RESEARCH ARTICLE

Evaluation Studies of Atenolol NLC-Loaded Transdermal Patches

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ABSTRACT
Transdermal patches were analyzed for weight variation to ensure uniform distribution of the drug. The patches were measured for thickness in order to determine their physical dimensions, which plays a crucial role in the consistency of drug release. We evaluated the patch's flexibility and durability by folding them repeatedly, simulating real-world conditions. Analyzing the percentage moisture content of the patches gave insight into their ability to absorb moisture during storage, which was crucial for maintaining their stability. Analysis of drug content ensures consistent dosage delivery by ensuring uniformity and accuracy. Testing the patches' ability to penetrate the skin barrier was conducted using skin membrane models. An evaluation of the patch safety profile was conducted and minimal irritation potential was ensured by testing the patches on the skin. A study of the atenolol release profile from transdermal patches over time was conducted *in vitro*, providing insight into the patches' potential for sustained release.
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INTRODUCTION

The newest generation of drug carriers is nano structured lipid carriers, which are similar to solid lipid nanoparticles (SLNs). An NLC carrier spatially arranges liquid and solid lipids[1-3].

Liquid and solid lipids are arranged spatially alternatively, which increases drug loading efficiency and prevents solid lipid from crystallizing. NLC consists of amorphous particles formed from lipid chains and blocks. The method prevents the ejection of drugs during storage. In addition to solutions, suspensions and ointments, NLC can also transport liquids. In the field of colloidal drug delivery, micellar colloidal drug carriers, or NLCs, are dispersions made from nanoparticles that range in size from 10 nanometers to 500 nanometers. In order to produce a good matrix for NLC, it is necessary to mix solid lipids with liquid lipids. It is expected that the melting point of NLC will be lowered as compared to the melting point of SLN due to the presence of oil[4].

MATERIALS AND METHODS

Materials

Atenolol purchased from aurobindo pvt Ltd. Hyderabad. Compritol 888AT0, Acconon C-44 EP/NF, Dynasan 114, Softigen, Witepsol H32, Stearic acid, Poloxamer, Cholesterol, Tween-20, Tween-80, Span-20, Span-80, Poly sorbate 20,Poly sorbate 80, Manittol, PVA, Polyvinylpyrolidine, DMSO, PEG, KH2PO4, NaOH, Methanol (HPLC Grade),Ammonium Acetate, Formic Acid, Tri fluro acetate, Perchloroacetic acid, ACN.

Methods

Following are the parameters that were evaluated on the transdermal patches prepared from NLC stacks. Three duplicates of all parameters were performed (n=3)

Physical Characteristics

Weight Variation

A total of ten Transdermal patches are selected at random from the batch. It can be precisely weighed individually by using a digital balance. From these weights, the mean weight was identified. A single patch weight was not more than ± 5% of the mean patch weight.

Thickness

Using Vernier Calipers, three different sites were measured for thickness of transdermal patches and the average value was calculated.

Folding Endurance

To determine the patch's elasticity efficiency and flexibility by means of folding endurance. The sample patch was folded until it broke in the same place. As a measure of folding endurance, we calculated the number of folds the film can withstand without breaking.

Percentage Moisture Content

In a desicator that was already saturated with calcium chloride, the formulated patches were individually weighed. Allow it at room temperature for 24hrs. A final weight was determined after 24 hours by weighing the patch again. The following formula was used to calculate the percentage moisture content.

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

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Table 1: Release Kinetics models, Equation, Plots and Limits

Kinetic Model	Equation	Specification	Plots	Acceptance criteria
Zero-Order	$C = k_0t$, Where, K_0- zero-order rate constant which can be expressing in units of conc/time and t – time	It can describes the systems in which the drug release rate has independent of its concentration	Cumulative % of drug release versus time	Good Linearity and regression 'r' value (0.996-1.0)
First-Order	$LogC = LogC_o - kt/2.303$, Where, C_0 = initial concentration of drug K is first order constant &t is the time	Describes the release from system where release rate is concentration dependent	Log cumulative of % drug remaining vs. time	Good Linearity and regression 'r' value (0.996-1.0)
Higuchi	$Q = Kt^{1/2}$, Where, K is the constant which was reflecting the variable design of the system.	It can described that, the drugs releasing from insoluble matrix as a square root of time dependent process based on fickian diffusion	Cumulative % drug release Vs square root of time	Good Linearity and regression 'r' value (0.996-1.0)
Hixson-Crowell Cube Root Law	$Q_0^{1/3} – Q_t^{1/3} = K_{HC}\, t$, Where, Qt is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is rate constant for Hixson-Crowell rate equation as the cube root of the percentage of drug remaining in the matrix vs. time.	It can describes, the release of drugs from systems where there is a change in surface area and diameter of particles or tablets	Cube root of drug % remaining in matrix Vs Time	Good Linearity and regression 'r' value 0.996-1.0
Korsmeyer Peppas	$Mt/M\infty = Kt^n$ Where,$Mt/M\infty$ is fraction of drug released at time t;k is the rate constant; n is the release exponent.The n value is used to characterize different release mechanisms as shown in Table.	It can described that, the drugs releasing from a polymeric system, first 60% drug release data was fitted in Korsmeyer–Peppas model	log cumulative % drug release vs. log time	Good Linearity and regression 'r' value 0.996-1.0

Drug Content

Taking one NLC patch loaded with a single formulation and putting it in a glass beaker of 100ml buffer solution (Phosphate buffer of pH 7.4). Then it was homogenized for 24hrs at 1000 rpm. A UV spectrophotometer at 224 nm was used to estimate the drug concentration in the filtrate for Atenolol.

$$Drug\ content\ = \frac{Concentration\ of\ Test\ sample}{Concentration\ of\ Standard\ sample} \times 100$$

Ex-vivo Drug Permeability Study

In this study*, franz-diffusion* cells were used to determine the skin permeation of NLC loaded transdermal patches. Patches attached to rats' skins act as donor compartments, with a diffusion area of 2.5cm^2 and each served as receiver compartments. The receiver compartments contain 10 ml of Buffer Solution (Phosphate Buffer- 7.1 pH) and must keep at 37±5°C. An albino Wistar rat's abdominal skin was freshly excised, mounted with the S.corneum facing the donor compartment and then removed.

It was then applied over the skin with the formulatRat stratum corneum should be hydrated overnight in Franz cells for this study. Magnetic beads were used to stir the solution in the receptor compartment continuously at 100 rpm, while all the instrument setup was fixed in the magnetic stirrer. The Magnetic stirrer have temperature should be maintained at 37±5ºC. At pre-determined intervals like 2, 4, 6, 8, 16, 24, 48 hrs, 0.5 ml of sample was removed from the receiver portion via the sampling port. This sample was replaced with an equal amount of PBS (7.4 pH) in order to maintain the sink condition. Spectrophotometers at 224 nm were used to determine atenolol concentrations in collected samples.

Table 2: Peppa's Diffusion Exponent and Drug release mechanism

Drug diffusion mechanism	Diffusion exponent (n)
Fickian diffusion	0.45
Anomalous non-Fickian diffusion	$0.45 < n < 0.89$
Case-II transport	0.89
Super case-II transport	$n > 0.89$

Skin Irritation Test

An optimal NLC stacked transdermal patch of 2.5cm^2 was applied once to each healthy rat after shaving the hair in the administration area on the abdominal part of the animal. Keep an eye on the animal for six hours. A visible change, such as erythema (redness), was observed after 6 hours after the patch was removed from the abdomen. According to Draize scale, mean score ranged from 0 to 4 for both erythema and edema. A score 0 means absence of erythema and edema, one indicates slight erythema and edema, two indicates medium erythema and edema and three indicates medium to high level erythema and edema and four indicates high degree of erythema (redness at administered sight,) as well as injury at depth and edema that extends

Table 3: Assessment of Atenolol NLC (AN6) transdermal patches

Evaluation Parameters	NT1	NT2	NT3	NT4	NT5	NT6	NT7	NT8
Uniformity of weight (mg /cm^2)*	0.064 ± 0.004	0.072 ± 0.002	0.054 ± 0.02	0.052 ± 0.012	0.074 ± 0.002	0.082 ± 0.004	0.088 ± 0.004	0.092 ± 0.004
Thickness (mm)*	0.44 ± 0.04	0.52 ± 0.12	0.66 ± 0.04	0.72 ± 0.12	0.66 ± 0.06	0.58 ± 0.22	0.56 ± 0.06	0.48 ± 0.12
Folding endurance*	120-135	130-140	125-145	115-120	110-115	90-100	85-105	70-95
Moisture content %*	0.08 ± 0.02	0.14 ± 0.04	0.12 ± 0.02	0.22 ± 0.02	0.28 ± 0.02	0.24 ± 0.04	0.28 ± 0.06	0.32 ± 0.04
Drug content %*	76.42 ± 2.12	78.26 ± 2.14	90.80 ± 3.54	82.20 ± 3.42	78.24 ± 3.12	76.60 ± 2.14	75.06 ± 2.24	70.26 ± 2.44
Skin irritation studies	Absence of erythema and edema	Absence of erythema and edema	Absence of erythema and edema	Absence of erythema and edema	Absence of erythema and edema	Absence of erythema and edema	Absence of erythema and edema	Absence of erythema and edema

* Values are expressed as mean ± SD, n=3

Table 4: Comparative e*x-vivo* drug release analysis between marketed dosage forms Atenolol Betacard 25mg; Atenolol drug loaded Transdermal Patch (10 mg); Atenolol NLC (AN6) (10 mg); Atenolol NLC loaded Transdermal Patch (NT3) (10 mg)

Time (min/hr)	Atenolol Betacard 25mg Tablet (%)	Atenolol drug loaded Transdermal Patch (%)	Atenolol NLC – AN6 (%)	Atenolol NLC loaded Transdermal Patch –NT3 (%)
0 min	0.0 ± 0.0	-	-	-
5 min	25.64 ± 2.60	-	-	-
15 min	76.54 ± 3.50	-	-	-
30 min	86.24 ± 3.12	-	-	-
45 min	92.46 ± 3.46	-	-	-
1 hr	98.66 ± 2.54	1.26 ± 0.12	10.64 ± 2.02	4.94 ± 1.76
2 hr	-	4.86 ± 1.24	24.68 ± 2.42	8.58 ± 2.46
4 hr	-	6.78 ± 2.52	36.64 ± 2.46	16.70 ± 2.46
8 hr	-	10.64 ± 2.62	64.72 ± 3.12	38.46 ± 2.68
16 hr	-	18.66 ± 3.12	83.42 ± 3.64	54.89 ± 2.66
24 hr	-	32.80 ± 3.24	98.54 ± 3.68	69.90 ± 2.88
32 hr	-	44.52 ± 3.10	-	76.88 ± 2.78
40 hr	-	56.58 ± 2.46	-	83.26 ± 2.78
48 hr	-	70.68 ± 3.12	-	95.48 ± 3.22

All values are expressed as mean ± SD, n=3

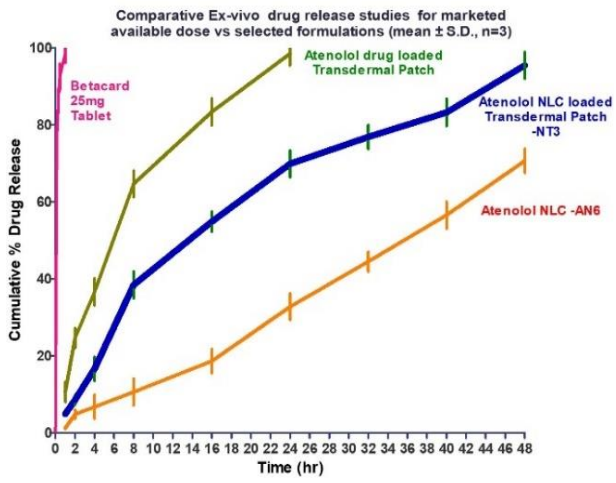

Figure 1: *Ex-vivo* drug release studies comparing Atenolol Betacard 25mg, Atenolol NLC (AN6), Atenolol Transdermal Patch and Atenolol NLC loaded hydrogel enriched transdermal patch (NT3)

beyond the site of administration. Using these studies, we can determine if the patch and drug can be administered to skin without producing any side effects.

In-vitro Drug Release Kinetics

Different kinetic equations had been fitted to the drug release data from NLC loaded transdermal patches in order to determine how the drug is released and also Zero-order, first -order, Higuchi Square Root, Hixson crowell & korsermeyer peppas types have included. Goodness of fit was determined by linearity as the criteria for choosing the most selective model. Table 1 shows the kinetic models, equation and plots[5-9].

RESULTS

Acceptance criteria: Weight ratio ± 5% of patch average; Patch thickness = uniform; Maximum Foldable Stamina shows versatility and flexibility; less than 1% water content; % 85-115% of drug content; *Ex-vivo* skin permeation studies should be >85%; release kinetics studies should be linear.

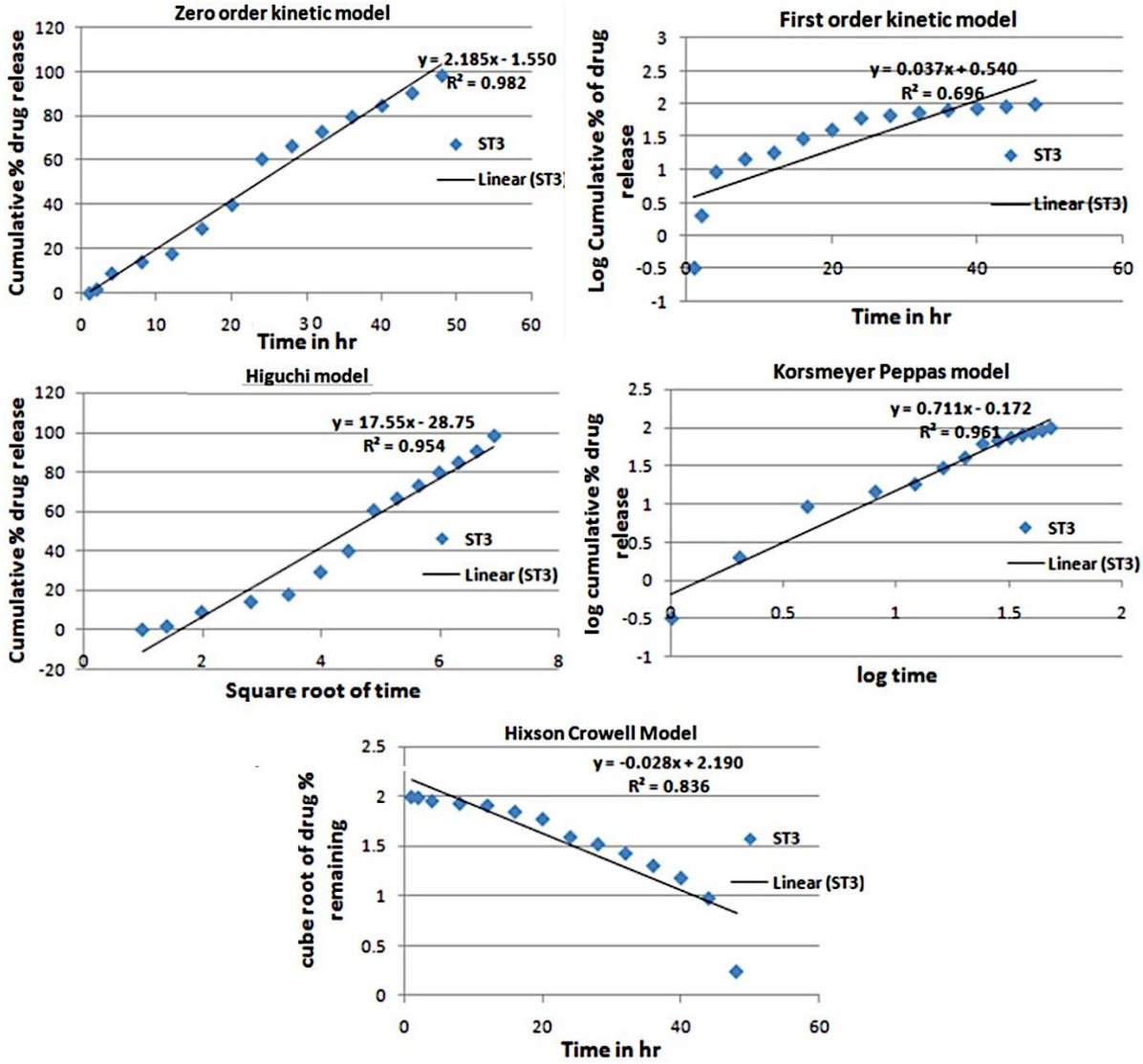

Figure 2: Release kinetics graphs of Atenolol NLC loaded Transdermal Patch (NT3)

DISCUSSION

The uniformity of weight across patches is crucial to ensuring that the drug is delivered efficiently and consistently.

An inconsistency in manufacturing can affect drug release and efficacy if there is a significant variation.

When drugs are released in a uniform thickness, they have consistent adhesive properties and a consistent release rate. It is possible that deviations may interfere with the adherence of the patch and the permeation of the drug through the skin. It is important to determine if patches have the strength and durability to withstand repeated folding in order to assess the degree of mechanical strength and durability they possess during handling and application. Having too much moisture can affect the stability and release of drugs from patches. Patch integrity and performance are ensured by maintaining optimal moisture levels. The amount of atenolol in each patch must be determined in order to ensure accurate dosing and therapeutic effectiveness of each patch. There may be formulation or manufacturing issues that may be causing deviations from the target drug content. An evaluation of the patch's ability to deliver atenolol transdermally through skin samples would provide insight into the patch's ability to penetrate the skin while delivering the drug. It takes into account factors such as penetration of the drug, the rate at which it is released and the potential barrier to the absorption of the drug. It is important to assess skin irritation before applying the patches in order to ensure their safety and tolerability. There may be possible risks associated with the application of patches if there are any signs of irritation or adverse reactions. It is possible to gain a significant amount of insight into the mechanisms and kinetics of drug delivery by studying the release profile of atenolol from patches over a period of time. A formulation optimization tool can be used to predict drug release behavior *in vivo* and optimize formulation parameters. This study plays a crucial role in the assessment of the quality, performance and safety of atenolol NLC-loaded transdermal patches by providing information about the quality, performance and safety of these patches.

CONCLUSION

In conclusion, the evaluation studies conducted on transdermal patches consisting of atenolol nanostructured lipid carrier (NLC) loaded with atenolol disclosed valuable information regarding the characteristics and performance of the formulation. Overall, the studies have demonstrated efficacy and safety for transdermal patch delivery of atenolol NLC. Several further studies, including *in vivo* pharmacokinetic and pharmacodynamic evaluations, must be conducted to validate and confirm the therapeutic benefits of these patches.

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