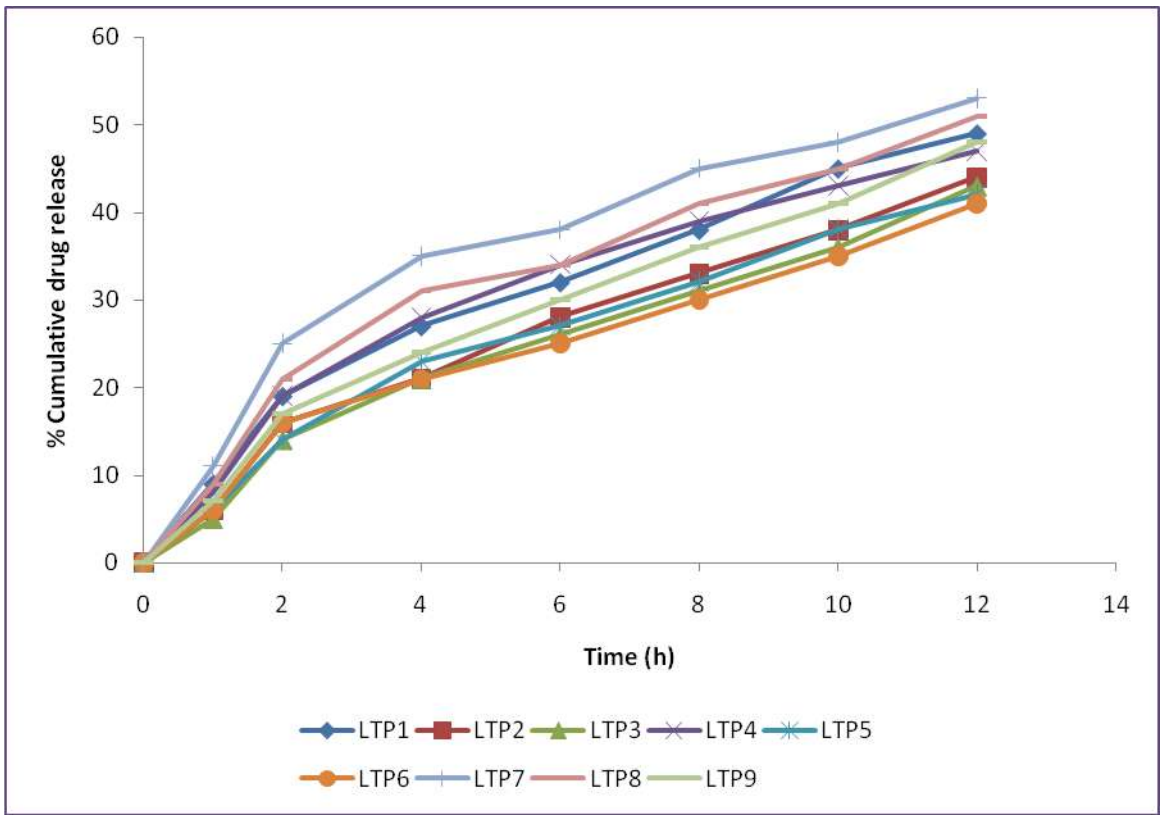

Figure 5.3. In vitro release of luteolin from transdermal patches

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Formulation Code	Zero order R^2	First order R^2	Higuchi' s model R^2	Peppas model R^2
LTP1	0.715	0.817	0.790	0.722
LTP2	0.657	0.913	0.768	0.698
LTP3	0.453	0.567	0.608	0.883
LTP4	0.724	0.830	0.844	0.961
LTP5	0.697	0.929	0.828	0.959
LTP6	0.740	0.952	0.828	0.948
LTP7	0.697	0.929	0.828	0.959
LTP8	0.724	0.830	0.844	0.961
LTP9	0.657	0.913	0.768	0.698

Table 5.7: Drug release kinetic model report

From the above table it can be concluded that the formulations are following mixed order kinetics.

IV. CONCLUSION

Luteolin exhibits great potential for administration via transdermal route for the treatment of neurological conditions. The objective of the present investigation was to evaluate the transdermal films of luteolin to its applicability to reduce the dose of the drug. It may be concluded that transdermal drug delivery system of luteolin can be formulated, which provides better compliance than conventional drug delivery system due to reduced dose and prolonged release of the drug.

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