RESEARCH PAPER

Development of Rutin nanosuspension decorated transdermal patches using Box-Behnken approach

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ABSTRACT
The goal of the current study is to create and improve transdermal patches that contain Rutin (RTN) nanosuspensions (NSPs). The goal of NSPs is to make hydrophobic actives more soluble. To ensure RTN's identity and necessary formulation elements, including λmax determination, FT-IR spectroscopic analysis, standard calibration curve, and saturation solubility, preformulation investigations were carried out. These studies guaranteed RTN's identity, purity, and compatibility. NSPs were made utilizing the Box-Behnken design in batches using the precipitation process. Particle size, zeta potential, and drug content were the dependent variables; poloxomer and sodium lauryl sulfate concentrations and homogenization speed were independent parameters. Particle size and zeta potential, drug content, drug loading efficiency, SEM, and in vitro dissolution experiments were all conducted on the formulated NSP batches of RTN. According to the results, NSPs from RTN batch B5 (600 mg poloxomer, 550 mg SLS, and 7000 rpm) were optimal and should be used going forward. The highest cumulative percentage of medication dissolved (99.36%) was found in RTN NSP (Batch S2). PVP, an ethyl cellulose mixture, dibutyl phthalate as a plasticizer, and oleic acid as a penetration enhancer were used to create transdermal patches utilizing an improved batch of RTN NSPs. Physical appearance, folding durability, film thickness, drug content, tensile strength, SEM, in vitro drug release testing, and ex vivo drug diffusion studies were among the evaluation procedures performed on these patch batches. All transdermal patches were shown to be capable of maintaining the drug's release from formulation. In 12 hours, RTN formulation P6 demonstrated 99.23 ± 0.43% drug release. Sustained drug release is resulted by variable quantities of oleic acid, a permeability enhancer, according to the findings of in-vitro and ex-vivo investigations of various batches. Better sustained release was demonstrated by formulations with 5% oleic acid. After three months of expedited stability testing, it was discovered that the improved transdermal patches of RTN and RTN were stable.

Keywords: Nanosuspensions, Rutin, Box-Behnken design, transdermal patches, penetration enhancer

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INTRODUCTION

Rutin (3,3′,4′,5,7-pentahydroxyflavone-3-rhamnoglucoside, is a flavonoid of the flavonol-type that is widespread in the plant kingdom (Hosseinzadeh and Nassiri-Asl, 2014).

Rutin is synthesized through the phenylpropanoid metabolic pathway, which involves the transformation of the amino acid phenylalanine to 4-coumaroyl-CoA. 4-coumaroyl-CoA can

be combined with malonyl-coA to produce the true backbone of flavonoids[1].

utin (3′,4′,5,7-tertrahyrdroxy-flavone-3-rutinoside), also referred to as quercetin-3-rutinoside or sophorin, is a compound consisting of the flavonol quercetin and the disaccharide rutinose. Rutin exhibits notable antioxidant capabilities against several oxidizing species, such as hydroxyl, superoxide, and peroxyl radicals. Hence, it harnesses various pharmacological functions including antiallergic, antiaging, anti-inflammatory, anticancer, antibacterial, antiviral, vasoactive, and antiprotozoal effects[2]. Over 70 plant species, such as Ruta graveolens L. (Rutaceae) and Sophora japonica L. (Fabaceae), have been proven to be excellent sources of rutin. Other examples include Strelitzia reginae Banks ex Aiton (Strelitziaceae), Maranta leuconeura (Marantaceae), Orchidantha maxillarioides (Lowiaceae), Eucalyptus spp. (Myrtaceae), Canna indica L. (Cannaceae), and Canna edulis Ker Gawl (Cannaceae). The antibacterial properties of these plant species have been attributed to flavonoids, terpenoids, and tannins. Flavonoids are typically found in cells that undergo photosynthesis. Moreover, rutin, a compound found in various plant species, demonstrates diverse pharmacological effects including potent antioxidant activity against reactive oxygen species[3,4]. Notably, studies have established rutin's effectiveness against both Gram-positive and Gram-negative bacterial strains, underscoring its potential for combating antibiotic resistance[5]. Throughout history, formulations containing these substances have been employed to alleviate human ailments5. The antibacterial potentials of this class of natural compounds have made them the primary focus of investigation. Rutin is primarily hindered by its reduced bioavailability, which is mostly due to its low solubility in water, instability, and restricted capacity to pass through cell membranes[6].

RTN has a relatively poor solubility in gastrointestinal fluids because it is not particularly soluble in water. Because dissolving is necessary for absorption, this restriction results in a reduced availability of medications. Additionally, because of its physicochemical features, RTN has a low permeability through cellular membranes, which limits its absorption[6]. Prolonged metabolism is the other important limitation. RTN is rapidly converted into urolithins by intestinal bacteria after oral administration, lowering the amount of unmodified medication in the blood. Low oral bioavailability and poor therapeutic efficacy result from their combination[7].

One method for overcoming the problems with the solubility and bioavailability of poorly water-soluble medications, including RTN, is nanosuspension technology. A colloidal suspension of drug carriers in the nanometer range (10–1000 nm) stabilized by polymers or surfactants is called a nanosuspension. According to the principles of surface area enhancement, a decrease in particle size also increases the drug particles' surface area, which raises the rate of dissolution[8]. This improves the drug solubility and absorption. Additionally, because surface energy is increased at the nanoscale, nanosuspensions increase the degree of saturation solubility. By improving adherence to biological membranes and residence time at absorption sites, nanosuspensions also improve bioavailability. Additionally, they can provide continuous and depot medication delivery, which can improve treatment[9].

Another method of delivering medications through the skin and into the bloodstream is using transdermal drug delivery systems (TDDS)[10]. This approach has several advantages over oral delivery, particularly when dealing with medications like RTN that have poor oral bioavailability. First, there is no first-pass metabolism, which greatly improves medication availability.

Additionally, regulated and sustained medication release via transdermal patches is proven to maintain a steady drug plasma level and minimal dosage frequency[11].

Additionally, because transdermal systems are non-invasive, painless, and easy to use, they improve patient compliance[12]. The fact that the patch can be taken off in the event of adverse effects can increase its safety. These advantages make TDDS a viable technique for RTN administration. In order to enhance drug delivery and therapeutic effects, the overall goal of the study was to develop and optimize RTN nanosuspension and incorporate it into a transdermal patch-based system.

MATERIALS AND METHOD

Materials

RTN (purity 98 and above) was acquired from Otto Chemie Pvt. Ltd. (Mumbai, India). Poloxamer 188 (analytical grade), a stabilizing agent in the nanosuspension formulation was acquired at BASF (Germany). Sodium lauryl sulfate (SLS) was purchased as a surfactant to enhance the dispersion and stability of the drug and it is produced from Loba Chemie Pvt. Ltd. (Mumbai, India). Polyvinyl pyrrolidone (PVP) that was used as the film forming polymer on the preparation of transdermal patches was provided by Colorcon Asia Pvt. Ltd. (Goa, India). Ethyl cellulose (rate controlling polymer 10 cps) was obtained at Himedia Laboratories Pvt. Ltd. (Mumbai, India). The plasticizer was Dibutyl phthalate that was sourced from Merck Life Science Pvt. Ltd. (India). Methanol (analytical grade solvent) was acquired from Merck. We made phosphate buffer solution (pH 7.4) by the dissolution of potassium

dihydrogen phosphate and sodium hydroxide of analytical grade in the presence of phosphate buffer solution.

Methods

Preparation of Nanosuspension of RTN:

The antisolvent precipitation approach (also known as the nanoprecipitation method) was used to create RTN nanosuspensions. To prepare the organic phase, RTN (100 mg) was fully dissolved in chloroform. The solution was then run through a 0.45-µm filter to exclude any potential contaminants. In the meantime, stabilizer Polaxomer-188 and surfactant SLS were dispersed in distilled water to create the antisolvent phase. A high-speed homogenizer running at 8000 rpm for an hour was used to rapidly inject 1 ml of organic solution by syringe into 30 ml of anti-solvent at a given temperature. Drug particles separated from the anti-solvent right away. The organic solvent was then evaporated by stirring the prepared nanosuspension for one hour at room temperature using a high-speed homogenizer13.The batches were prepared according to the formulation design in Table 1.

Table no.1: Composition of RTN NSPs (S1 -S15) according to Box-Behnken Design (BBD)

Formulation code	A: polaxomer-188 (mg)	B: sodium lauryl sulphate(mg)	C: speed (rpm)
B1	600	600	8000
B2	650	650	8000
B3	650	600	9000
B4	600	550	7000
B5	600	600	8000
B6	600	600	8000
B7	600	550	9000
B8	550	550	8000
B9	650	550	8000
B10	550	600	7000
B11	600	650	9000
B12	650	600	7000
B13	550	600	9000
B14	600	650	7000
B15	550	650	8000

Table no.1: Composition of RTN NSPs (S1 -S15) according to Box-Behnken Design (BBD)

Evaluation of RTN NSPs

Particle size, zeta potential and total drug content determination

Particle size, zeta potential, total drug content, and percent drug loading was assessed for the prepared RTN NSPs. Using dynamic light scattering in a Malvern zeta sizer (Nano ZS; Malvern Instruments, UK), the average particle size of nanosuspensions was determined. Triple distilled water was used to dilute 0.1 mL of the corresponding formulation 10 times for analysis. Zeta potential was measured using a Zetasizer (HORIBA, SZ100, Japan). The dispersed solution was placed in an ultrasonicator bath for five minutes to stop the agglomeration.

After that, the sample was placed in a glass cuvette, and a zetasizer was used to measure the zeta potential. An aliquot (0.5 ml) was evaporated to dryness in order to determine the overall drug content. After being dissolved in methanol, the residue was filtered through 0.45 µm filter paper. A UV spectrophotometer (Shimadzu-1700, Japan) with a λmax of 262 nm was used to evaluate the samples. The following formula was used to determine the total drug content (TDC) and percentage TDC.

$$TDC = \frac{Total\ volume\ of\ nanosuspension}{Volume\ of\ aliquot} \times Amount\ of\ drug\ in\ aliquot$$

Drug loading efficiency:

A fixed amount of RTN nanosuspension (10 ml) was taken with a pipette (10 ml, Borosil), and transferred into a centrifuge tube and centrifuged at 14000 rpm for 10 min at 20°C. The absorbance of the drug in the supernatant was determined spectroscopically using UV-VIS Spectrophotometer (Shimadzu) at 262 nm.

Drug excipient compatibility studies:

RTN and excipients were initially triturated and uniformly dispersed with potassium bromide. KBr coupled RTN-excipient compacts were prepared by compression method. These compacts were subjected to scanning between 4000-400cm-1 on a FTIR spectrophotometer instrument (Model No. 84005 Schimadzu Asia Pacific Pvt. Ltd, Singapore).

In-vitro drug dissolution studies:

In vitro drug dissolution testing was conducted using USP class II paddle type dissolving apparatus (Electro lab Dissolution Tester USP TDT-10L) at 100 rpm and 37±0.5°C. A dialysis bag containing precisely weighed NSPs (about 10 mg of RTN) was sealed. The dissolution test device was used after the bag was submerged in 500 cc of pH 7.4 buffer. Every so often, 5 ml aliquots were taken out and an equivalent volume of buffer was added. The obtained aliquots were then diluted after being filtered via 0.1 µm filters. A UV spectrophotometer was used to measure the drug content at λmax 262 nm.

Scanning Electron Microscopy:

To examine the particle nature in NSPs in desiccated form, samples were analyzed by using a Scanning Electron Microscope (Hitachi S-3700N). The

surface morphology (roundness, smoothness, and formation of aggregates) was also determined.

Preparation of RTN nanosuspension loaded transdermal patch:

PVA backing membrane, was molded by adding pouring 12 ml 5 %w/v (PVA in water). on a surface of petri plate and dehydrated at 42℃ for one day. RTN (Batch B5) NSPs (equivalent to 50 mg RTN) loaded transdermal patches were casted via solvent vaporization method using a film former. The required amount of Polyvinyl pyrrolidone and ethyl cellulose were dissolved in chloroform (Table no. 2). RTN NSPs were added to the above polymeric blend and stirred for 4h. To this resulting solution mixture ratios of dibutyl phthalate (plasticizer) and oleic acid (penetration enhancer) was added. This mixture was added over preformed PVA backing film and dehydrated at 42 ℃ for overnight. To regulate the solvent vaporization, an upturned funnel was kept on the plate. The prepared patches were stored at controlled humidity.

Table no. 2. Compositions of formulations (P1-P6) of nanosuspension Loaded transdermal patch of RTN

Formulation code	Ethyl cellulose (mg)	Polyvinyl pyrrolidone(mg)	Dibutyl phthalate (%w/w)	Oleic acid (%w/w)
P1	375	125	10	5
P2	375	125	20	10
P3	375	125	30	5
P4	375	125	10	10
P5	375	125	20	5
P6	375	125	30	10

Evaluation of RTN NSPs embedded transdermal films:

The surface texture, color, clarity, and pliability of the casted NSP-loaded transdermal films were examined visually. Using a screw gauge, the thickness of the film was measured at three different locations, and a mean value was noted. The patch was repeatedly creased in the same dimension until it broke in order to measure folding endurance. This value comes from the count that causes patch breakage. Iterative folding indicates the patch's resilience to breakage. The following method was used to estimate the uniformity of drug content.

Transdermal patches were dissolved in 4 milliliters of dichloromethane, which was then adjusted to 10 milliliters using buffer 7.4 before being evaporated. These combinations were diluted and then submitted to UV-Vis spectrophotometric measurement against a blank after being cleared using a 0.45 m filter media. A pulley mechanism was used to stretch the film in order to measure its tensile strength. Three 2 cm2 circular patches were cut. Weights were added to the pan to progressively increase the force until the patch broke. The tensile strength was calculated using following formula.

$$\text{Tensile strength(S)} = \frac{(Applied\ force)}{(Cross\ section\ area)}$$

In-vitro drug release study of RTN from NSP loaded transdermal patches

The drug release studies of RTN NSPs loaded transdermal patch were performed using the USP dissolution test apparatus V (paddle over disc method) at a rotation of 50 rpm. Studies were carried out in 500.0ml of pH 7.4 phosphate buffer and temperature maintained at 37 ± 0.5°C for a period of 12 hrs. The film was adhered to an inverted petri dish using epoxy adhesive, permitting drug diffusion solely from the top surface, and was positioned at the base of a vessel containing 500 ml of buffer pH 7.4. periodically, 5ml aliquots were taken at 5 min, 15 min, 30 min, 1hr with regular interval of 1hr for 12hrs, replenishing with fresh medium. The samples were analyzed spectrophotometrically at respective wavelengths for RTN and calculations were performed using equation from standard curve.

Ex-vivo drug diffusion study of RTN from NSP loaded transdermal patches:

Franz diffusion cells with a 20 ml receptor compartment and a 3.14 cm2 diffusion area were used for the ex-vivo drug diffusion experiment. An excised goat abdominal corpse was used, and it was positioned between the diffusion cell's donor and acceptor sections before an experimental patch and 7.4 buffer was added. The entire apparatus was set up to run at 32 ± 0.5°C and 500 rpm on a magnetic stirrer. The amount of medication diffused was measured using a spectrophotometer after the aliquots were taken out at certain intervals (5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, up to 12 hours). The amount of medication that diffused from the films was plotted against time.

RESULTS AND DISCUSSION

Preformualtion studies

RTN's melting point and solubility were examined in order to verify its identity. All of these tests' outcomes met the manufacturer's specifications. The substance was found to meet the official criteria based on the results of the initial identification test. The supplier's identification test official in IP and BP verified the polymers Polaxomer-188, Polyvinyl pyrrolidone (PVP), and Ethyl cellulose as excipients. Every excipient demonstrated

results that met standard specifications. The λmax was determined to be 262 nm based on the scanning of RTN in pH 7.4 buffer.

Formulation and optimization of RTN nanosuspension using Box-Behnken Design (BBD)

BBD was applied to detect the impact of three input factors on output variables.

Following the constraint exhibited (Table No.12 and 13), the Design Expert software generated 15 runs, that were formulated and quantified for the output responses, i.e. the independent variables were amount of polymer Polaxomer-188(X1), amount of surfactant SLS(X2) and Speed(X3). While Particle Size(Y1), Zeta potential(Y2) and Total drug content (Y3) were used as dependent variables (responses).

The responses indicated, that with increasing poloxomer concentration, zeta potential increases, whereas particle size and drug content reduces with increasing surfactant concentration, speed lowered the particle size and zeta potential, and enhanced drug content (Figure no. 1).

Equation generated for correlating particle size with input variables is

$$Particle\ size = 258.40 - 45.18\ A - 5.98\ B - 2.78\ C + 1.28\ AB + 77.28\ AC + 63.13\ BC + 53.91\ A2 - 54.39\ B2 + 24.16\ C2)$$

Where, A - Poloxamer 188, B - Sodium lauryl sulphate, C - Speed

F-value of 7.95 reveals significant value, with only 1.72% probability of noise that could occur with this value.

Equation generated for correlating zeta potential with input variables is

$$Zeta\ potential = -15.89 + 1.41\ A - 1.10\ B - 0.1125\ C - 0.6250\ AB + 4.00\ AC + 5.98\ BC$$

Where, A - Poloxamer 188, B - Sodium lauryl sulphate, C - Speed

F-value of 1.35 reveals significant value, with only 38.67% probability of noise that could occur with this value.

Equation generated for correlating total drug content with input variables is

$$(Total\ drug\ content = +63.90 + 3.64\ A - 4.09\ B - 2.64\ C + 7.24\ AB + 8.21\ AC - 17.54\ BC)$$

Where, A - Poloxamer 188, B - Sodium lauryl sulphate, C - Speed

F-value of 2.17 reveals significant value, with only 20.44% probability of noise that could occur with this value.

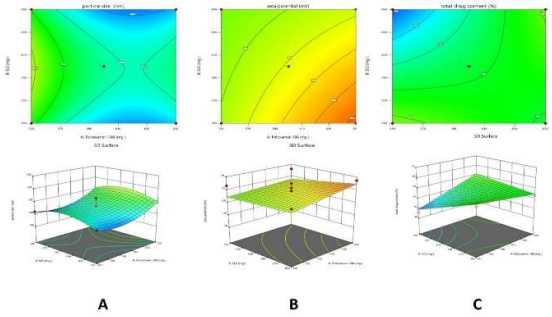


Figure 1. Contour and 3D plot showing A. Effect of the amount of Poloxamer 188 and SLS concentration on particle size of RTN nanosuspension, B. Effect of the amount of Poloxamer 188 and SLS concentration on zeta potential of RTN nanosuspension, C. Effect of the amount of Poloxamer 188 and SLS concentration on total drug content of RTN nanosuspension

Inference drawn from the findings of the optimization conducted by BBD 15

The results suggests that the concentration of surfactants and the rate of processing is very important with regard to decreasing the size of the particles, probably because the surfactants are more effective in stabilizing and size reduction is efficient during the homogenization process. Smaller size is also a benefit because it increases the rate of dissolution and bioavailability of poorly soluble drugs, such as RTN.

Conversely, the zeta potential model was not found significant (F-value = 1.38) and this means that the variables chosen did not have a significant impact on surface charge. Nonetheless, the negative zeta potential values obtained indicate moderate stability of the nanosuspension system, which is probably attributed to the repulsive force of the electrostatic force caused by the surfactant system. Even though this was not statistically significant, it is important to keep zeta potential sufficient to avoid aggregation.

The total drug content model likewise was not significant (F-value = 2.28), except the quadratic term B2 which showed significant nonlinear response of the sodium lauryl sulphate concentration on drug entrapment. The surplus of the surfactant can cause solubilization of the drug not in nanoparticles, thus lowering the encapsulation efficiency.

Evaluation of NSPs 16

Particle size, zeta potential and total drug content and drug loading efficiency were determined (Table no. 3).

The results indicated that particle size of all the NSPs was between 153.8 to 451.6 nm. The size of particles depends on the concentration of stabilizers and homogenization speed. Low stabilizer results in formation of clusters and high stabilizer quantum avoids clustering 17.

To examine the surface characteristics of the nanosuspension, an analysis of the zeta potential was conducted. The zeta potential value is crucial for the stability of NPs. More zeta potential signifies a stronger charge on the particle, which leads to particle repulsion and minimizes the likelihood of particles clumping together. Therefore, a high zeta potential value signifies the physical stability of NSP. Zeta potential value of all the NSP batches was in the range of -11.2 to -29.4 mV18. Total drug content was between 45.18 to 88.66 %, which indicates negligible drug loss during the formulation cycle. The drug loading efficiency was in the range of 39.26 ± 0.57 to 69.06 ± 0.89%, which indicates that the drug was uniformly distributed throughout the RTN nanosuspension formulations. Comparison of these evaluation parameters indicated that batch S2 of NSP showed optimum results19.

Table no.3: Observed responses for RTN nanosuspension batches generated using Box-Behnken design

Formulation code	Particle size (nm)	Zeta potential (Mv)	Total drug content (%)	% drug loading efficiency
S1	326.5	-12.5	55.34	45.61±0.82
S2	213.2	-11.9	68.40	51.34±0.91
S3	375.9	-15.6	74.51	48.26±0.72
S4	315.3	-11.2	48.68	61.25±1.22
S5	175.6	-29.4	88.66	69.03±0.89
S6	259.1	-14.2	59.09	42.12±0.62
S7	153.8	-18.6	87.54	44.67±0.75
S8	305.2	-15.4	69.26	64.12±1.34
S9	221.8	-11.4	62.98	67.23±1.55
S10	451.6	-13.5	82.51	63.56±1.21
S11	267.3	-11.8	45.18	40.23±0.82
S12	197.2	-18.6	72.46	39.26±0.57
S13	321.2	-26.5	51.74	62.23±0.98
S14	176.3	-28.3	76.48	43.76±0.43
S15	291.5	-13.4	45.72	40.21±0.32

Drug-excipient compatibility study

The drug-excipient compatibility study conducted by FT-IR spectroscopy indicated, no significant changes in the prominent peaks exhibited by RTN alone, when combined with all the excipients. The findings are exhibited in Figure no 2.

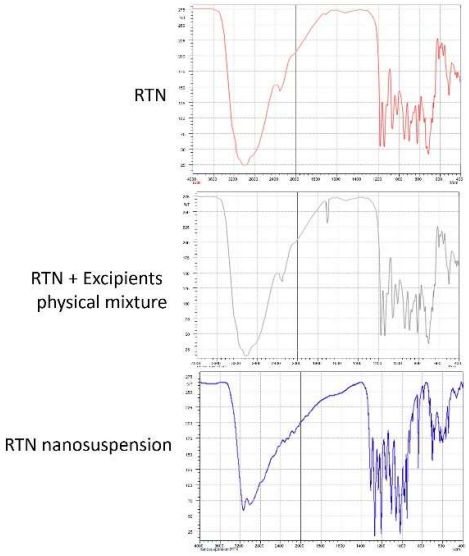
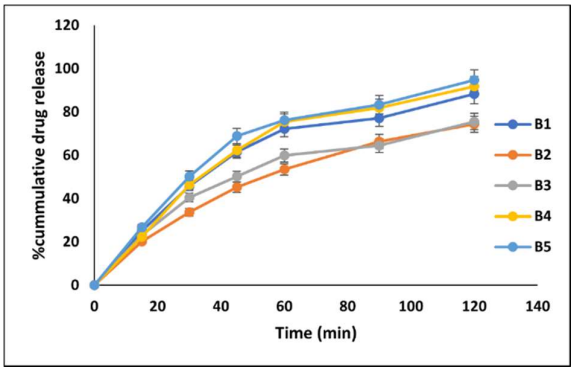
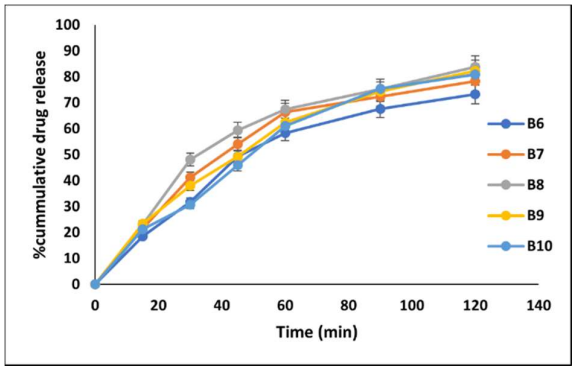


Figure no. 2. FT-IR spectrum of RTN alone, in combination with polymers and RTN NSP

In-vitro drug dissolution studies of RTN NSP:

The key advantage of NSPs lies in its ability to enhance the rate of dissolution, which is attributed not only to an increase in surface area but also to a rise in equilibrium solubility. In-vitro dissolution data of RTN NSPs were carried out for 120 min and graphically represented as % drug release v/s time profile. The drug release of optimized batch (B2) was found to be 94.67±0.23% with 120 min. These findings (Figure no. 3) are in congruence with the fact that reduction in particle dimensions enhances solubilization rate and extent.





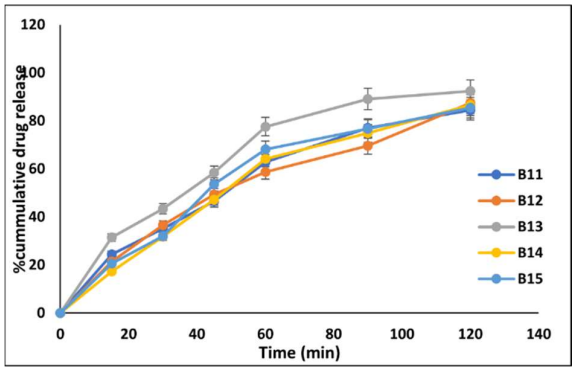
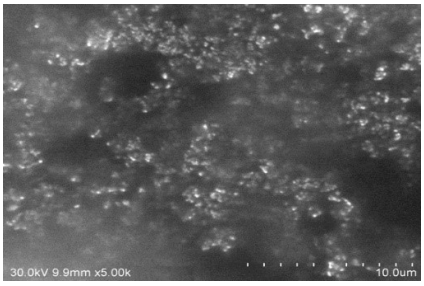


Figure no. 3. In vitro dissolution profile of various bathes of RTN NSPs

Scanning electron microscopy:

SEM was performed to investigate the surface characteristics of particulates. The RTN NSPs revealed a smooth appearance. The surface structure of optimized nanosuspension batches appeared fairly smooth as showed in Figure 4.

Figure no. 4. Scanning electron microscopy of optimized RTN NSP Batch S2



Preparation of RTN nanosuspension loaded transdermal patch:

RTN NSPs loaded transdermal patch was prepared using solvent evaporation method using PVP and Ethyl cellulose as polymer, Dibutyl phthalate as plasticizer and oleic acid as permeation enhancer in different concentrations. Equivalent concentration of RTN NSPs

(50 mg) optimized batch was incorporated in transdermal patch polymeric matrix. Composition of RTN nanosuspension transdermal patch are given in Table no. 2.

Evaluation of RTN NSPs loaded transdermal patches

Physical evaluation of all the transdermal patches was done and were found to be flexible, smooth, opaque and non-sticky (Table no. 4)20. All the prepared NSPs loaded transdermal patch were evaluated for their physical parameters (Flexibility, smoothness, transparency, stickiness), and they were found to be flexible, uniform, smooth, opaque, and non-sticky. RTN nanosuspension loaded transdermal patch gave acceptable folding endurance values. The folding endurance value was observed 120±4.32 which indicate the good mechanical properties of prepared transdermal patches. Use of plasticizer Dibutyl phthalate enhance the flexibility of patch and provide the integrity to prepared formulation. The thickness of prepared batches RTN transdermal patches was in ranged between 0.26 ± 0.02 to 0.33±0.02 mm. Very low value of standard deviation in all batches indicated that the prepared patches were uniform in thickness21.

The average value of drug content in prepared formulations was in the range of 91.05±0.6 to 96024±0.5 % respectively. This result revealed that the uniform dispersion of drug in film and solvent evaporation method used to prepare transdermal patch was capable of producing transdermal patch with uniform drug amount. Tensile strength of transdermal patch formulations was found to be between 0.245 ±0.075 to 0.386±0.054 kg/cm2. This result reveals that tensile strength of transdermal patch formulation was satisfactory (Table no. 5)22.

SEM study is qualitative mode to study morphology of RTN NSPs loaded transdermal patch, the visual observations provide an indication of nanosuspension dispersion. At higher magnification aggregates of nanosuspension can be seen. SEM images show uniform distribution of nanosuspension in transdermal patch (Figure no. 5)23.

Table no. 4. Physical evaluation of RTN NSPs loaded transdermal patches

Formulation code	Flexibility	Smoothness	Transparency	Stickiness
P1	Flexible	Smooth	Opaque	Non sticky
P2	Flexible	Smooth	Opaque	Non sticky
P3	Flexible	Smooth	Opaque	Non sticky
P4	Flexible	Smooth	Opaque	Non sticky
P5	Flexible	Smooth	Opaque	Non sticky
P6	Flexible	Smooth	Opaque	Non sticky

Table no. 5. Physical evaluation of RTN nanosuspension loaded transdermal patch

Formulation code	Thickness(mm)	Folding Endurance	Tensile Strength (Kg/cm²)	Drug content uniformity (%)
P1	0.28±0.01	85±0.98	0.247±0.063	94.32±1.2
P2	0.31±0.03	98±2.67	0.251±0.085	92.46±0.8
P3	0.26±0.02	115±4.32	0.386±0.054	98.24±0.5
P4	0.32±0.04	78±3.97	0.245±0.075	91.02±0.6
P5	0.33±0.02	110±2.45	0.352±0.086	95.30±1.1
P6	0.29±0.05	105±1.96	0.326±0.096	94.69±1.3

Each value represents the mean ± standard deviation (n=3)

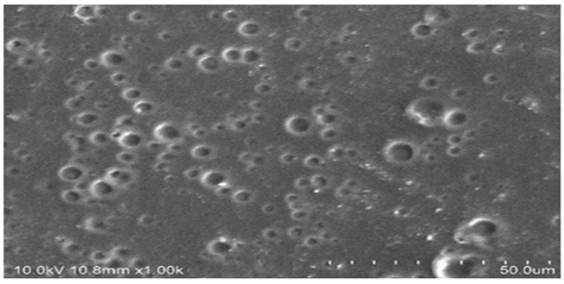


Figure no. 5. Scanning electron microscopy of optimized P6 RTN nanosuspension loaded transdermal patches

In vitro drug diffusion of RTN NSPs loaded transdermal patches24

RTN nanosuspension loaded transdermal patch were prepared with different concentrations of permeation enhancer oleic acid. It was revealed that all transdermal patches were able to sustain the release of drug from formulation. RTN formulations P1, P2 and P3 showed 75.62 ± 0.46, 98.43 ± 0.15 and 99.23 ± 0.43 % of drug release and P4, P5, and P6 showed 75.45 ± 0.23, 84.23 ± 0.29, 93.14 ± 0.65 percent of drug release (Figure no. 6).

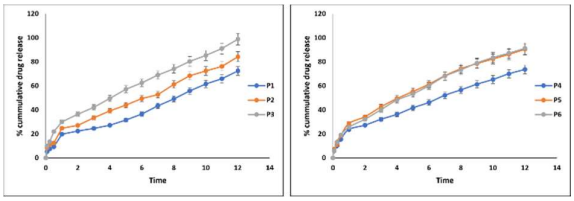


Figure no. 6. In vitro drug diffusion of RTN from NSPs loaded transdermal patches

Ex vivo drug permeation of RTN NSPs loaded transdermal patches25

Formulation RTN P6 being the best with highest drug permeated through the membrane at the end of 12 hr. Penetration enhancers typically boost the rate at which a drug permeates through the stratum corneum (Figure 7).

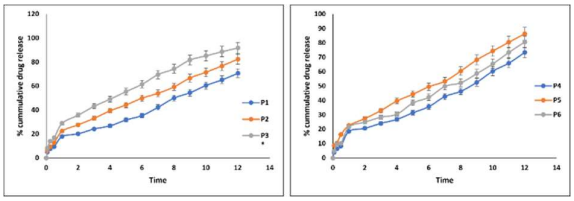


Figure no. 7. Ex vivo drug permeation of RTN NSPs loaded transdermal patches

CONCLUSION

The study succeeded in producing and refining RTN nanosuspension and applying it to transdermal films with desired physicochemical properties. The optimization revealed that the formulation's variables had a significant impact on particle size but minimal effects on drug content and zeta potential. The produced films had enough mechanical strength, were flexible, and had a consistent thickness. In vitro and ex vivo tests revealed sustained drug release and enhanced skin penetration, particularly in formulation P3. RTN's solubility and bioavailability were generally improved by the nanosuspension-based transdermal system, indicating that it may be a useful transdermal drug delivery method.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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None

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