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FORMULATION AND EVALUATION OF IBUPROFEN CUBOSOMAL TRANSDERMAL PATCH

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ABSTRACT

Cubosome loaded transdermal patch formulation may enhance the release rate of drug for quick onset of action. With this view the present study was aimed to formulate and evaluate the ibuprofen cubosome loaded transdermal patches. In our previous effort, nine ibuprofen loaded cubosome formulations were prepared and evaluated successfully. Based on the results of evaluation, three cubosome formulations namely C3, C6 and C9 were selected for the preparation of transdermal patches namely TP1, TP2 and TP3 respectively. The transdermal patches were formulated by solvent casting method. The prepared patches were evaluated to ensure their quality. The physical appearance evaluation revealed that all the patches were white in colour, had the appearance of a smooth, translucent flat surface with good flexibility. Results of average weight, thickness uniformity, drug content, folding endurance and percentage moisture absorption assessment ascertained the quality of prepared transdermal patches. The *in vitro* drug release evaluation and drug release kinetics study indicated that the formulation TP3 was best fit towards zero order and Higuchi models followed by TP1 formulation and TP2 formulation showed significant results in terms of both zero order and Higuchi models evaluation. The formulation TP3 was selected for the stability study based on the scores of release kinetics study which indicated that there was no significant changes in the physical characteristics and drug content of the tested transdermal patch TP3. Summarily, all the cubosome loaded transdermal patches (TP1, TP2 and TP3) prepared in this study revealed a significant results in all the evaluation procedures employed. Further research in these cubosome loaded transdermal patches in the direction of *in vivo* evaluations may give more crucial data valuable for successful development of a novel sustained release drug delivery system in the future.

KEYWORDS: Ibuprofen, Cubosome, Transdermal patch, Formulation, Characterization.

INTRODUCTION

A transdermal patch is a medicated patch that can deliver drugs directly into the bloodstream through the layers of the skin at a prescribed rate. In fact, patches are the most convenient method of administration. They are non-invasive and treatment can last for several days and can be stopped at any time. They come in different sizes and contain multiple ingredients. When applied to the skin, the patch can deliver active ingredients into the systemic circulation via diffusion processes. Transdermal patches may contain high doses of active substances that remain on the skin for an extended period of time. One of the first transdermal patches developed in 1985 was the nitroglycerin patch. Currently, several drugs are available as transdermal patches, including estradiol, clonidine, fentanyl, nicotine, scopolamine (hyoscine) and estradiol with norethisterone acetate. The site of application may vary depending on the therapeutic category of the drug. For example, nitroglycerin can be applied around the chest and estradiol around the buttocks or abdomen. The duration of drug release also varies depending on the usage, from the shortest (up to 9h) to the longest (up to 9 days).[1]

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.[2] Vesicular drug delivery is one of the approaches which encapsulate the drug to overcome the barrier function of stratum corneum. There are huge number of vesicular drug delivery systems that allow drug targeting and the sustained or controlled release of conventional medicines. Cubosome is one among them. Cubosomes are discrete, sub-micron, nanoparticles of the bi-continuous cubic liquid crystalline phase with solid-like rheology that provides unique properties of practical interest.[3-7] It is a novel biocompatible drug delivery system. It becomes an attractive vehicle for *in-vivo* drug delivery due to their low cost, versatility and potential

for controlled release and functionalization. Preparation of cubosomes may be helpful in future by targeting the drug to a particular site and achieve therapeutic efficacy and also improve patient compliance.[7,8]

With this view, in our previous study[7] nine ibuprofen loaded cubosome formulations were prepared and subjected to evaluation. Three formulations namely C3, C6 and C9 were showed significant results in the all the parameters evaluated. In the present study, transdermal patches were prepared by using these three cubosome formulations and evaluated with the view of developing a novel sustained release drug delivery system.

MATERIALS AND METHODS

Preparation of ibuprofen cubosomes

In our previous study[7] totally nine ibuprofen cubosome formulations (C1-C9) were prepared by top-down technique and evaluated for several parameters such as morphological characters, drug content, entrapment efficiency, particle size, zeta potential and polydispersity index. Ultimately, *in vitro* drug release and kinetics of drug release were evaluated. Three formulations namely C3, C6 and C9 were showed significant results in the all the parameters evaluated which were selected for the preparation of transdermal patches viz., TP1, TP2 and TP3.

Preparation of cubosome loaded transdermal patch

Preparation and evaluation of cubosome loaded transdermal patch was done in reference with the procedure in previous literature.[9] Transdermal patch was developed using the solvent casting method. Initially, Hydroxypropyl methylcellulose (150mg) and Eudragit RL-100 (150mg) was dissolved in ethanol and tri ethyl citrate solvent system (1:1) and stirred on a magnetic stirrer until a semi-solid consistency was formed. Then, the selected cubosomal dispersion (12ml) was incorporated into the solution and stirred continuously. Polyethylene glycol-400 (plasticizer) was gradually added in drop wise manner. The resulting mixture was poured into a petri dish and an inverted funnel was placed on the top of it and allowed to dry for 24h to yield a patch. The patches formed were extracted using a sharp knife inserted along the edge of the patch and stored for further examination.

Evaluation of transdermal patches prepared

Physical appearance

The prepared patches were evaluated visually for colour, clarity, flexibility and smoothness.

Thickness uniformity

Digital vernier caliper was used to determine thickness of designed patches. The formulated patches were placed in between the two external jaws which were fixed with the help of locking screw so that these jaws cannot move ensuring a proper hold and the readings were displayed by pressing the inch button. Three consecutive readings were taken using five different sites and the average were measured to find out the thickness uniformity.

Folding endurance

The folding endurance of the prepared patches was evaluated by repeatedly folding a 1cm^2 patch strip in the same location until it reached a point of snapping. The folding endurance value is determined by the number of times the patch can be folded in the same spot without breaking or cracking.

Percentage moisture absorption

An accurately weighed patch was placed in the desiccator for 24h. Subsequently, the patches were reweighed and the percentage of moisture absorption was determined by

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

Drug content

Small segment was cut from the circular patch and immersed in methanol (100 ml). The mixture was stirred with magnetic stirrer for 24h and then subjected to sonication for approximately 15min. The resulting solution was filtered and analysed using UV Spectrophotometer (214nm).

Uniformity of weight

An area 2x1 cm square was taken from the prepared patch and weighed by electronic balance. It is mainly used to find out the weight uniformity and thereby ensuring batch variation. The weight taken individually should not alter significantly from that of average weight.

In-vitro diffusion study

Franz diffusion cell was used for the study. The Franz diffusion cell comprises two compartments - the donor and receptor compartments - with the egg membrane positioned between them. A patch is applied to one side of the egg membrane, facing the donor compartment. The receptor compartment is filled with phosphate buffer (pH 6.8) and stirred continuously at 900rpm using a magnetic stirrer to ensure the uniformity. Small samples (aliquots) are collected over a 24h period and subjected to UV analysis (214nm) to assess the degree of permeation through the egg membrane. The results were used to plot a graph with time on the X-axis and % cumulative drug release on the Y-axis.

Kinetic study

Zero order, First order, Hixon-Crowell's, Higuchi and Korsmeyer-Peppas kinetic models were used to fit the release data of the selected formulations.

Stability study

Stability study of the cubosome loaded transdermal patches was done in reference with the procedure in previous literature.[10] The short term stability studies of the prepared transdermal patches were carried out at

different temperature and humidity conditions according to ICH guidelines: 25 ± 2°C (60%RH) and 45 ± 2°C (75%RH) for a period of 60 days. The patches were wrapped in aluminum foil and stored in desiccator for stability study. The patches were characterized for drug content and other parameters at regular intervals.

RESULTS AND DISCUSSION

In the present study, three cubosome loaded transdermal patch formulation namely TP1, TP2 and TP3 were prepared. The selected cubosome formulation C3 was loaded in TP1 patch formulation while C6 cubosome was loaded in TP2 patch formulation and the cubosome C9 was loaded in TP3 formulation. The prepared patches were evaluated to ensure their quality. Initially, the physical appearance viz., colour, clarity, flexibility, appearance and smoothness of the prepared patches was evaluated by visual checking. All the prepared transdermal patches were white in colour, had the appearance of a smooth, translucent flat surface with good flexibility. Results of this evaluation is presented in Table 1. Results of the assessment of average weight, thickness uniformity, drug content, folding endurance and percentage moisture absorption of prepared transdermal patches is presented in Table 2 which revealed the quality of prepared transdermal patches.

Table 1: Evaluation of physical characters of cubosome loaded transdermal patches.

Cubosome loaded transdermal patch	Observation			
	Colour	Appearance & Smoothness	Clarity	Flexibility
TP1	White	Smooth & Flat surface	Translucent	Flexible
TP2	White	Smooth & Flat surface	Translucent	Flexible
TP3	White	Smooth & Flat surface	Translucent	Flexible

Table 2: Physicochemical properties of cubosome loaded transdermal patches.

Formulation	*Average Weight (mg)	*Thickness Uniformity (mm)	*Drug Content (%)	*Folding Endurance	*% Moisture absorption
TP1	340.14 ± 0.15	0.320 ± 0.02	99.51	58 ± 0.96	5.32
TP2	340.23 ± 0.26	0.322 ± 0.01	99.40	57 ± 1.25	5.64
TP3	340.74 ±0.13	0.335 ± 0.03	99.75	59 ± 1.05	5.72

*Average of three determinations

The *in vitro* drug release evaluation these patch formulation was done by Franz diffusion cell method. The results obtained in this evaluation is presented in Table 3 & Figure 1. A significant percentage drug release (94.33%) was found in the TP3 formulation. Next to that the formulation TP2 showed 91.55% and TP1 formulation showed 88.10% drug release.

Table 3: Percentage drug release found in the *in vitro* evaluation of prepared transdermal patches.

Time (h)	TP1	TP2	TP3
1	6.70	5.10	7.15
2	11.60	13.23	13.05
3	18.05	19.71	21.10
4	24.36	26.44	29.45
5	31.55	33.45	36.15
6	37.80	39.03	41.32
7	41.34	44.52	49.66
8	48.17	51.28	57.12
9	57.08	57.80	65.33
10	65.11	63.20	71.21
11	72.20	75.11	79.36
12	79.63	80.34	86.08
24	88.10	91.55	94.33

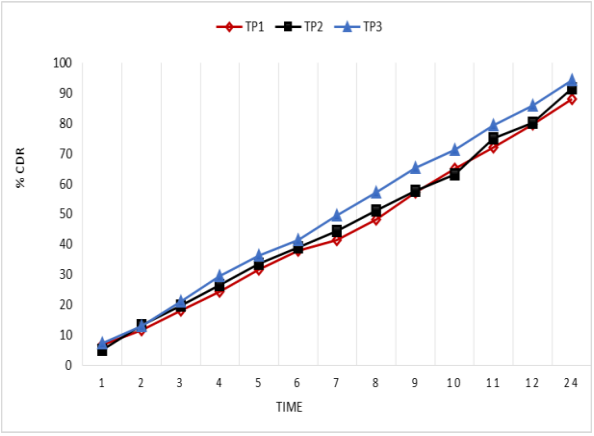


Figure 1: Percentage release of ibuprofen from the transdermal patch formulations.

In the evaluation of drug release kinetics of transdermal patch formulations, the zero order, first order, Hixon-Crowell's, Higuchi and Korsmeyer-Peppas release model were focused. Various drug release parameters analysed for the transdermal patch formulation TP1, TP2 and TP3 is tabulated in Table 4, 5 and 6 and Figure 2, 3 and 4 respectively. The statistical kinetic values (R^2 and the slope) obtained were presented in Table 7.

The data obtained from the above models indicated that the formulation TP3 was best fit towards zero order and Higuchi models with R^2 value of 0.999. Next to that, the formulation TP1 and TP2 showed a significant release

data as per zero order and Higuchi models. The TP1 formulation showed 0.995 and the TP2 showed 0.994 as R^2 values in both zero order and Higuchi models. (Table 7). Obviously, when a formulation obey the zero order release, it indicated a constant release of drug from that formulation and obeying Higuchi model indicated the drug is released from the formulation by diffusion process. According to this benchmark, the cubosome (C9) loaded transdermal patch named as TP3, then the cubosome (C3) loaded transdermal patch named as TP1 and then the cubosome (C6) loaded transdermal patch namely TP2 showed a better results in terms of a constant drug release by diffusion process with R^2 value of in the order of 0.999 for TP3, 0.995 for TP1 and 0.994 for TP2. In the formulation of transdermal patch, equal quantity of HPMC and Eudragit RL 100 (150mg) were used. The polymer matrix of these additives facilitate the control release of drug from the transdermal patch formulation which was clearly revealed in the release kinetics studies.

Table 4: *In vitro* drug release parameters for transdermal patch TP1.

Time	% CDR	Log % CDR remaining	Cube root of % drug remaining	Log % CDR	Square root time	Log of time
1	6.70	1.9698	4.5355	0.8260	1	0
2	11.60	1.9464	4.4546	1.0644	1.4142	0.3010
3	18.05	1.9135	4.3435	1.2564	1.7320	0.4771
4	24.36	1.8787	4.2291	1.3866	2	0.6020
5	31.55	1.8353	4.0906	1.4989	2.2360	0.6989
6	37.80	1.7937	3.9621	1.5774	2.4494	0.7781
7	41.34	1.7683	3.8855	1.6163	2.6457	0.8450
8	48.17	1.7145	3.7284	1.6827	2.8284	0.9030
9	57.08	1.6326	3.5012	1.7564	3	0.9542
10	65.11	1.5427	3.2676	1.8136	3.1622	1
11	72.20	1.4440	3.0293	1.8585	3.3166	1.0413
12	79.63	1.3089	2.7310	1.9010	3.4641	1.0791
24	88.10	1.0755	2.2830	1.9449	4.8989	1.3802

Table 5: *In vitro* drug release parameters for transdermal patch TP2.

Time	% CDR	Log % CDR remaining	Cube root of % drug remaining	Log % CDR	Square root time	Log of time
1	5.10	1.9772	4.5613	0.7075	1	0
2	13.23	1.9383	4.4271	1.1215	1.4142	0.3010
3	19.71	1.9046	4.3140	1.2946	1.7320	0.4771
4	26.44	1.8666	4.1899	1.4222	2	0.6020
5	33.45	1.8231	4.0524	1.5243	2.2360	0.6989
6	39.03	1.7851	3.9358	1.5913	2.4494	0.7781
7	44.52	1.7441	3.8139	1.6485	2.6457	0.8450
8	51.28	1.6877	3.6523	1.7099	2.8284	0.9030
9	57.80	1.6253	3.4815	1.7619	3	0.9542
10	63.20	1.5658	3.3262	1.8007	3.1622	1
11	75.11	1.3960	2.9197	1.8756	3.3166	1.0413
12	80.34	1.2935	2.6989	1.9049	3.4641	1.0791
24	91.55	0.9268	2.0368	1.9616	4.8989	1.3802

Table 6: *In vitro* drug release parameters for transdermal patch TP3.

Time	% CDR	Log % CDR remaining	Cube root of % drug remaining	Log % CDR	Square root time	Log of time
1	7.15	1.9677	4.5282	0.8543	1	0
2	13.05	1.9392	4.4301	1.1156	1.4142	0.3010
3	21.10	1.8970	4.2890	1.3242	1.7320	0.4771
4	29.45	1.8484	4.1320	1.4661	2	0.6020
5	36.15	1.8051	3.9968	1.5581	2.2360	0.6989
6	41.32	1.7684	3.8859	1.6161	2.4494	0.7781
7	49.66	1.7019	3.6923	1.6960	2.6457	0.8450
8	57.12	1.6322	3.5001	1.7567	2.8284	0.9030
9	65.33	1.5399	3.2607	1.8151	3	0.9542
10	71.21	1.4592	3.0648	1.8525	3.1622	1

11	79.36	1.3147	2.7430	1.8996	3.3166	1.0413
12	86.08	1.1436	2.4055	1.9349	3.4641	1.0791
24	94.33	0.7535	1.7831	1.9746	4.8989	1.3802

Table 7: Statistical kinetic values of transdermal patch formulations.

Release kinetic models	Formulations					
	TP1		TP2		TP3	
	R^2	Slope	R^2	Slope	R^2	Slope
Zero order	**0.995**	6.751	**0.994**	6.852	**0.999**	7.256
First order	0.892	– 0.065	0.852	– 0.071	0.865	– 0.084
Hixon- Crowell	0.944	– 0.174	0.926	– 0.183	0.943	– 0.207
Higuchi	**0.995**	6.751	**0.994**	6.852	**0.999**	7.256
Korsmeyer-Peppas	0.917	0.083	0.868	0.085	0.892	0.082

Based on the results obtained in the study of release kinetics, the formulation TP3 was selected for the stability study, the results of stability study indicated that there was no significant changes in the physical characteristics and drug content of the tested transdermal patch (Table 8).

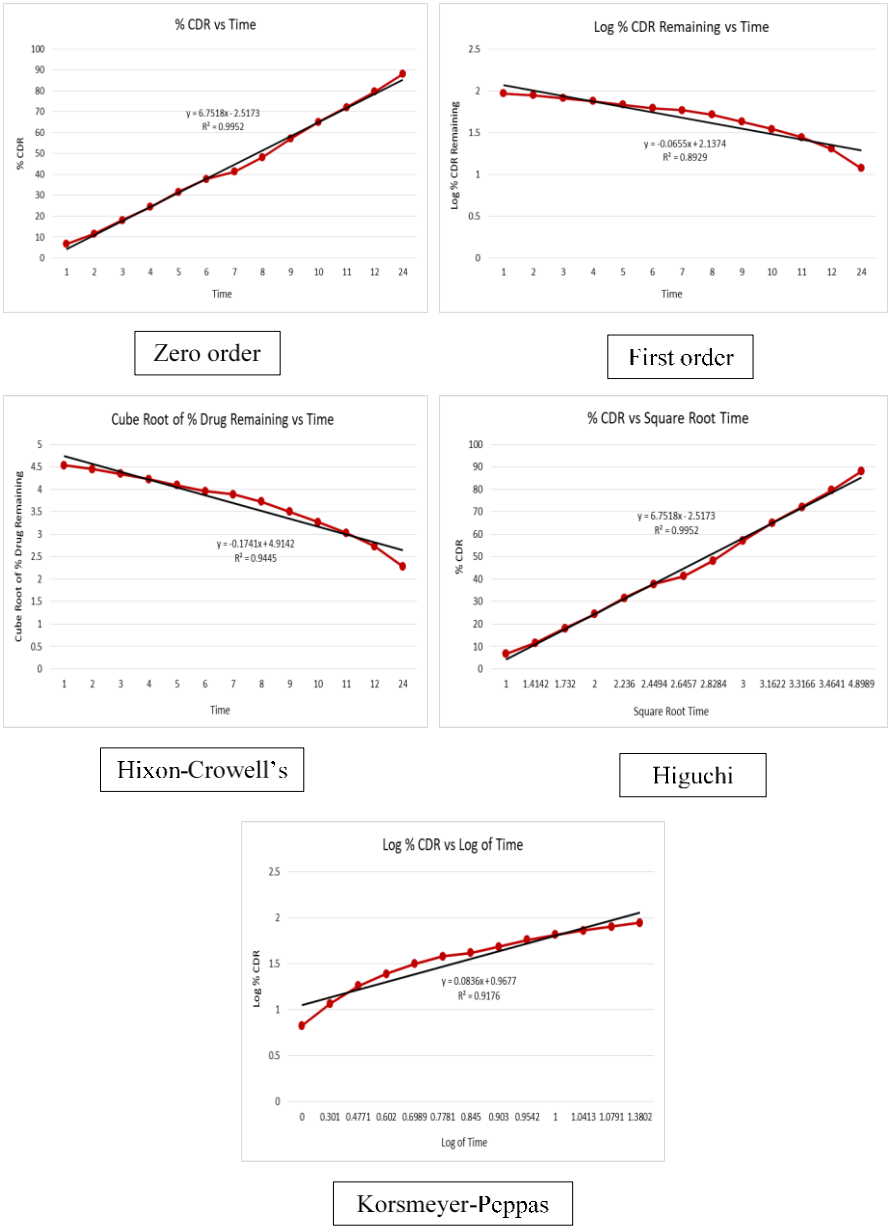
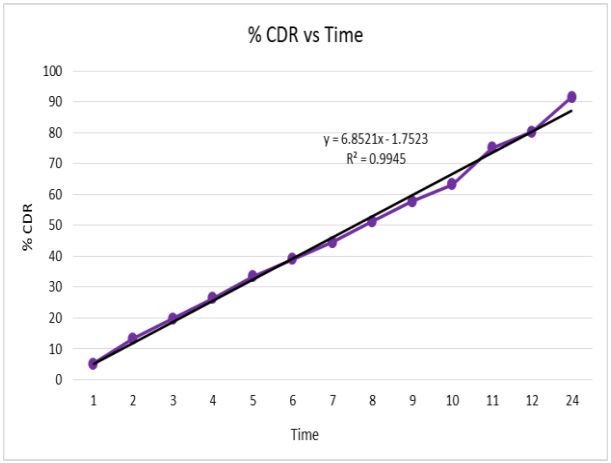
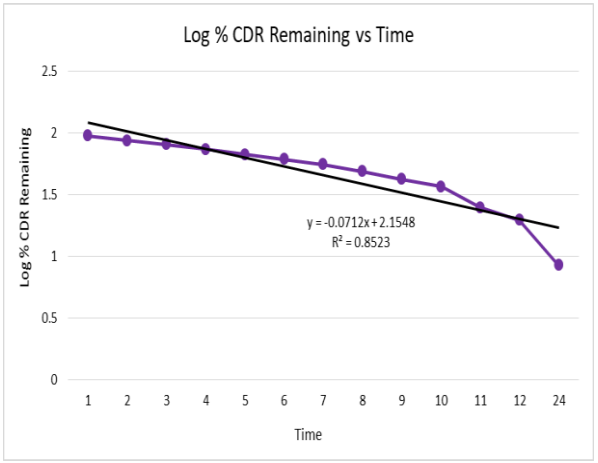


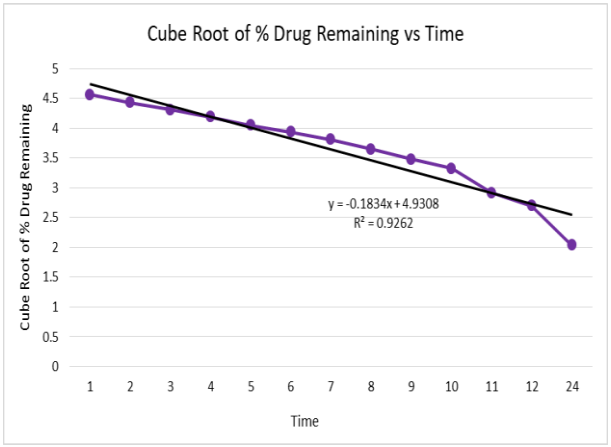
Figure 2: The release kinetics of TP1 formulation according to different models.



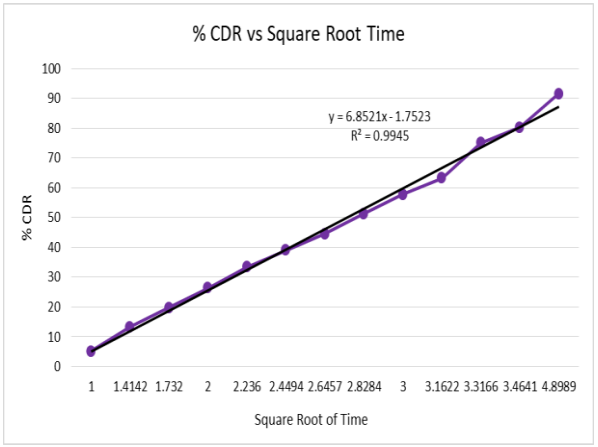
Zero order



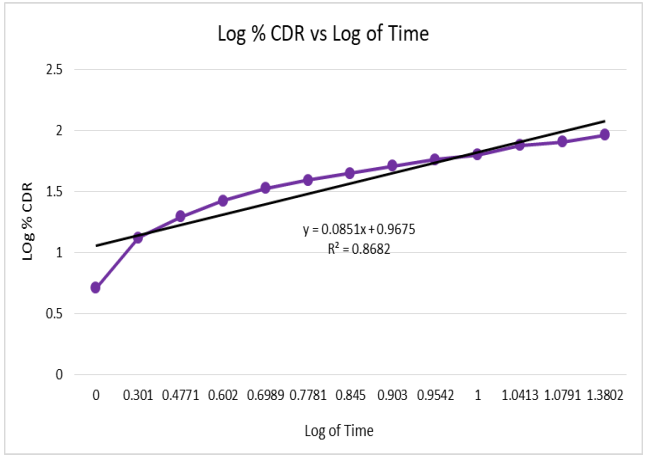
First order



Hixon-Crowell's

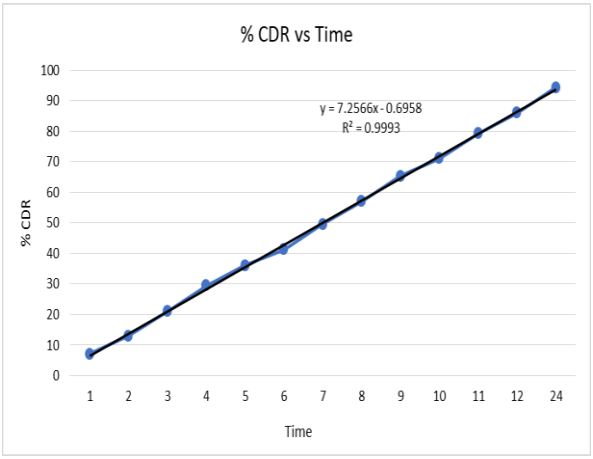


Higuchi

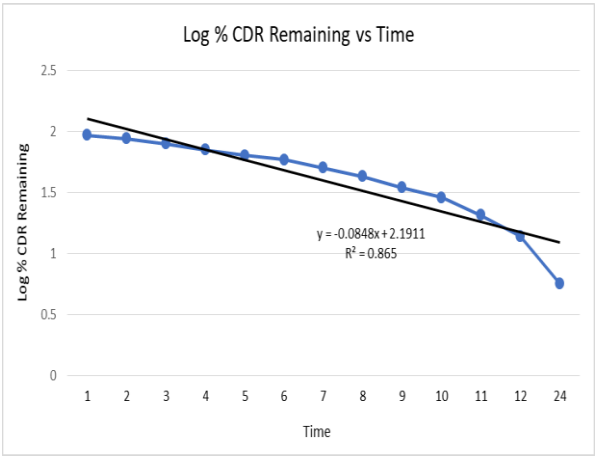


Korsmeyer-Peppas

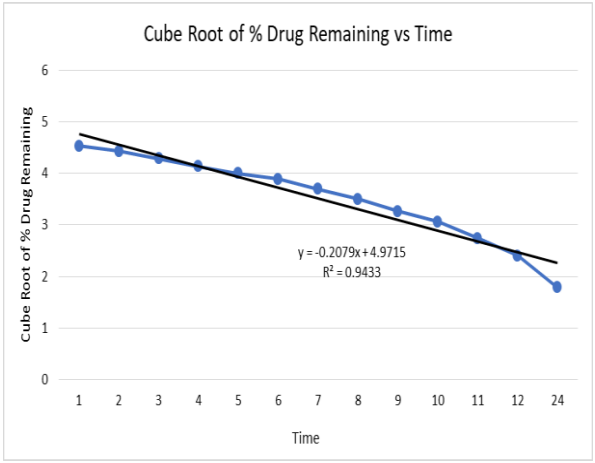
Figure 3: The release kinetics of TP2 formulation according to different models.



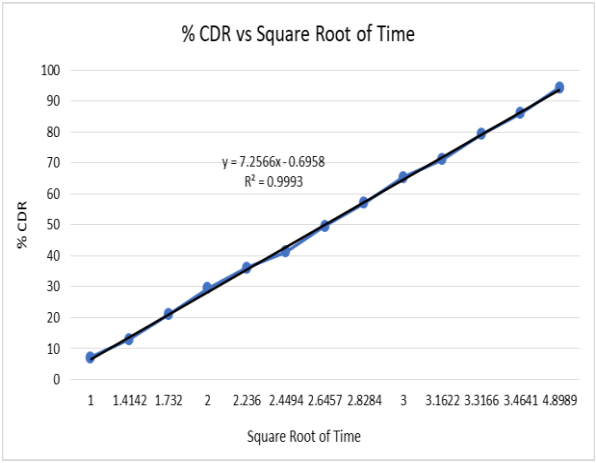
Zero order



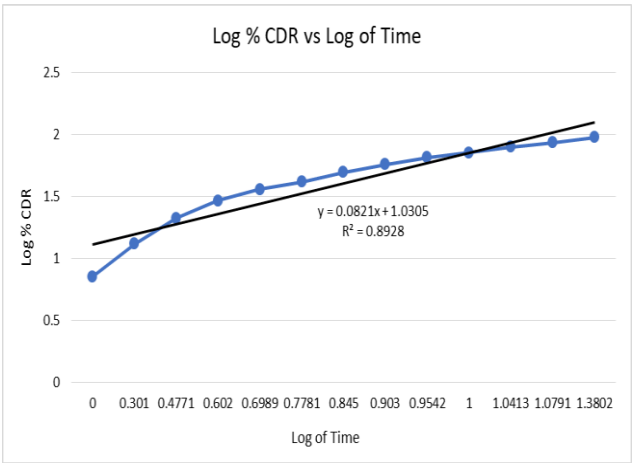
First order



Hixon-Crowell's



Higuchi



Korsmeyer-Peppas

Figure 4: The release kinetics of TP3 formulation according to different models.

Table 8: Stability study of transdermal patch TP3 at different temperature and humidity.

Parameter	Initial	25 ± 2ºC (60 ± 5% RH)			25 ± 2ºC (60 ± 5% RH)		
		15 days	30 days	60 days	15 days	30 days	60 days
Drug content (%)	99.50	99.20	98.70	98.30	99.80	99.10	99.40
Average weight (mg)	340.50	341.30	340.10	341.30	341.15	340.20	340.10
Thickness (mm)	0.334	0.331	0.320	0.330	0.329	0.330	0.333
In vitro drug release (%CDR)	94.33	94.30	94.30	94.10	94.33	94.20	94.30

CONCLUSION

In the present study, ibuprofen cubosome loaded transdermal patches were prepared and characterized. Three cubosome formulations namely C3, C6 and C9 were selected for the preparation of transdermal patches namely TP1, TP2 and TP3. The selected cubosome formulation C3 was loaded in TP1 patch formulation while C6 cubosome was loaded in TP2 patch formulation and the cubosome C9 was loaded in TP3 formulation. The transdermal patches were formulated by solvent casting method. The quality of prepared transdermal patches were ascertained by the physicochemical characterization. The *in vitro* drug release evaluation and drug release kinetics study indicated that the formulation TP3 was best fit towards zero order and Higuchi models followed by TP1 formulation and TP2 formulation showed significant results in terms of both zero order and Higuchi models evaluation. The formulation TP3 was selected for the stability study based on the scores of release kinetics study which indicated that there was no significant changes in the physical characteristics and drug content of the tested transdermal patch TP3. Summarily, all the cubosome loaded transdermal patches (TP1, TP2 and TP3) prepared in this study revealed a significant results in all the evaluation procedures employed. Further research in these cubosome loaded transdermal patches in the direction of *in vivo* evaluations may give more crucial data valuable for successful development of a novel sustained release drug delivery system in the future.

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