
International Journal of Research in Pharmacy and Life Sciences
Home Page: https://pharmaresearchlibrary.org/journals/index.php/ijrpls
CODEN (USA): IJRPL | e-ISSN: 2321–5038 | Publisher: Pharma Research Library
Int. J. Pharm. Natural Med., 2025, 13(1): 15-20
DOI: https://doi.org/10.30904/j.ijrpls.2025.4790

# Formulation and Evaluation of a Transdermal Drug Delivery System for a Lipid Lowering Drug Fluvastatin sodium

B. Leela Gayathri[1]*, S. Naziya[2], P. Navya Sree[2], B. Kavitha[2], P.S. Harshavardhan[2], A. Sai Rakshitha[2], G. Mohan[2], Rakshith[2], M. Manju Naik[2]

[1]Assistant Professor, Department of Pharmaceutics, Saastra College of Pharmaceutical Education & Research, Varigonda, Totapalligudur, Nellore, A.P
[2]B.Pharm 4th Year, Saastra College of Pharmaceutical Education & Research, Varigonda, Totapalligudur, Nellore, A.P

**ABSTRACT**

The present study focuses on the development of a fluvastatin sodium-loaded drug-in-adhesive (DIA) patch designed to address the limitations of daily oral drug administration. The patches were fabricated using the solvent casting method, incorporating acrylate emulsion polymers such as Covinax 525-78, Mowinyl 461, and Novacryl PSR32, which served as both sustained-release matrix polymers and adhesives. Methocel K-15M was included as a solubilizer, while permeation enhancers Transcutol, oleic acid, and isopropyl myristate were evaluated for their effectiveness. The Mowinyl–isopropyl myristate combination was further optimized using a $3^2$ factorial design to investigate the impact of two independent variables: the concentration of the solubilizer and the permeation enhancer. The study measured responses including the percentage of drug release, tensile strength, and peel adhesion strength. The optimized patch demonstrated a cumulative drug release of 87.74% after 24 hours, a tensile strength of 12.75 kg/cm², and a peel adhesion strength of 32.44 N/25 mm. The Primary Irritation Index (PII) for the DIA patch was determined to be 0.22, indicating minimal skin irritation. Furthermore, in a Triton WR 1339-induced hyperlipidemic rat model, the transdermal patch significantly reduced serum cholesterol and triglyceride levels compared to oral administration ($p < 0.01$). These findings suggest that the developed fluvastatin sodium DIA patch is a promising candidate for transdermal drug delivery.

**Keywords:** Fluvastatin sodium, Drug-in-adhesive (DIA) patch, Solvent casting method, Acrylate emulsion polymers (Covinax 525-78, Mowinyl 461, Novacryl PSR32), Hyperlipidemia model, Triton WR 1339.

**A R T I C L E I N F O**

***Corresponding Author**
**B. Leela Gayathri**
Assistant Professor, Department of Pharmaceutics
Saastra College of Pharmaceutical Education & Research,
Varigonda, Totapalligudur, Nellore, A.P, India.

**Article History:**
**Received** 09 Mar 2025
**Revised** 28 Mar 2025
**Accepted** 05 April 2025
**Published** 27 April 2025



***Citation:*** *B. Leela Gayathri et al., Formulation and Evaluation of a Transdermal Drug Delivery System for a Lipid Lowering Drug Fluvastatin sodium. Int. J. Res. Pharm, L. Sci., 2025,13(1): 15-20.*

**C O N T E N T S**

1. Introduction . . . . . 15
2. Materials and Methods. . . . . 16
3. Results and Discussion . . . . . .18
4. Conclusion. . . . . .19
5. References. . . . . .19

## 1. Introduction

Transdermal patch designs are generally categorized into three basic types: reservoir patches (RP), matrix or monolithic patches (MP), and drug-in-adhesive patches (DIAP) [1,2]. Among these, MP and DIAP offer significant advantages over RP in terms of patient compliance, ease of manufacturing process control, quality assurance, and opportunities for continuous product improvement. Statins are widely recognized as the first-line treatment for patients with hypercholesterolemia. Fluvastatin sodium [3], one of the most potent statins, is approved for the reduction of circulating low-density lipoprotein cholesterol (LDL-C) levels. Although fluvastatin sodium is rapidly and

extensively absorbed (>90%), it undergoes significant first-pass hepatic metabolism, resulting in a low oral bioavailability of approximately 24% following a 1 mg dose. Consequently, higher doses are often required to achieve therapeutic efficacy. Moreover, immediate-release formulations exhibit nonlinear pharmacokinetics at doses above 20 mg, increasing the risk of dose-related adverse effects such as musculoskeletal and hepatic toxicities. TDDS offers several advantages over traditional oral routes, including the avoidance of first-pass metabolism, protection from gastrointestinal degradation, controlled and sustained drug release, reduced systemic toxicity, and minimized side effects, ultimately enhancing therapeutic outcomes. Given its molecular weight (411.46 Da) and short half-life (~3 hours), fluvastatin sodium is an appropriate candidate for transdermal delivery systems.

In this study, three water-based acrylate pressure-sensitive adhesives (PSAs) were selected based on key properties such as pH, glass transition temperature (Tg), and solid content [4]. Acrylate PSAs typically exhibit a Tg of around –20°C, and ideally between –40°C and –80°C, conferring the necessary soft, tacky characteristics. These polymers were initially evaluated for their film-forming capabilities using the solvent evaporation method [5-10]. However, films prepared with these polymers alone were extremely tacky and difficult to remove from the molds after drying at room temperature.

Preliminary in vitro diffusion studies of the formulated drug-loaded patches indicated that each polymer system released 30–40% of the drug within the first 1–3 hours, with maximum cumulative release ranging between 45–48% at 24 hours. Drug crystallization is a commonly reported issue in drug-in-adhesive patches. Additives such as hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP) are known to inhibit crystallization by preventing crystal nucleation, adsorbing onto growing crystals, or forming co-precipitates with the drug, thereby enhancing drug release and permeation [11,12]. Consequently, it was decided to partially replace the acrylate emulsion polymer with Methocel K15M to improve the formulation's performance.

## 2. Materials and Methods

### Preformulation study

Preformulation studies are intended to ensure the development of stable as well as safe and efficacious dosage form. Before the formulation of a transdermal patch, it is essential that the active pharmaceutical ingredient i.e. the drug and excipients like film forming polymer, permeation enhancer etc. are evaluated for their physiochemical properties and compatibility with each other. The following properties were evaluated for the drugs under investigation and the polymers that were used as film formers in the formulation of transdermal patch.

### Organoleptic properties

The samples of Rosuvastatin calcium and Fluvastatin sodium were evaluated for their organoleptic properties like colour, odour and nature.

### Solubility of drug in different solvents

Solubility may be defined as the amount of a substance that dissolves in a given volume of solvent at a specified temperature. To determine the solubility in different solvent systems, the saturated solution of the drug was obtained by placing an excess amount of drug in various solvents at 25°C on a mechanical shaker for 72 h to attain equilibrium. The samples were withdrawn and filtered using Whatman filter paper and analysed by UV visible spectrophotometer. Solubility of drug was determined in distilled water, pH 7.4 phosphate buffer, methanol and ethanol.

### Melting point determination

It is a key parameter to identify a given drug sample and also determine its purity. The drug samples were packed into glass capillaries to a height of about 1 cm which were then tied to thermometers and the thermometers were immersed in a heated oil bath contained in Thieles tubes. The range of temperature over which the drug samples was completely liquefied was noted as the melting points for the drugs.

### FTIR spectroscopy

Fourier transform infrared spectrophotometer {Shimadzu IR affinity -1 (18400S)} was used for recording the FTIR spectra of Rosuvastatin calcium and Fluvastatin sodium.

### Determination of maximum absorbance

A stock solution of Rosuvastatin calcium (1000µg/ml) was prepared by accurately weighing10mg of the drug and dissolving in 10ml of methanol and further diluted with phosphate buffer pH 7.4 to prepare 10µg/ml solution of Rosuvastatin calcium. The U.V spectrum was recorded in the range of 200-400nm using phosphate buffer pH7.4 as blank. The maximum absorbance for the drug was determined. The same procedure was repeated for Fluvastatin sodium.

### Construction of calibration curve

Accurately weighed 20 mg Rosuvastatin calcium was dissolved in 40ml methanol (500µg/ml).1 ml of this solution was diluted to 25 ml with phosphate buffer pH7.4 (100µg/ml). From this solution different dilutions were prepared with phosphate buffer pH7.4 in concentration range of 3-18µg/ml. The absorbance of these solutions was measured at maximum wavelength of 241.6nm using phosphate buffer pH 7.4 as blank solution by UV Visible spectrophotometer. Absorbance values were plotted against concentration to obtain standard graph. The same procedure was repeated for Fluvastatin sodium and absorbance of the various dilutions was measured at 237 nm.

**UV spectroscopy of drug and PSA polymer:** 10 µg/ml solutions each of Rosuvastatin calcium, Fluvastatin sodium, Mowinyl 461 and Novacryl PS-R 32 were prepared. These solutions were analyzed spectrophotometrically in the range of 200-400 nm to determine interference, if any.

### Formulation of Fluvastatin sodium loaded DIA patch

DIA patches were made from three different acrylate emulsion polymers Covinax, Mowinyl and Novacryl using different permeation enhancers like transcutol, oleic acid and isopropyl myristate as seen in Tables 16 to 18. Weighed quantities of drug, acrylate polymer, Methocel K15M and permeation enhancer were taken, water was added to make up the required weight and the mixture

stirred on a magnetic stirrer for one hour. The patches were prepared by solvent evaporation method using rectangular glass moulds of size 6.7cm ×4.5 cm. Till further evaluation patches were wrapped in aluminium foil and were stored in a desiccator.

**Evaluation of drug-in-adhesive patch**

**Thickness:** A micrometer screw gauge was used to measure the thickness of the patch at three different points to calculate the mean value.

**Drug content:**

The DIA patches were placed in a stoppered flask containing 100 ml of phosphate buffer pH7.4. The flask was placed on a mechanical shaker and shaken for 4 hours. At the end of 4 hours solution was filtered. A 1 ml aliquot was removed from the filtered solution and volume was made upto10 ml with phosphate buffer and then the absorbance was measured at 241.6nm and 237 nm for Rosuvastatin calcium and Fluvastatin DIA patches (V-630 JASCO, Japan) respectively using placebo patch solution as blank and the drug content was calculated.

**Percentage moisture content:**

DIA patches were weighed individually. The patches were placed in a desiccator containing anhydrous calcium chloride. The weighed patches were monitored for change in weight until the patches reached a constant weight. The patches were reweighed and the percent moisture content per patch was determined.

Content of moisture (%) = [(W1-W2) /W1] ×100. (Equation 6.1) where,

W1-Initial weight of patch W2-Final weight of patch

**Percentage moisture uptake:**

Three DIA patches were weighed individually. A desiccator containing saturated solution of aluminium chloride was prepared which is considered to be equivalent to a relative humidity of 75 %.The weighed patches were placed in the desiccator and monitored for change in weight until the patches reached a constant weight. The patches were reweighed and the percent moisture taken up by each patch was determined.

Percentage moisture uptake= [(W2-W1) /W1] ×100.

(Equation 6.2)

where,

W1-Initial weight of patch W2-Final weight of patch

**Folding endurance:**

Square pieces, 2cmx 2cm was cut out from the DIA patches and they were folded across the same line repeatedly till the pieces broke. The number of times the patch was folded prior to its breaking is an estimation of the folding endurance value of the patch.

**In-vitro diffusion study:**

In- vitro diffusion profile of the DIA patch was studied using Franz diffusion cell. The receptor compartment of the cell had a capacity of 20 ml. A dialysis membrane (Dialysis membrane- 60Av. diameter- 15.9 mm, HIMEDIA) was used to separate the two compartments of the cell. The DIA patch was placed over the dialysis membrane and the diffusion medium used for the study was phosphate buffer pH 7.4. The assembly was mounted on a magnetic stirrer. The stirrer was operated at an rpm of 150 and the solution in the receptor compartment was kept in the stirred state using a star shaped magnetic bead. The temperature of the diffusion medium was equilibrated with that of skin i.e. 32 ± 0.5oC. Aliquots of 1 ml were withdrawn at various time intervals and analyzed for drug content by UV-visible spectrophotometry. Each time the sample was withdrawn, an equal volume of phosphate buffer was used to replenish the diffusion medium thus ensuring that sink conditions were maintained during the entire duration of the diffusion study. The % cumulative amounts of drug released per square centimetre of patch was plotted against time.

**Table 1.**Composition of Fluvastatin sodium loaded DIA patch using Covinax asmatrix polymer

| Content | Formulation code | | |
|---|---|---|---|
| | CT | CO | CIPM |
| Fluvastatin | 0.01 | 0.01 | 0.01 |
| Covinax | 0.80 | 0.80 | 0.80 |
| Transcutol | 0.18 | -- | -- |
| Oleic acid | -- | 0.05 | -- |
| Isopropyl myrisitate | -- | -- | 0.09 |
| Methocel K15M | 0.10 | 0.10 | 0.10 |
| Distilled water .q.s | 10 | 10 | 10 |

*All weights are in grams

**Table 2.** Composition of Fluvastatin sodium loaded DIA patch using Novacryl asmatrix polymer

| Content | Formulation code | | |
|---|---|---|---|
| | NT | NO | NIPM |
| Fluvastatin | 0.01 | 0.01 | 0.01 |
| Novacryl | 0.80 | 0.80 | 0.80 |
| Transcutol | 0.18 | -- | -- |
| Oleic acid | -- | 0.05 | -- |
| Isopropyl Myrisitate | -- | -- | 0.09 |
| Methocel K15M | 0.10 | 0.10 | 0.10 |
| Distilled Water .q.s | 10 | 10 | 10 |

*All weights are in grams

**Table 3.**Composition of Fluvastatin sodium loaded DIA patch using Mowinyl asmatrix polymer

| Content | Formulation code | | |
|---|---|---|---|
| | CT | CO | CIPM |
| Fluvastatin | 0.01 | 0.01 | 0.01 |
| Mowinyl | 0.80 | 0.80 | 0.80 |
| Transcutol | 0.18 | -- | -- |
| Oleic acid | -- | 0.05 | -- |
| Isopropyl myrisitate | -- | -- | 0.09 |
| Methocel K15M | 0.10 | 0.10 | 0.10 |
| Distilled water .q.s | 10 | 10 | 10 |

*All weights are in grams

## 3. Results and Discussion

**Organoleptic properties:**

From visual observation Rosuvastatin calcium was found to be white to off white crystalline powder and Fluvastatin sodium was found to be a pale yellow colored powder. Both the drugs were odorless.

**Solubility of drug in different solvents**

Rosuvastatin calcium was found to be sparingly soluble in water, methanol, slightly soluble in ethanol and soluble in phosphate buffer pH 7.4. Fluvastatin sodium was found to be soluble in water, ethanol, methanol and phosphate buffer pH 7.4.

**Melting point determination:**

Melting point of Rosuvastatin calcium was found to be 158-160$^0$C and that of Fluvastatin sodium in the range of 195-200$^0$C as reported in literature, thus indicating purity of drug samples.

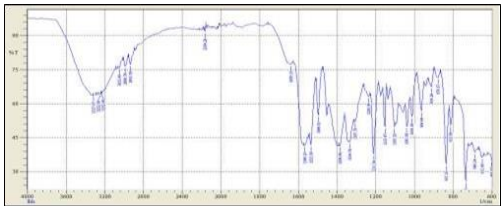

Figure 1. FTIR spectrum of Fluvastatin sodium

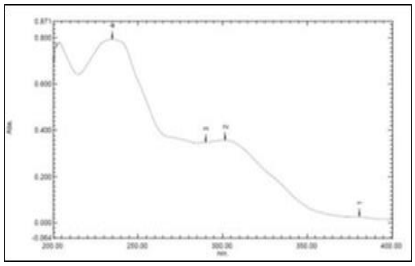

Figure 2. UV spectrum of Fluvastatin sodium in phosphate buffer pH 7.4

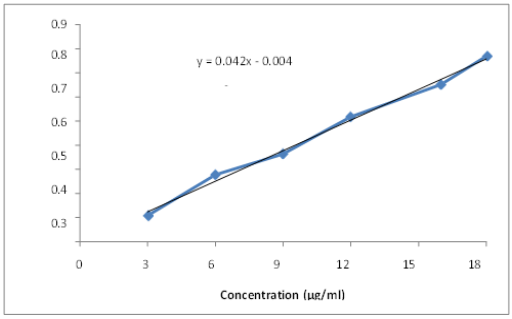


Figure 3.Calibration curve of Fluvastatin sodium in phosphate buffer pH 7.4

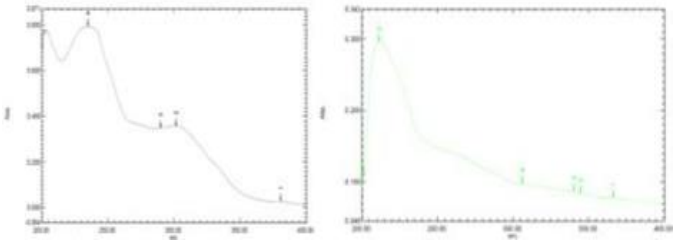

Figure 4. UV spectrum of (A) Fluvastatin sodium (B) Mowinyl in phosphate buffer pH 7.4

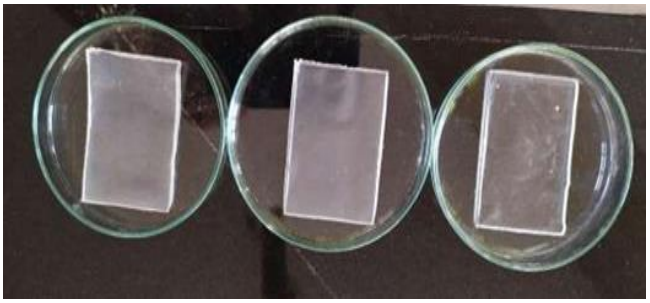

Figure 5. Placebo patches made from (A) Covinax (B) Novacryl (C) Mowinyl acrylate polymer

**Table 4.** Result of analysis of variance for % cumulative release

| Source | Sum of squares | df | Mean square | F-value | p-value |
|---|---|---|---|---|---|
| **Model** | 773.19 | 5 | 154.64 | 540.58 | 0.0001 |
| A-Crystallization Inhibitor | 713.51 | 1 | 713.51 | 2494.30 | < 0.0001 |
| B-Penetration Enhancer | 22.82 | 1 | 22.82 | 79.76 | 0.0030 |
| AB | 3.15 | 1 | 3.15 | 11.01 | 0.0451 |
| $A^2$ | 33.37 | 1 | 33.37 | 116.67 | 0.0017 |
| $B^2$ | 0.3362 | 1 | 0.3362 | 1.18 | 0.3577 |

**Table 5.** Result of analysis of variance for peel adhesion strength

| Source | Sum of squares | df | Mean square | F-value | p-value |
|---|---|---|---|---|---|
| **Model** | 41.81 | 2 | 20.91 | 56.71 | 0.0001 |
| A-Crystallization Inhibitor | 1.25 | 1 | 1.25 | 3.39 | 0.1150 |
| B-Penetration Enhancer | 40.56 | 1 | 40.56 | 110.02 | < 0.0001 |
| Residual | 2.21 | 6 | 0.3686 | | |
| Cor Total | 44.02 | 8 | | | |

**Table 6.** Result of analysis of variance for tensile strength

| Source | Sum of squares | df | Mean square | F-value | p-value |
|---|---|---|---|---|---|
| **Model** | 4.71 | 2 | 2.36 | 169.16 | < 0.0001 |
| A-Crystallization Inhibitor | 0.5104 | 1 | 0.5104 | 36.66 | 0.0009 |
| B-Penetration Enhancer | 4.20 | 1 | 4.20 | 301.66 | < 0.0001 |
| Residual | 0.0835 | 6 | 0.0139 | | |
| Cor Total | 4.79 | 8 | | | |

## 4. Conclusion

Transdermal drug-in-adhesive (DIA) patches using acrylic pressure-sensitive adhesives (PSAs) were formulated for the delivery of statins like Rosuvastatin calcium and Fluvastatin sodium, demonstrating effectiveness in controlling lipidaemia. Acrylic PSAs (Covinax 525-78, Novacryl PS-R 32, Mowinyl 461) combined with permeation enhancers (e.g., transcutol, PEG 400, isopropyl myristate) and cellulosic polymers (Methocel K15M, K100M) improved drug release, adhesive properties, and stability. High cumulative drug release (86.4–96.3%) and consistent release profiles. Drug release mechanisms aligned with Higuchi and Korsmeyer-Peppas models, indicating diffusion and non-Fickian transport due to polymer swelling and relaxation. Stable physicochemical properties, minimal skin irritation, and compliance with ICH stability guidelines for six months under real-time conditions. Validated HPLC methods confirmed drug stability and compatibility with patch components. The study concluded that these solvent-free systems are effective, environmentally friendly, and suitable for transdermal delivery of statins.

## 5. References


[1] Al Hanbali O, Khan H, Sarfraz M, Arafat M, Ijaz S, Hameed A. Transdermal patches: design and current approaches to painless drug delivery. Acta Pharm. 2019, 69(2): 197–215.

[2] Puri A, Bhattacharjee S, Zhang W, Clark M, Singh O, Doncel G, Banga A. Development of a transdermal delivery system for tenofovir alafenamide, a prodrug of tenofovir with potent antiviral activity against HIV and HBV. Pharmaceutics. 2019;11(4):173.

[3] Regenthal R, Voskanian M, Baumann F, Teichert J, Brätter C, Aigner A, Abraham G. Pharmacokinetic evaluation of a transdermal anastrozole-in-adhesive formulation. Drug Des Devel Ther. 2018; 12: 3653-3664.

[4] Siafaka P, Barmpalexis P, Lazaridou M, Papageorgiou G, Koutris E, Karavas E, Kostoglou M, Bikiaris D. Controlled release formulations of risperidone antipsychotic drug in novel aliphatic polyester carriers: data analysis and modelling. Eur J Pharm Biopharm. 2015, 94: 473-484.

[5] Parhi R, Padilam S. In vitro permeation and stability studies on developed drug-in-adhesive transdermal patch of simvastatin. Bull Fac Pharm Cairo Univ. 2018; 56(1): 26-33.

[6] Okur NÜ, Filippousi A, Okur ME, Ayla Ş, Çağlar E, Yoltas A, Siafaka PI. A novel approach for skin infections: controlled release topical mats of poly(lactic acid)/polyethylene succinate blend containing voriconazole. J Drug Deliv Sci Technol. 2018;46:74-86.

[7] Okur NÜ, Hökenek N, Okur ME, Ayla Ş, Yoltaş A, Siafaka PI, Cevher E. An alternative approach to wound healing field: new composite films from natural polymers for mupirocin dermal delivery. Saudi Pharm J. 2019;27(5):738-752.

[8] Jafri I, Shoaib M, Yousuf RI, Ali F. Effect of permeation enhancers on in vitro release and transdermal delivery of lamotrigine from Eudragit® RS100 polymer matrix-type drug-in-adhesive patches. Prog Biomater. 2019, 8(2): 91-100.

[9] Hsieh L, Box K, Taylor S. Assessing the impact of polymers on the pH-induced precipitation behaviour of poorly water soluble compounds using synchrotron wide angle X-ray scattering. J Pharm Sci. 2014; 103(9): 2724-2735.

[10] Suys EJ, Chalmers DK, Pouton CW, Porter CJ. Polymeric precipitation inhibitors promote fenofibrate supersaturation and enhance drug absorption from a type IV lipid-based formulation. Mol Pharm. 2018; 15(6): 2355-2371.

[11] Pastore M, Kalia Y, Horstmann M, Roberts M. Transdermal patches: history, development and

pharmacology. Br J Pharmacol. 2015, 172(9): 2179–2209.

[12] Schechter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005;19(1):117-125.