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FORMULATION DEVELOPMENT AND CHARACTERIZATION OF TRIAMCINOLONE LOADED CUBOSOMES FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT: Psoriasis is a chronic condition that is caused by the negative signals given by immune system, which leads to hyperproliferation and other inflammatory reactions on the skin. These conditions may adversely affect the quality of the patient's life leading to psychological stress. Topical delivery of drug is always preferred for Psoriasis because other treatments may lead to systemic intoxication and other adverse reactions. Triamcinolone is a topical corticosteroid belonging to BCS class IV (low solubility and permeability) used to treat Psoriasis. The limitations with transdermal delivery is that only a small amount of the drug can be transferred through the skin tissue due to the barrier effects of the Stratum corneum. Therefore, Novel transdermal delivery system, Cubosomes belonging to Nanostructured lipid carriers were chosen to overcome the issues of solubility and permeability. Twelve formulations were prepared with various ratios of Glyceryl monooleate (2.5 to 5%) & Poloxamer 407 (0.5 to 2%) and the formulations were evaluated for particle size, PDI, zeta potential, entrapment efficacy, drug content and in-vitro release. The best composition of Cubosomes was selected and incorporated into transdermal patch and the formulated patches were evaluated.
KEYWORDS: Cubosomes, Transdermal patch, Permeability

INTRODUCTION

Psoriasis is a skin disorder that is chronically proliferative and inflammatory. The extensor surfaces, scalp, and lumbosacral area are all affected, with erythematous plaques coated with silvery scales. The pathogenesis involves activated T lymphocytes infiltrating the skin and stimulating keratinocyte production. The formation of thick plaques is caused by a disruption in keratinocyte turnover. Other symptoms include epidermal cells failing to release lipids, resulting in flaky, scaly skin, which is typical of Psoriasis. [1] It is linked to a number of serious medical issues, including depression, psoriatic arthritis, and cardiometabolic syndrome. Although psoriasis cannot be cured, it can be managed to reduce physical and psychological harm by treating patients early in the disease process, recognising and preventing related multimorbidity, establishing lifestyle changes, and using a personalised therapy approach. [2] The scalp, elbows, knees, umbilicus, genitalia, sacrum, and shins are the most typically affected areas. Emollients, dithranol, tar, and corticosteroids are the first-line therapies. Phototherapy and systemic medicines are examples of second-line treatments that have more adverse reactions. [3]

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Due to the advantages presented, oral delivery systems are still the most preferred technique for delivering API. Despite these benefits, oral administration systems have numerous drawbacks, including low drug stability in the gastrointestinal tract and first-pass metabolism. The transdermal route has been investigated as a potential route for improving medication delivery in order to potentially overcome some of these drawbacks[4]. The risk of liver malfunction and gastrointestinal tract irritation as side effects is low since medications delivered via transdermal delivery systems avoid the gastrointestinal tract and hence avoid conversion by the liver. Other advantages of drug administration through the skin include maintaining an effective rate of drug delivery in time, a consistent rate of circulation, and the advantages of a passive delivery mechanism and diffusion [5].

The most difficult part of developing a transdermal drug delivery system is overcoming the stratum corneum's barrier effect, delivering the drug to skin tissue, and passing through cellular and vascular tissue to reach the target region. The issue is that skin tissue can only transport a minimal amount of the medication. Various innovative transdermal drug delivery strategies have been intensively studied to overcome these challenges and have emerged as desirable administration routes. Furthermore, in terms of the administered dose, cost-effectiveness, and therapeutic efficacy, such development could provide a competitive advantage over existing drug administration strategies. [6]

Because of a variety of enticing qualities, nanostructured lipid carriers (NLC) have been promoted as feasible carriers for transdermal medication administration for the past decade. Traditional topical medicines have a variety of drawbacks, including impermeability of the epidermal barrier, limited efficacy, and frequent administration. Part of the researcher's current focus in the pharmaceutical and cosmetic industries is on developing NLC for topical and dermal applications. NLCs are lipids that are physiologically active, biodegradable, low in toxicity, and contain a variety of advantageous qualities. The low therapeutic efficacy and adverse side effects of conventional topical carriers can be solved by using dermal NLC. [7]

Cubosomes are bicontinous cubic liquid crystalline phase particles that are unique, sub-micron nano-structured particles. They are nanoparticles that are self-assembled liquid crystalline particles of specific surfactants that have an appropriate water ratio and have a solid-like rheology. Cubosomes have the same microstructure as the parent cubic phase, but have a greater specific surface area and smaller viscosity dispersions than the bulk cubic phase. Cubosomes are commonly made by dispersing bulk-cubic phase at a high energy, then stabilising the colloidal phase with polymeric surfactants. Lipids, surfactants, and polymer molecules with both polar and non-polar components constitute these vesicles. Amphiphilic molecules in polar compounds spontaneously self-assemble into an array of thermodynamically stable liquid crystalline phases with lengths on the nanometer scale due to the hydrophobic effect. Cubosomes are thus bicontinous cubic liquid phases that include two distinct water regions separated by surfactant-controlled bilayers. Cubic phases are more bioadhesive, making them ideal for topical and mucosal depositions for drug delivery. Topical delivery methods focus on the use of liquid crystal's unique characteristics and Liquid Crystal Nanoparticle Technology (LCNT). This intriguing technology creates a thin surface coating at surfaces made up of a liquid crystal matrix with a nanostructure that can be adjusted for an ideal delivery profile and provides good temporary protection for painful and sensitive skin. [8]

The most effective treatment for psoriasis is topical steroids, which are quite efficient in treating mild to moderate illness. In moderate to severe disease, they can be administered alone or in conjunction with other drugs. Corticosteroids depress the immune system by decreasing lymphatic system function, decreasing

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immunoglobulin and complement concentrations, precipitating lymphocytopenia, and interfering with antigen-antibody interaction. Triamcinolone is a topical corticosteroid that is used to treat a number of skin problems (e.g., eczema, psoriasis, dermatitis, allergies, rash, and mouth ulcers). It is a low-solubility, low-permeability BCS Class IV medication. When used orally, triamcinolone undergoes substantial first-pass metabolism. Thus from above listed characteristics of drug and taking into account that for psoriasis disease first line of treatment is done by topical route the current study is focused on the development of Cubic nanoparticles for enhanced transdermal delivery.[9,10]

MATERIALS REQUIRED

Triamcinolone was obtained as a gift sample from Pharmafabrikon, Madurai. Poloxamer 407 was obtained from Apex Laboratories Private Limited.,Chennai. HPMC was obtained as a gift sample from Shasun Pharmaceuticals Limited,Chennai. Glyceryl monooleate, Glycerol and ethanol were purchased from Universal scientific appliances, Madurai. All chemicals used were of analytical grade and double distilled water was used throughout the experiments.

METHODOLOGY

PREPARATION OF CUBOSOMES

The bottom-up technique was used, in which the nanostructure building blocks were first formed and then gathered into the final substance. It is a more recently established method of cubosome generation that allows cubosomes to synthesize and crystallise from molecular precursors. The sonication approach was chosen for subsequent research because of maximum entrapment efficiency and the smallest particle size is possible.

Glyceryl mono oleate and Poloxamer 407 were used to make the cubosomal formulation. Glyceryl mono oleate was altered from 2.5 % to 5 %, while Poloxamer 407 was varied from 0.5 %to 2 %, resulting in twelve separate batches. GMO was gently melted in a water bath at 70°C, then injected dropwise into a preheated poloxamer 407 solution at 70°C, and drug 5mg was added before gradually adding distilled water to make up to 20 mL. For 5 minutes, these solutions were mechanically stirred at 1500 rpm. After cooling to ambient temperature, the dispersions were sonicated for 5 minutes at maximum power of 120 W. Cubosome milky white dispersions were formed after a 24-hour equilibration period. [11]

EVALUATION OF CUBOSOMES

Particle size and Polydispersity index

The particle size and polydispersity index of cubosomes were determined using a computerised zeta sizer device (Malvern Mastersizer 2000 Ver 2.00) at 25°C using the dynamic light scattering approach. The zeta sizer cell was filled with cubosomal formulation and the size and Polydiepersity index were measured. [12]

Zeta Potential

The levels of electrophoretic mobility (zeta potential) of cubosomal dispersions were determined using a zeta sizer and the values were obtained. At 25 °C, the zeta potential was measured using Zetasizer. The samples were stored in a polystyrene cuvette, and the zeta potential was measured using a zeta dip cell. Zeta potential for a stable formuluation is found to be +/-30mV.

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Entrapment efficiency

The centrifugation method was used to determine the entrapment effectiveness of the developed cubosomal mixture. Cubosomes were centrifuged for 1 hour at 10000 rpm at room temperature. Supernatant containing unentrapped medication in cubosomes was isolated and analyzed against phosphate buffer using a UV spectrophotometer at λ_{max} 239nm (PH 7.4). After rupturing the cubosomes, the remaining entrapped drug was quantified using Triton X 100. [13]

The amount of drug entrapped in cubosomes was determined by calculating the entrapment efficiency by the equation:

$$\% \text{ Entrapment efficiency} = \frac{\text{Total drug content} - \text{Drug content in supernatant}}{\text{Total drug content}} \times 100$$

Drug Content

The drug content of cubosomal formulation was determined by mixing the formulation with methanol and sonicated for 10 minutes to obtain a clear solution and filtered. The filtrate was analysed for drug content by UV at λ max 239 nm.

$$\text{Drug content} = \frac{\text{Actual yield} \times 100}{\text{Theoretical yield}}$$

Scanning Electron Microscopy

A scanning electron microscope was used to examine the surface features of prepared cubosomes for morphology. This image was used to confirm the cuboidal geometry of the formulations.10µl of cubosomes were uniformly dispersed on a glass slide and allowed to dry at room temperature for SEM visualisation. The morphology was studied with a Philips 505 electron microscope at an accelerating voltage of 2.0 kV after gold coating the sample with a Polaron E5100 gold sputter coater. [14]

In-vitro release study

The dialysis membrane was used in the release study. The cubosomal formulation was placed on the dialysis membrane and the ends were clamped shut before being suspended in phosphate buffer ph 7.4 in a beaker.The samples were taken at predetermined intervals (1,2,3,4,5,6,7,8,9,10,11,12, and 24 hours) and the same volume of buffer solution was immediately replaced to keep the sink condition. Using a UV Spectrometer, the materials were examined at λ_{max} 239 nm. The data were plotted on a graph with time on the X-axis and percent cumulative medication release on the Y-axis. [13]

In-vitro Permeation study

Vertical Franz diffusion cells were used to determine In-vitro Permeabilty of the selected best formulation of Cubosomes using the goat skin obtained from the local slaughter house.The skin was stored in a freshly prepared saline solution for 24 hours a day before the study. An epidermal layer of surface area of 1.5cm^2 from the goat skin was placed facing the donor compartment. About 10ml of Cubosomal formulation was placed on the donor compartment and the receptor compartment was filled with 100ml of buffer pH 7.4 maintained at 37 ±1ºC. Then this design was placed on the magnetic stirrer and maintained at 100 rpm. Samples

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were withdrawn at pre-determined inetervals (at 1,2,3,4,5,6,7,8,9,10,11,12 and 24 h) from the receptor compartment and replaced immediately with equal volumes of fresh buffer solution. The samples obtained were analyzed using UV Spectrometer at 239 nm as $\lambda_{max.}$ The cumulative percentage of drug permeated per unit area (µg/cm2) of the skin was plotted as a function of time (h) and the slope was calculated from the linear portion of the curve. The flux (µg/cm2) at steady state was calculated by dividing the slope by area of the skin surface through which permeation took place.[15]

Kinetic study

The first order mode, zero order model, Higuchi, and Korsemeyer-Peppas kinetic models were used to fit the release data of the selected formuation. n=0.5 for fickian diffusion, for anomalous transport n=0.5-1 and for case II transport, n=1.[12]

FORMULATION OF CUBOSOMES LOADED TRANSDERMAL PATCH

The solvent evaporation process was used to develop the transdermal patch. iThe hydroxy propyl methyl cellulose was dissolved in ethanol and magnetically stirred until it reached a semisolid consistency. The drug was mixed in these solvents as a cubosomal dispersion and agitated constantly. As a plasticizer, glycerol was added drop by drop to this composition. Poured it onto petridish, covered it with the inverted funnel, and let it dry for 24 hours to obtain a patch. After 24 hours, the patches were removed using a sharp knife inserted along the edge of the patch and stored for future research. [16]

EVALUATION OF TRANSDERMAL PATCHES

Physical appearance

Prepared patches were visually inspected for colour, clarity, flexibility and smoothness.[17]

Thickness uniformity

Thickness of the patch was determined by using digital thickness gauge. The thickness was measured at 4 different points and the average thickness was obtained. [18]

Folding Endurance

For the prepared patches, the folding durability was carefully measured. A 1cm2 patch strip was cut and folded repeatedly in the same spot until it snapped. The value of folding endurance is determined by the number of times the patch may be folded in the same location without breaking or cracking. [17]

Percentage Moisture Absorption

The patch were weighed accurately and placed in dessicators for 72 hours and after that the patches were reweighed and the percentage moisture absorption was calculated using the formula:

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

Drug content

Short circular patch were cut out into small pieces and soaked in 100 ml of methanol and stirred using magnetic stirrer consecutiovely for 36 hours and sonicated for about 36 minutes. The solution was filtered and evaluated using UV Spectrophotometer at wavelength 239nm.**[19]**

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Flatness test

Each film was divided into longitudinal strips, one in the centre and two on either side. The length of each strip was measured, as well as the variation in length caused by nonuniformity in flatness.

In-vitro release study

The drug release from the formulated patches were evaluated using USP (apparatus I) Basket type apparatus. The patches were placed in their appropriate baskets, with their drug matrix exposed to phosphate buffer (pH 7.4). All dissolution tests were carried out at 37±0.5ºC and 100 rpm, using 900mL of buffer in each dissolving jar. Samples were taken at various intervals (1,2,3,4,5,6,7,8,9,10,11,12, and 24 hours) and evaluated against a blank using a UV Spectrophotometer at 239nm. For the formulations, cumulative amounts of drug released were plotted against time. [20]

In-vitro Permeation study

Vertical Franz diffusion cells were used to determine In-vitro Permeabilty of cubosomes loaded transdermal Patches using the goat skin obtained from the local slaughter house. The skin was stored in a freshly prepared saline solution for 24 hours a day before the study. An epidermal layer of surface area of 1.5cm^2 from the goat skin was placed facing the donor compartment. A section of cubosomal patch was placed on the donor compartment and the receptor compartment was filled with 100ml of buffer pH 7.4 maintained at 37 ±1ºC. Then this design was placed on the magnetic stirrer and maintained at 100 rpm. Samples were withdrawn at pre-determined inetervals (at 1,2,3,4,5,6,7,8,9,10,11,12 and 24 h) from the receptor compartment and replaced immediately with equal volumes of fresh buffer solution. The samples obtained were analyzed using UV Spectrometer at 239 nm as $\lambda_{max.}$ The cumulative percentage of drug permeated per unit area (µg/cm2) of the skin was plotted as a function of time (h) and the slope was calculated from the linear portion of the curve. The flux (µg/cm2) at steady state was calculated by dividing the slope by area of the skin surface through which permeation took place.[15]

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RESULTS AND DISCUSSION

PREPARATION OF CUBOSOMES

The effect of GMO concentration on physical appearance and stability of cubosomal nanoparticles were studied by adding various concentration of GMO such as 2.5%,3.75%,5%.10%,15% and 20% .From the results 2.5%,3.75%,5% v/v of GMO was suitable for cubosomal nanoparticles due to desired physical appearance and stability. Various concentrations (0.5%,1%,1.5% and 2%) of stabilizer were optimised and results showed that 0.5%,1%,1.5% was sufficient to obtain a stable cubosome formulation.

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Table 1 : Formulation codes with quantities

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug (mg)	5	5	5	5	5	5	5	5	5	5	5	5
GMO (g)	2.5	2.5	2.5	2.5	3.75	3.75	3.75	3.75	5	5	5	5
Poloxamer 407 (g)	0.5	1	1.5	2	0.5	1	1.5	2	0.5	1	1.5	2

EVALUATION OF CUBOSOMES

Particle size and Polydispersity index

The particle size range of all formulations are within the nanometer range. The particle size was found to be in the range of 163 – 357.3nm and PDI was found to be in the range of 0.244 – 0.642.The results are shown in table 3 and the image of the optimised formulation measurement is shown in figure 3.

Zeta Potential

The results obtained here indicates that there is no aggregation in the formulations due to usage of surface stearic stabilizer, poloxamer 407. It produces an envelope around the surface of the nanoparticles and protects from aggregation. Hence the formulation (F6) was observed to be better stable than other formulations. The results are shown in table 3.The image of the zeta potential measurement of the optimised formulation was shown in figure 4.

Entrapment efficacy

The entrapment efficacy of the formulations increased when higher amounts of GMO was used due to the lipophilic nature of the drug. The enhanced lipid values would improve the solubilisation of the lipophilic drug and provides more space for the entrapment of drug. F6 formulation exhibited maximum entrapment efficiency and the results are shown in table 3.

Drug content

F6 has the greater content of drug in it 93.66±3.22 and it is suitable for further studies. The results are shown in table 3.

Scanning electron Microscopy

No aggregation was observed among the particles and the particle surface was smooth without surface deformations and visible pinholes. . The image was shown in figure 2.

In-vitro release studies

Sustained drug delivery of the drug was provided since it produced a maximum of 39.61% of release at the end of 24 hours. High entrapment of the lipophilic drug in the lipid matrix attributed to the sustained release. F6 achieved the highest release and it is considered for further studies. The results are shown in table 3 and the graph is shown in figure 5.

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Selection of best formulation

Optimum particle size, good entrapment efficacy and stability are all desired for good penetration of the formulation across the skin. Considering these factors, formulation F6 was found to be the best formulation, since it has a particle size of 219.3nm and 91.5% entrapment efficacy and was used for further studies.

In-vitro permeation study

In-vitro permeation study was carried out for the selected best formulation (F6) using goat skin. The Permeation occurs in two steps, initial transfer of drug from the formulation on to the surface of the skin and finally the drug was transferred from the surface of the skin to the receptor containing buffer solution. The amount of drug permeated across the skin was found to be 98.35%. Enhanced Permeability across the skin may be due to the cubic structure of the particles, their small size, lipid content of the cubosomes and presence of surfactants. The results are shown in table 4 and the graph is shown in figure 6.

Kinetic study

The korsemeyer peppas kinetic plots were found to be fairly linear as indicated by their highest regression values (0.953) for optimised cubosome formulation. As per peppas model 0.953 is the "n value" in order to characterise the different release mechanisms. In this release n value was found to be nearly 1 for mass transfer following a non fickian model. The results are shown in table 5.

FORMULATION OF CUBOSOMES LOADED TRANSDERMAL PATCH

The cubosomal patch was prepared using optimised formulation F6 .It was loaded in the patch by calculating the amount of drug needed to be loaded as per the formula. HPMC and ethanol provided good consistency and Glycerol assisted in plasticizer activity. The formulated patch was stored by packing in butter paper and wrapped in an aluminium foil sheet. (Figure 1)

$$\text{Total amount of drug to be loaded} = \frac{\text{Area of petridish} \times \text{Desired drug}}{\text{Area of small circular patch}}$$

Table 2: Preparation of transdermal patch

Ingredients	Quantity
HPMC	200mg
Ethanol	Q.S
Glycerol	0.5ml
Drug loaded Cubosomes	2ml

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EVALUATION OF TRANSDERMAL PATCHES

Physical appearance

White in colour, smooth and flexible.

Thickness uniformity

A measuring caliper was used to measure the thickness at 3 different areas and from the results it was indicated that the patch has better uniformity in terms of its thickness. It exhibited an average thickness of 1.4mm.

Folding endurance

By measuring the formulated patch by folding reveals that it has the ability of 20 times to withstand folding without breaking or visible damage of cracks. The results indicate satisfactory good strength and flexibility.

Folding endurance = 20

Percentage Moisture absorption

The percentage moisture content was found to be 4.6%. The lower the moisture content in the patch helps to protect it from microbial contamination and remains stable as it is completely dried.

Drug content

Drug content was calculated as 96 % in the formulated patch.

Flatness test

The patches exhibited 0% constriction and no amount of constriction in the prepared patches indicates 100% flatness. Thus, these patches could maintain a uniform and smooth surface when they are applied onto the skin.

In-vitro release study

The drug release from the patch was found to be 40.64% at the end of 24 hours. It helps in avoiding frequent administration of patches as it exhibited the sustained release. The results are shown in table 6 and the graph is shown in figure 7.

In-vitro Permeation study

It showed a better permeability of 94% at the end of 24 hours across the skin. As Triamcinolone belongs to BCS Class IV with low permeability the formulated cubosomal patch has improved its permeability characteristics. Results were plotted in the graph by taking time in x-axis and % cumulative drug release in y-axis. The results are shown in table 6 and the graph is shown in figure 8.

Kinetic study

The Higuchi kinetic plots were found to be fairly linear as indicated by their highest regression values (0.951) for patch. This value indicates that the release was based on diffusion mechanism. The results are shown in table 7.

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CONCLUSION

The aforesaid findings demonstrated that cubosomal formulations improved the solubility and permeability of the medication triamcinolone. Because the drug has low solubility and permeability, it was overcome and generated a better result in the form of cubosomes, which boosted the drug's solubility and permeability by a significant amount. The formulation F6 was considered to be the best preparation in terms of Particle size, Polydispersity index, entrapment efficacy, drug content, zeta potential and in-vitro release study and hence it was used in the formulation of transdermal patches. Patches made with the optimised composition produced similar outcomes to cubosomes and were more successful than cubosomal dispersion. As a result, it is concluded that when triamcinolone is administered as a cubosomal patch, its efficacy in the treatment of psoriasis is increased. In the future, more in vivo investigations could be conducted to have a deeper knowledge of the formulations and their properties.

Table 3: Evaluation parameters of Cubosomes

Formulation code	Particle size(nm)	PDI	Zeta potential (mV)	Entrapment efficacy (%)	Drug content (%)	In-vitro release (%)
F1	275.6	0.482	-28.3	86.5± 0.51	88.00± 1.40	26.41± 0.21
F2	225.1	0.390	-29.6	88.5± 0.42	87.78±2.15	21.92± 0.52
F3	221.6	0.312	-36.3	83.6 ±0.34	89.11±2.34	23.67± 0.37
F4	357.3	0.600	-33.2	82.5 ±0.45	87.02±1.45	23.64± 0.35
F5	327.3	0.322	-34.2	90.8± 0.23	88.65±4.01	34.74± 0.44
F6	219.3	0.366	-43.6	91.5± 0.20	93.66±3.22	39.61± 0.26
F7	217.3	0.642	-34.9	88.7± 0.56	89.92± 2.24	34.18± 0.36
F8	280.2	0.244	-22.5	89.3± 0.61	89.71± 2.88	30.50± 0.59
F9	190.6	0.446	-27.4	91.3± 0.55	87.01± 2.67	37.23± 0.20
F10	165.5	0.288	-38.9	90.7± 0.45	89.01± 3.24	27.51± 0.25
F11	163.0	0.362	-36.3	90.5± 0.62	86.05± 1.48	19.46± 0.64
F12	226.7	0.532	-16.6	91.2± 0.39	86.98± 2.21	19.88±0.54

Table 4 : In-vitro release study of the best selected formulation (F6)

Time (hours)	% Drug Permeation
1	19.87± 0.21
2	23.68± 0.28
3	31.90± 0.25
4	39.66± 0.37
5	47.98± 0.35
6	52.42± 0.26
7	59.02± 0.41
8	64.73± 0.38
9	76.26± 0.40
10	81.63± 0.57
11	86.81± 0.44
12	92.41± 0.32
24	98.35± 0.54

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Table 5: Kinetic study of cubosomes (F6)

Formulation F6	Kinetic Studies			
	Zero order	First order	Higuchi model	Korsmeyer Peppas model
R^2 value	0.908	0.808	0.953	0.908

Table 6 : Evaluation parameters of Cubosomes loaded transdermal patch

Time (hours)	In – vitro release (%)	In-vitro Permeation (%)
1	3.69	10.60
2	6.12	14.79
3	9.11	16.52
4	11.16	20.47
5	13.72	31.00
6	15.65	40.55
7	16.99	48.10
8	18.95	54.46
9	21.18	59.89
10	23.39	68.24
11	29.77	72.75
12	33.08	82.45
24	40.64	94.16

Table 7: Kinetic study of Cubosomes loaded transdermal patch

Transdermal Patch	Kinetic Studies			
	Zero order	First order	Higuchi model	Korsmeyer Peppas model
R^2 value	0.951	0.934	0.951	0.934

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Figure 1 : Cubosomes loaded transdermal patch

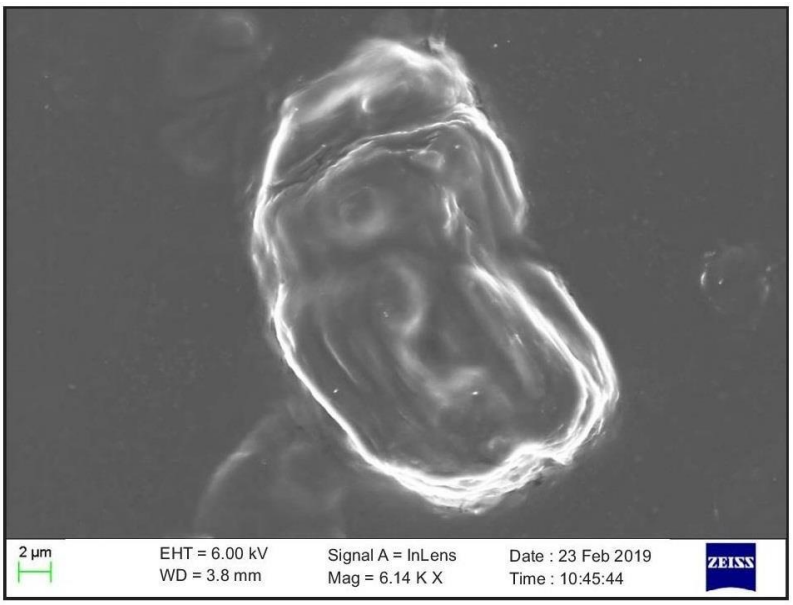

Figure 2: SEM study of Cubosomes

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Size Distribution Report by Intensity

v2.2

Malvern

Sample Details

Sample Name: F5 1
SOP Name: mansettings.nano
General Notes:

File Name:	F3.dts	**Dispersant Name:**	Water
Record Number:	7309	**Dispersant RI:**	1.330
Material RI:	1.59	**Viscosity (cP):**	0.8872
Material Absorbtion:	0.010	**Measurement Date and Time:**	Monday, February 25, 2019 2:...

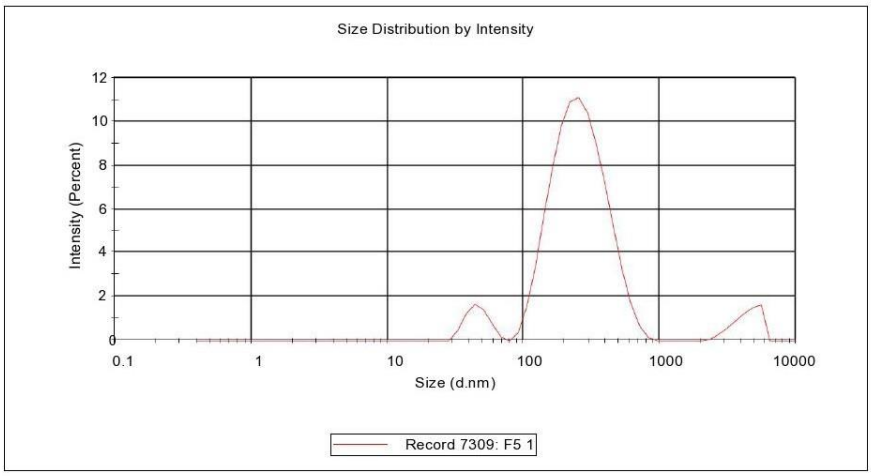
System

Temperature (°C):	25.0	**Duration Used (s):**	40
Count Rate (kcps):	332.6	**Measurement Position (mm):**	4.65
Cell Description:	Disposable sizing cuvette	**Attenuator:**	9

Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 219.3	**Peak 1:**	277.5	88.1	123.4
PdI: 0.366	**Peak 2:**	4420	6.2	914.3
Intercept: 0.894	**Peak 3:**	46.13	5.8	8.472

Result quality : Good



Malvern Instruments Ltd
www.malvern.com

Zetasizer Ver. 7.11
Serial Number : MAL1063652

File name: F3
Record Number: 7309
25 Feb 2019 4:26:45 PM

Figure 3: Particle size distribution of Cubosomes

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Zeta Potential Report

v2.3

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Sample Details

Sample Name: F5 Z 1
SOP Name: mansettings.nano
General Notes:

File Name: F3.dts
Record Number: 7310
Date and Time: Monday, February 25, 2019 2:26:...
Dispersant Name: Water
Dispersant RI: 1.330
Viscosity (cP): 0.8872
Dispersant Dielectric Constant: 78.5

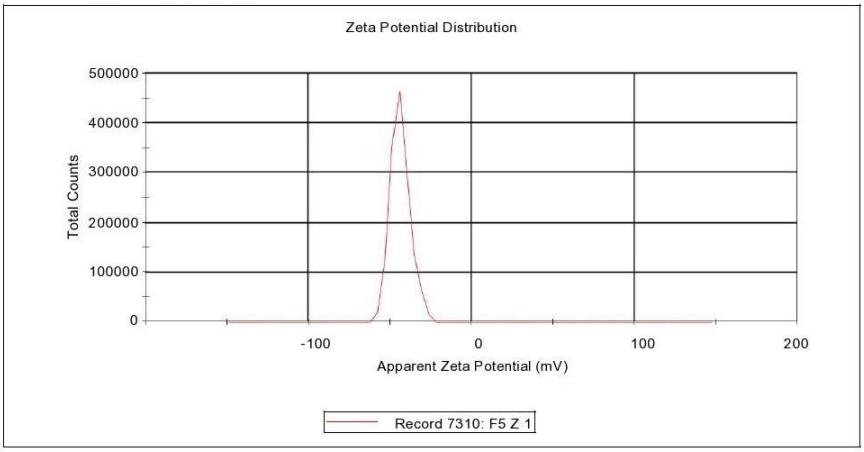
System

Temperature (°C): 25.0
Count Rate (kcps): 324.0
Cell Description: Zeta dip cell
Zeta Runs: 12
Measurement Position (mm): 4.50
Attenuator: 7

Results

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -43.6	**Peak 1:**	-43.6	100.0	6.09
Zeta Deviation (mV): 6.09	**Peak 2:**	0.00	0.0	0.00
Conductivity (mS/cm): 0.0202	**Peak 3:**	0.00	0.0	0.00

Result quality : Good



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Zetasizer Ver. 7.11
Serial Number : MAL1063652

File name: F3
Record Number: 7310
25 Feb 2019 4:26:31 PM

Figure 4: Zeta Potential of Cubosomes

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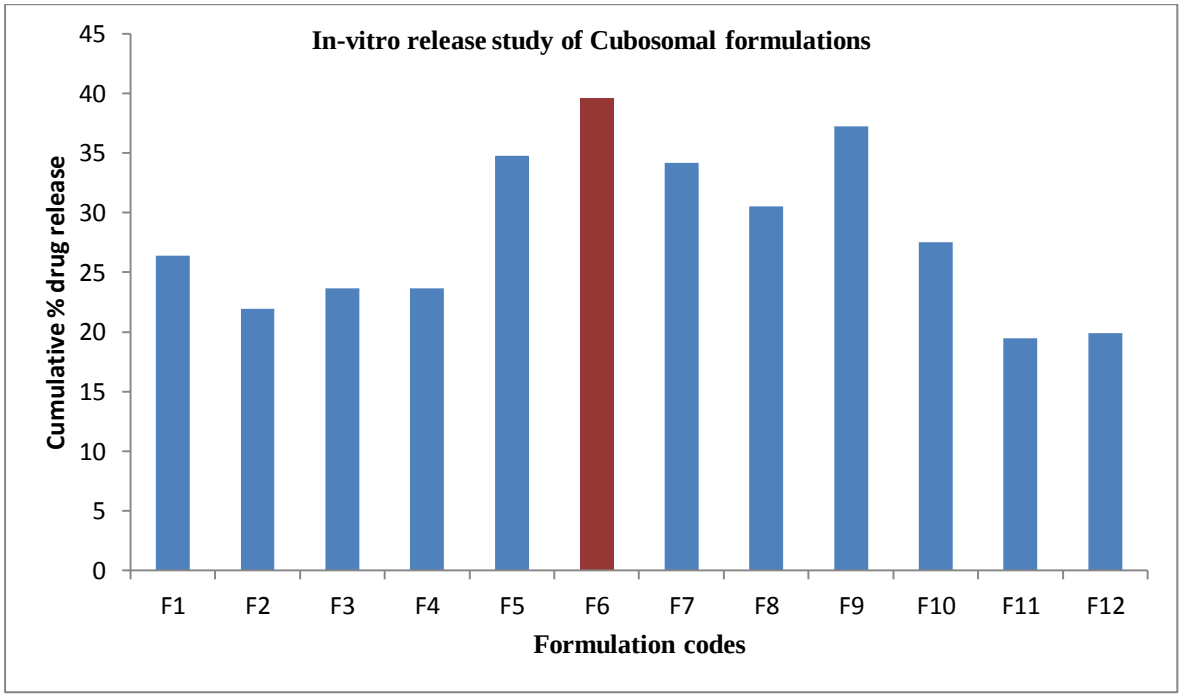

Figure 5: In-vitro drug release of Cubosomes

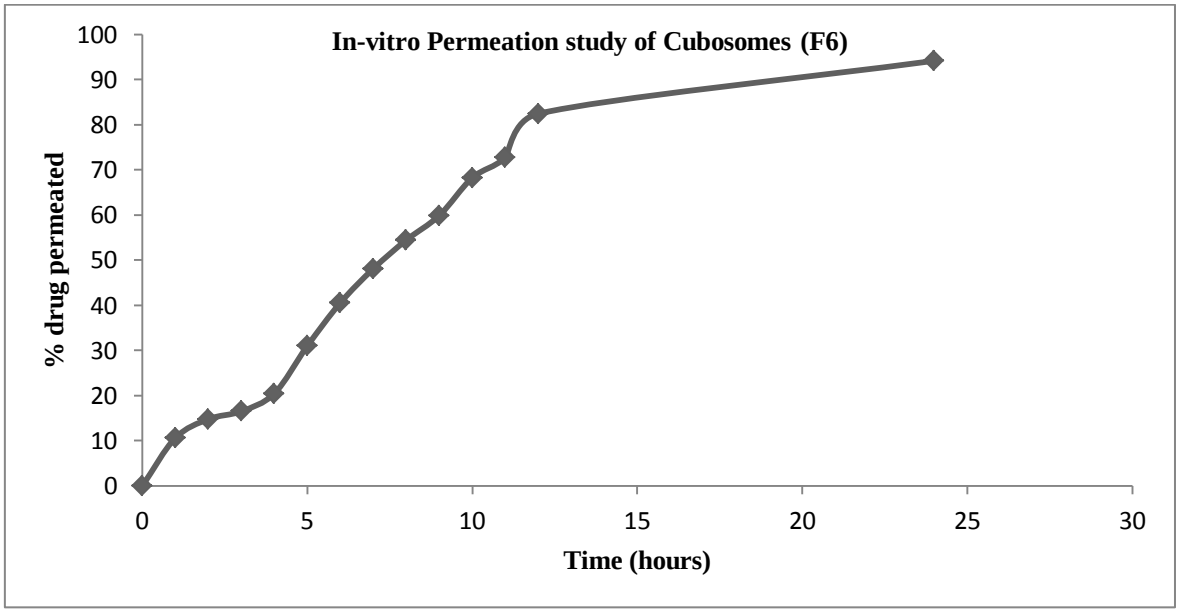

Figure 6: In-vitro permeation of the best selected Cubosomal formulation (F6)

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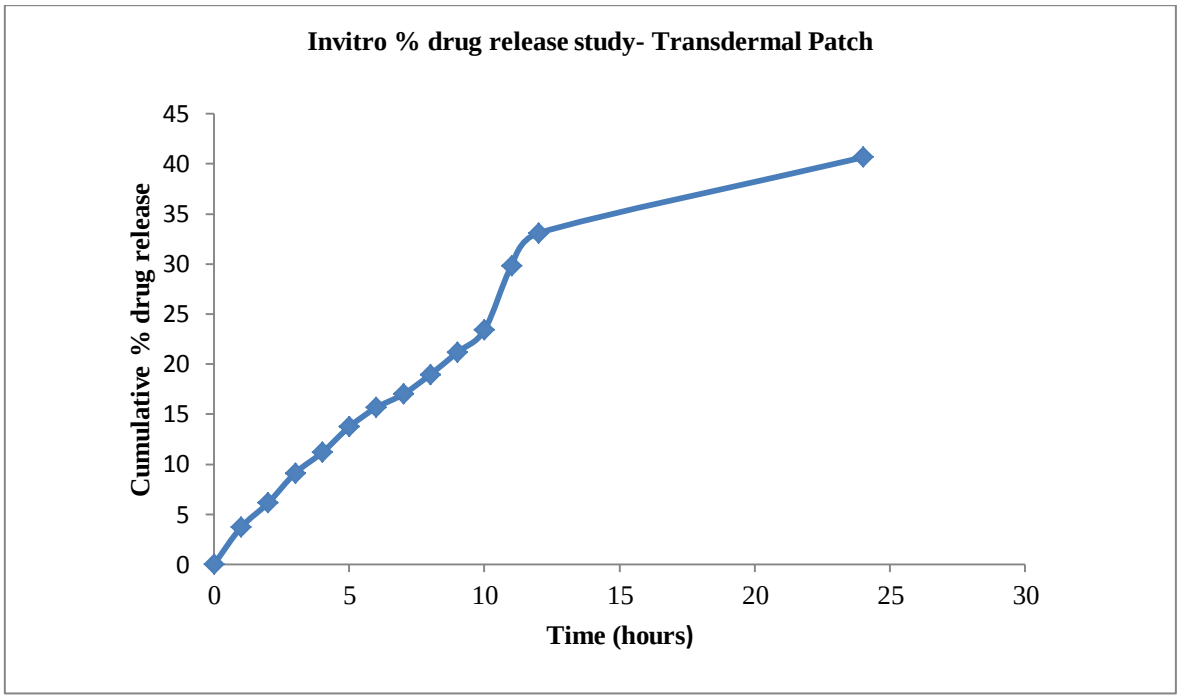

Figure 7: In-vitro release study of Transdermal patch

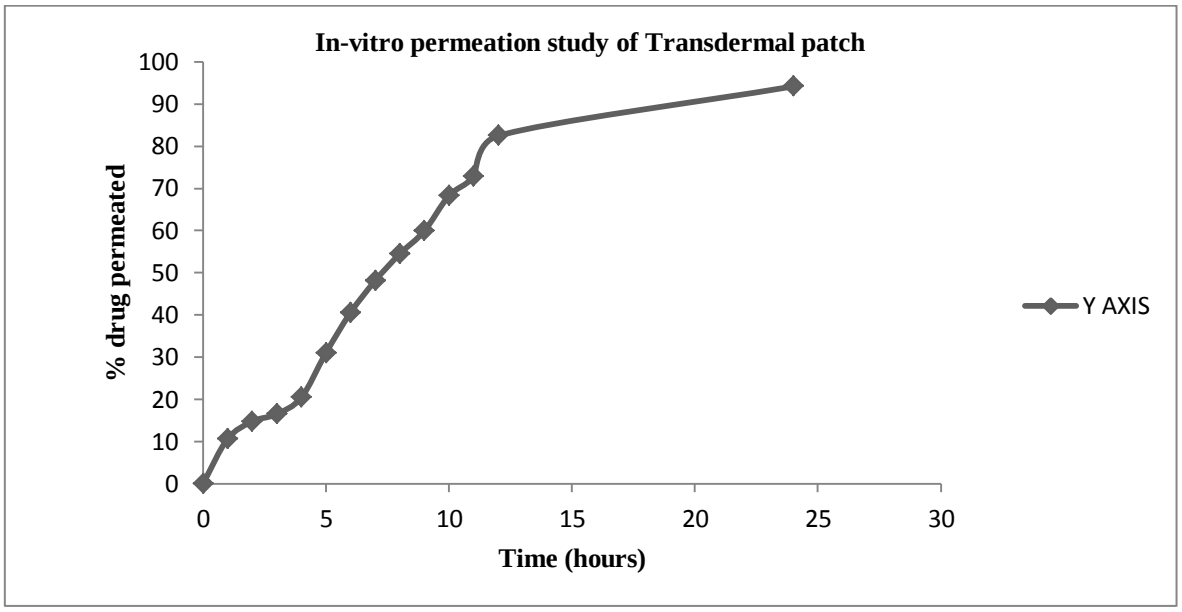

Figure 8: In-vitro permeation of Transdermal patch

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