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FORMULATION AND EVALUATION OF TRANSDERMAL THERAPEUTIC SYSTEM FOR DELIVERING NANO SIZED ROSUVASTATIN

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Abstract:

The objective of present study was to formulate and evaluate transdermal patches for delivering nano sized rosuvastatin. As we know that Rosuvastatin belongs to the BCS class II having low solubility and high permeability. It exhibits poor aqueous solubility, high hepatic first-pass metabolism, and oral bioavailability of less than 20% .To overcome such criteria, efforts have been made to improve bioavailability by preparing Nano sized rosuvastatin and delivering it through the transdermal system.

Rosuvastatin was nano sized by preparing nanosuspension, the best one of having the particle size 854nm was selected and fabricated into the transdermal patch. Prepared transdermal patches were evaluated for various physicochemical parameters. The transdermal patches were found to be thin, clear, smooth, uniform, and flexible. From the study, it was concluded that out of various formulations, the P4 formulation was found to be the optimum formulation with 86.01 % drug release within 24 hours.

Keywords: *Nanosized, Transdermal Drug Delivery system, Rosuvastatin*

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INTRODUCTION

Transdermal Drug Delivery System (TDDS) are defined as self-contained, discrete dosage forms which are also known as "patches" [1, 2] when patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation [3][4] .Transdermal patches play a vital role to decrease the patient non-compliances which used to be occurred due to the conventional dosage forms such as first-pass metabolism and degradation of drugs due to the presence of enzymes or pH in the gastrointestinal tract. The purpose behind the development of a transdermal drug delivery system was to provide a controlled amount of drug release through the skin into the systemic circulation and increase the bioavailability.[5][6] In the transdermal drug delivery system, the drug to be released is incorporated within the polymeric membranes which diffuse the drug to the skin at a predetermined controlled rate. It has fewer dosing frequencies as compared to oral dosage forms that reduce the over-dosing of a drug into the systemic circulation which leads to minimal side effects.[4]

Types of Transdermal Patch

Adhesive Dispersion Type TDDS

The preparation of drug reservoir takes place by directly dispensing the drug into an adhesive polymer and then spreading of medicated polymer is done by solvent film over a flat sheet of drug impermeable backing membrane such as polyester film which forms a thin layer reservoir layer. The drug reservoir layer is then covered by a non-medicated rate controlling adhesive polymer of constant thickness. [7]

Matrix Diffusion controlled TDDS

The drug is homogenously dispersed in a mixture of hydrophilic polymer (matrix). Medicated disc of defined surface area and thickness is used for molding the polymer and then glued over occlusive base plate. Adhesive rim is formed by applying polymer along the circumference around the medicated disc.[8]

Membrane Moderated TDDS

Metallic-plastic lamination is done over a drug reservoir in a shallow compartment. Delivery site of drug is then covered by controlling polymeric membrane. In the reservoir a paste like suspension is formed by suspending the solid drug polymer matrix in an unleachable viscous fluid. A thin layer of adhesive polymer applied for an intimate delivery.[9]

Micro Reservoir TDDS

Micro reservoir is a type of delivery system in which both reservoir and matrix dispersion type TDDS is used. In this the solid drug is suspended in an aqueous solution of water-soluble polymer. Then it is dispersed homogeneously in a lipophilic polymer by mechanical agitation to form thousands of unleachable microspheres of the drug and it is highly unstable and stabilized by cross linking the polymer chain. Hence a medicated disc is positioned at center and surrounded by an adhesive rim.[10]

Materials and Methods

Rosuvastatin calcium was received as a gift sample from the IPCA laboratory, Selaqui, Uttarakhand. Hydroxypropyl methylcellulose, Eudragit RS 100, Methanol, Tween 80, and Polyethylene glycol 400 from Central Drug House Pvt Ltd. All the chemicals used in this study were of analytical grade.

Preparation of Transdermal Patch

Nano sized Rosuvastatin was prepared and the best formulation having the size 854 nm was fabricated into the transdermal patches. The transdermal patches were prepared by using Hydroxypropyl methylcellulose (HPMC) and Eudragit with different concentrations as shown in Table 1. The polymers were accurately weighed and dissolved in 10 ml of the above-prepared best-optimized nano sized formulation. The solution was then kept on a magnetic stirrer for 30 minutes at 100 rpm. Then the solution was poured into the Petri plate and dried at room temperature. Patches were further evaluated for thickness, weight variation, folding endurance, percentage moisture loss, percentage moisture uptake, and analyzed its release character.

Table 1: The composition of transdermal patches

Formulation code	Nano Solution (ml)	Polymer (mg)	
		HPMC	Eudragit
P1	10	25	25
P2	10	10	50
P3	10	25	25
P4	10	10	50

Evaluation of Rosuvastatin Calcium nanosuspension loaded transdermal patch

Thickness

The thickness of the transdermal patch can be measured by a micrometer at different points of patches. [11]

Weight uniformity

Weigh Patches and calculate their average weight. The individual weight of patches does not deviate significantly from the average weight. [12]

Folding endurance

Folding endurance is performed to determine the folding capacity of the patch at extreme conditions. The film was folded in the same place until it break. The number of times film folded without breaking was folding endurance value. [13]

Moisture uptake

Weighed films were kept for 24 hours in a desiccator at room temperature. Then these films were taken out and by the use of a saturated solution of potassium chloride 84% relative humidity was maintained and exposed to the film until a constant weight was achieved. [14]

$$\% \text{ Moisture Uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Final weight}} \times 100$$

Moisture content

The films were weighed individually and then placed in a desiccator containing calcium chloride for 24 hours at room temperature. These films were then again weighed after a specified interval of time until the constant weight was achieved. [15]

$$\% \text{ Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Drug content

A patch was cut and dissolved in 100 ml of pH7.4 buffer using a magnetic stirrer. Then, the solution was filtered through filter paper. 1 ml of filtered solution was diluted with 10 ml of buffer, and the drug content was analyzed with the ultraviolet (UV) spectroscopic method. [16]

$$\% \, Drug \; Content = \frac{Actual \; quantity \; of \; drug \; in \; film}{theoretical \; quantity \; of \; drug \; in \; film} \times 100$$

***In vitro* drug release study of transdermal patch**

The paddle over disc method was employed for assessment of drug release from the prepared patches. Dry patch was fixed over a petri dish at the bottom of the dissolution bowl and then placed in a 900 ml of dissolution medium phosphate buffer (pH 7.4), and the apparatus was equilibrated to 37 ± 0.5°C. The paddle was operated at a speed limit of 50 rpm and depth of 20 mm. Samples (5 ml aliquots) were withdrawn at every 1 hour intervals and analyzed by UV spectrophotometer at 240 nm. [17]

Model fitting Analysis of best optimized formulation

Kinetic models describe drug release from dosage forms. Thus, the model fitting analysis (Zero Order, Higuchi, First Order and Korsmeyer-Peppas Model) were done by comparing the coefficient of regression (R) values and corresponding n value of all the kinetic equations. The correlation coefficient (R) values were used as criteria to choose the best model for the drug release from the formulations.

RESULTS AND DISCUSSION:

Evaluation of prepared transdermal patch:

The transdermal patches were found to be thin, clear, smooth, uniform, and flexible. All the formulations were evaluated for thickness, weight uniformity, folding endurance, moisture uptake, moisture loss and for the drug content. All the formulations (P1-P4) come under within range limits as shown in the table 2.

Table 2: Evaluation of transdermal patch

Formulation Code	Thickness (mm) ±SD	Weight uniformity (mg) ±SD	Folding endurance (No.) ±SD	Moisture Uptake (%) ±SD	Moisture Loss (%) ±SD	Drug Content (%) ±SD
P 1	0.7 ±0.08	283.3 ±8.49	279.3 ±9.39	7.06 ±1.75	6.81 ±2.34	90.6 ±0.89
P 2	0.76 ±0.12	345.3 ±4.49	267.3 ±9.10	4.17 ±1.00	5.54 ±0.63	89.0 ±0.97
P 3	0.86 ±0.47	453 ±8.83	269.3 ±8.57	2.13 ±0.55	2.33 ±0.28	90.9 ±1.55
P 4	0.83 ±0.09	475 ±8.60	276.1 ±5.02	1.97 ±0.53	2.41 ±0.53	91.7 ±0.86

***In vitro* drug release study of transdermal patch:**

In vitro drug release study was performed for the all prepared formulation (P1-P4) as shown in fig. 1 and in table 3.The P4 formulation shown maximum drug release i.e. 86. 01±0.05% as compare to the other formulations and it was found to be the best optimized formulation.

Table 3: *In-vitro* release profile study

Time (hours)	Formulation code			
	P1 (%)	P2 (%)	P3 (%)	P4 (%)
0	0±0	0±0	0±0	0±0
1	3.05±0.07	2.99±0.09	4.46±0.06	4.16±0.09
2	12.46±0.03	13.60±0.07	16.80±0.03	12.38±0.01
3	16.28±0.06	18.96±0.01	23.16±0.07	23.93±0.04
4	26.65±0.09	29.94±0.09	30.00±0.05	36.19±0.07
5	39.91±0.05	39.87±0.06	39.69±0.09	44.10±0.07
6	46.24±0.06	48.61±0.04	47.80±0.02	56.21±0.03
7	59.79±0.05	56.35±0.07	59.74±0.06	68.39±0.01
8	68.46±0.09	66.99±0.01	73.89±0.04	75.06±0.03
24	78.09±0.08	73.77±0.09	82.21±0.07	86.01±0.05

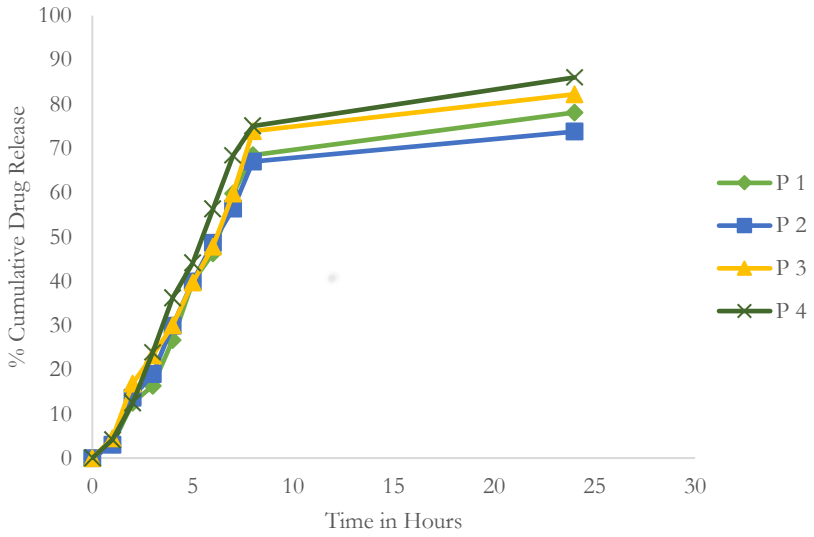

Fig. 1: *In vitro* dissolution study of prepared transdermal patches

Model fitting Analysis of best optimized formulation

The best optimized formulation P4 follows Higuchi model and its mechanism of action was Supercase II transport as shown in the table 4.

Table 4: Release kinetics of formulation P4

Formulation Code	r^2			n	Best Fit model	Mechanism of action
	Zero order	First order	Higuchi			
P4	**0.6487**	**0.8254**	**0.9293**	**1.0148**	**Higuchi -matrix**	**Supercase II transport**

CONCLUSION:

From the study, it was concluded that out of various formulations, the P4 formulation was found to be the optimum formulation with 86.01±0.65 % drug release within 24 hours. The kinetic profile validated for optimized formulation shows the product follows Higuchi equation and its mechanism of action was Supercase II transport.

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