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DESIGN, FORMULATION AND EVALUATION OF IBUPROFEN LOADED CUBOSOMES

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ABSTRACT

There are huge number of vesicular drug delivery systems that allow drug targeting and the sustained release of conventional medicines. Cubosome is one among them. Non-steroidal anti-inflammatory drugs (NSAIDs) are most commonly used medications for the treatment of pain and inflammation, but numerous well-described side effects limit their use. With this view, the present study was aimed to formulate and evaluate the ibuprofen loaded cubosomes an attempt to provide a platform for further research. Initially, the pre-formulation study of drug substance ibuprofen was done. After the pre-formulation studies, the ibuprofen cubosomes was prepared by top-down technique and the prepared cubosomes were evaluated for their morphological characters, drug content, entrapment efficiency, particle size and zeta potential and the drug release by *in vitro* method. The pre-formulation study confirmed the physicochemical quality of drug substance ibuprofen used in this study. Results of drug-excipient compatibility study revealed the compatibility exist between the drug ibuprofen and the excipients used in the formulation of cubosome. After pre-formulation study, totally nine cubosome formulations (C1-C9) were prepared. Morphological characterization of cubosomes revealed no aggregation among the particles and the particle surface was smooth without surface deformations and visible pinholes. Based on the results of drug content, entrapment efficiency, particle size, zeta potential and polydispersity index (PDI) analysis of the cubosomes, the formulations namely C3, C6, C8, and C9 were selected for *in vitro* drug release evaluation. Analysis of release data indicated that the selected formulation, particularly, the formulations C3, C6 and C9 were best fit towards Zero order and Higuchi model. Further research such as loading these cubosome formulations in transdermal patches and their evaluations may leads to successful development of a novel sustained release drug delivery system in the future.

KEYWORDS: Ibuprofen, Preformulation studies, Cubosome, Synthesis, Characterization.

INTRODUCTION

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.[1] It is a novel biocompatible drug delivery system. Cubosomes receiving great significance in cosmeceutical and pharmaceutical fields due to their unique features. Interests on cubosomes being formulated as cosmetics products like skin care, hair care, antiperspirants has been increased. It becomes an attractive vehicle for *in-vivo* drug delivery due to their low cost, versatility and potential for controlled release and functionalization. Reports documented that the cubosome formulations have been revealed to be safe in brain targeted drug delivery. A previous literature reported that the preparation of cubosomal gels of fluconazole which resulted in enhanced pay load, entrapment efficiency and drug permeability compared with conventional gels.

Recently, scientists are interested in preparing cubosomes for the treatment of cancer therapy, topical applications and other drug delivery systems. Even though liposomes, niosomes, nanocochleates, micro sponges, micro particles and other carrier systems have been used as targeted/novel drug delivery systems, the cubosomes are more thermally stable. So that 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.[2] Non-steroidal anti-inflammatory drugs (NSAIDs) represents the most commonly used medications for the treatment of pain and inflammation, but numerous well-described side effects can limit their use.[3] With this view, the present study was aimed to formulate and evaluate the ibuprofen loaded cubosomes an attempt to provide a platform for further research.

MATERIALS AND METHODS

Preformulation studies of drug substance (Ibuprofen)

It was done in reference with the standard procedure.[4,6] Various aspects of selected drug substance such as organoleptic characters, absorption maxima ((λmax), melting point, solubility and drug-excipient compatibility were evaluated in the preformulation study.

Organoleptic evaluation and identification of drug substance

Organoleptic characters such as colour, odour and taste of the drug substance was evaluated and recorded.

Determination of λmax

Preparation of stock solution I & II

λmax of the drug substance was determined as a part of identification. It includes preparation of stock solution I, II and the determination of λmax in final.

An accurately weighed quantity of drug substance (100mg) was transferred to volumetric flask (100ml), diluted using phosphate buffer (pH 6.8) and made up to the volume. From this stock solution I, 2ml was transferred to 100ml volumetric flask and diluted up to the mark to prepare the stock solution II.

λmax assessment

0.5ml of stock solution II was taken and diluted to 10ml with phosphate buffer (pH 6.8) and the resultant solution was scanned spectrophotometrically (300nm) to determine the wavelength of maximum absorbance for the selected drug substance.

Preparation of standard calibration curve

Stock solution II was serially diluted (up to 20µg/ml) and scanned spectrophotometrically (238nm). Calibration curve was plotted by taking concentration on x-axis and absorbance on y-axis.

Determination of melting point

Capillary method was employed to determine the melting point of selected drug substance ibuprofen. Capillary tube with closed one end was used in this experiment. Initially, the capillary tube was filled with finely ground drug powder and then the filled capillary tube was inserted in to the melting point apparatus. The temperature at which the drug substance get melted was noted.

Determination of solubility

Solubility test of selected drug substance ibuprofen was carried out by using different solvents such as water, ethanol, acetone and methanol.

Drug-excipient compatibility study

FTIR spectroscopy was used to study the drug-excipient compatibility. Shimadzu IRPrestige-21 spectrometer was used for this purpose. In this study, the drug and drug-excipient mixture was subjected to spectral evaluation with the aim to identify that if any changes has been occurred in chemical composition of drug after mixing with the excipients. In this evaluation, KBr was used as pelletizing material. The KBr was completely dried at 100°C for 1h and after drying it was thoroughly mixed with the sample in the ratio 1:100 (1 part of sample and 100 parts of KBr). The mixture was compressed to form a disc using dies. This disc was placed in the sample chamber and a spectrum was obtained through the software program which is further subjected to interpretation.

Preparation of ibuprofen cubosomes

The preparation was done by top-down technique in reference with the standard procedure.[7,8] Initially, the bulk cubic phase was prepared. For that accurately weighed quantity of glyceryl mono oleate and poloxamer 407 in different concentration (Table 1) were heated on electric water bath (40-45ºC) until the poloxamer was completely dissolves in glyceryl mono oleate. Then the weighed quantity of drug ibuprofen (Table 1) was added to the prepared bulk cubic phase solution and mixed well. Now the clear lipid solution obtained was slowly added to distilled water and subjected to bath sonication for 45min. with intermittent shaking and stirring. A white opaque dispersion without any aggregates was formed. It was stored in well closed amber coloured bottles at room temperature in dark place.

Table 1: Ratio of glyceryl mono oleate and poloxamer 407 used in the preparation of cubosomes

Formulation code	Glyceryl mono oleate (% w/v)	Poloxamer 407 (% w/v)	Drug (% w/v)
C1	2	0.5	0.5
C2	4	0.5	0.5
C3	6	0.5	0.5
C4	2	1	0.5
C5	4	1	0.5
C6	6	1	0.5
C7	2	1.5	0.5
C8	4	1.5	0.5
C9	6	1.5	0.5

Evaluation of cubosomal dispersion prepared

Morphological characterization

Scanning electron microscopy was used to analyse the morphological characters such as size and shape of the cubosomal granules. The samples were examined in different magnification at suitable accelerating voltage of 15-20kV.

Drug content

The drug content in the prepared cubosomal dispersion was evaluated in reference with the standard procedure.[9] Cubosomal dispersion (10ml) was mixed with methanol (5ml) and this mixture was subjected to sonication for 10min. After filtering the mixture, appropriate dilution was done by phosphate buffer (pH 6.8) and the drug content was estimated by measuring the absorbance at 238 nm by using UV-Visible spectrophotometer.

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

Entrapment efficiency

The entrapment efficiency of cubosomal dispersion was evaluated in reference with the standard procedure.[10] The cubosomal dispersion was centrifuged at 15000rpm for 90min. Supernatant liquid collected was diluted appropriately with phosphate buffer (pH 6.8) and estimated spectrophotometrically at 233nm. The percentage entrapment efficiency was determined by

$$\text{Entrapment efficiency} = \frac{\text{Total drug conc.} - \text{Supernatant drug conc.}}{\text{Total drug conc.}} \times 100$$

Particle size and zeta potential analysis

The particle size and zeta potential of the prepared cubosome was determined by dynamic light scattering technique using the Horiba particle size analyser in reference with the standard procedure.[8] Sample (1ml) was diluted (10ml) in particle-free purified water and measured at 25°C.

***In vitro* drug release study**

The study was designed in reference with the standard procedure.[6,11] It was done by using Franz diffusion cell (bi-chambered donor receiver compartment model) placed on magnetic stirrer (37ºC). One end of the compartment was covered with the cellophane membrane which was previously soaked in phosphate buffer saline (PBS). PBS (pH 6.8) was placed in the receptor compartment. Cubosomal formulation was placed on the dialysis membrane which was in contact with receptor medium. Samples were withdrawn from the receptor compartment at specified intervals (1,2,3,4,5,6,7,8,9,10,11,12 & 24h) Receptor medium was replaced with the equal amount of fresh phosphate buffer (pH 6.8) after each withdrawal. The samples were analysed spectrophotometrically (238nm) for drug content.

RESULTS AND DISCUSSION

In the present research, the pre-formulation study began with the organoleptic evaluation of selected drug substance, the colour, odour and taste of the selected drug material was evaluated and recorded (Table 2).

Table 2: Organoleptic evaluation of selected drug substance.

Drug substance	Parameter	Observation
Ibuprofen	Colour	Colourless
	Odour	Characteristic odour
	Taste	Characteristic bitter taste

As a part of the identification, determination of λmax and the preparation of standard calibration curve of the selected drug substance was done by spectrophotometric method. In the present study, λmax of ibuprofen was found as 223nm. For plotting the calibration curve, absorbance was measured by UV Visible Spectrophotometer at 223nm for the concentration of 4µg, 8µg, 12µg, 16µg and 20µg respectively (Table 3). The curve was plotted by taking absorbance on y-axis and concentration on x-axis (Figure 1). The graph shows a linear relationship between concentration and the absorbance.

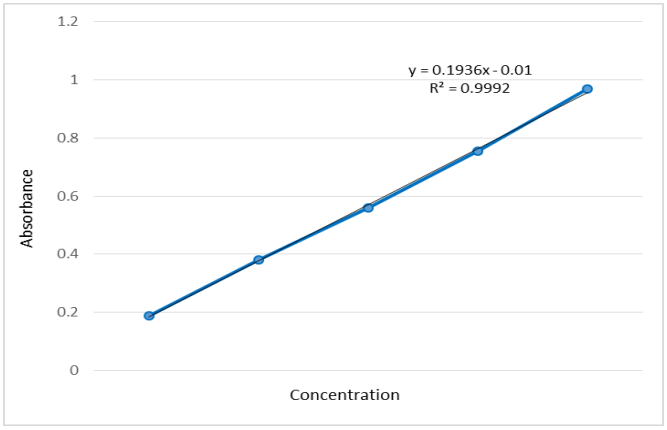

Figure 1: Calibration curve of ibuprofen sample.

Table 3: Data of absorbance showed by ibuprofen in different concentration.

Concentration (µg/ml)	Absorbance
4	0.187
8	0.382
12	0.561
16	0.756
20	0.968

In this study, the melting point of the selected drug substance was determined by capillary method. 75.5-77ºC was found as the melting point range of the selected drug ibuprofen. The solubility test done with different solvents such as water, ethanol, acetone and methanol showed that the ibuprofen is insoluble in water and readily soluble in remaining solvents used in the test.

In the present study, FTIR spectroscopy was employed to study the drug and drug-excipient compatibility. The FTIR report of selected drug ibuprofen is shown in Figure 2.

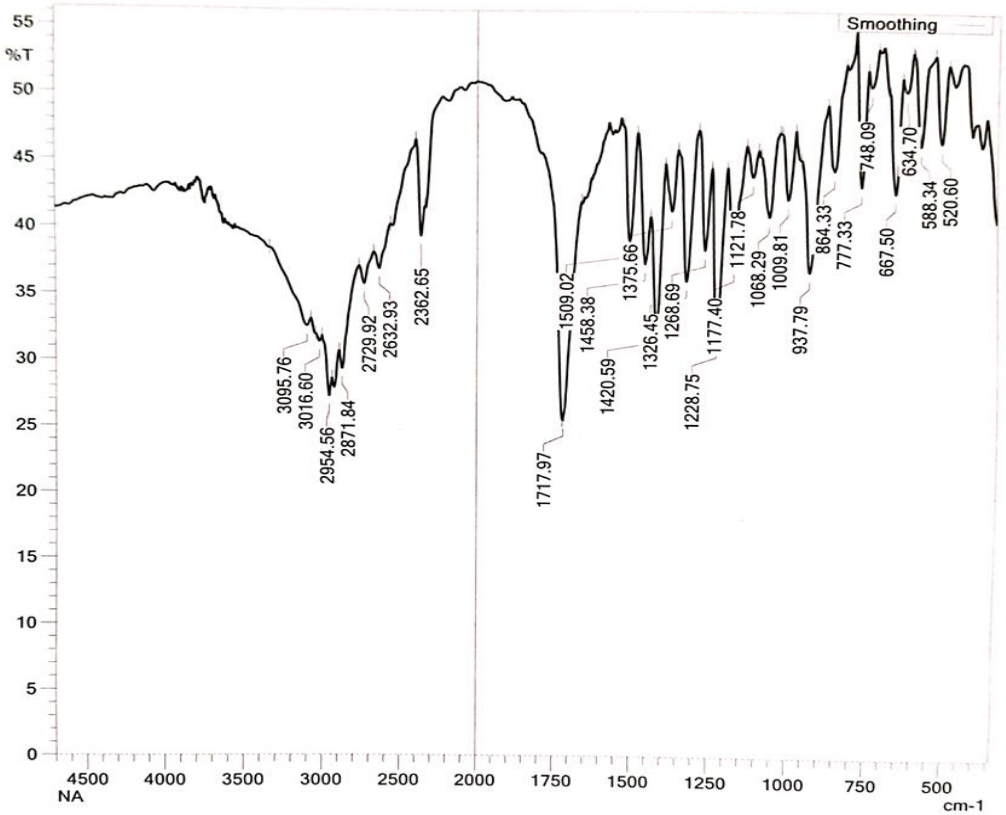

Figure 2: FTIR report of selected drug ibuprofen.

The Figure 3 shows the FTIR graph of the mixture of excipients (glycerylmonooleate + poloxamer + HPMC + Eudraagit) used in the formulation of cubosome and transdermal patch.

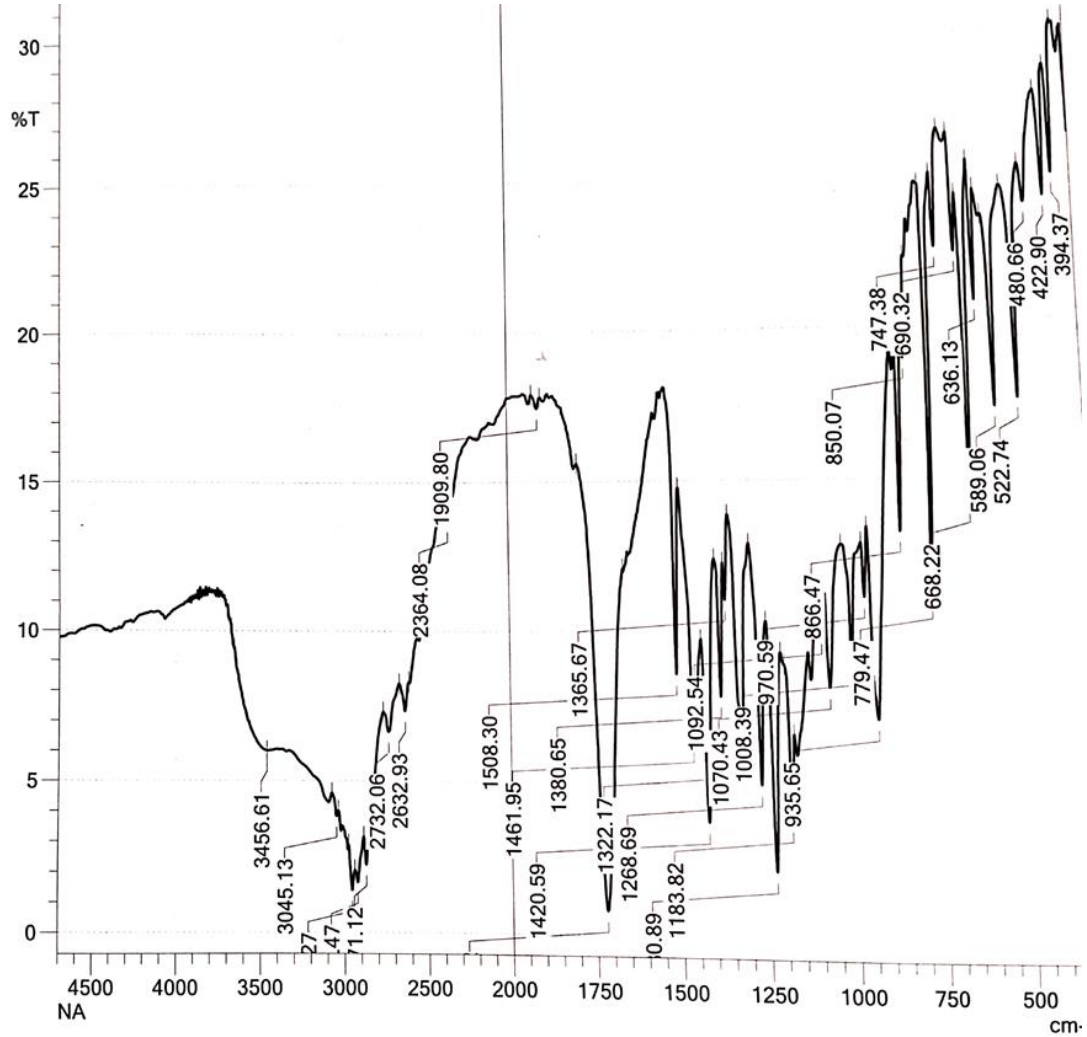

Figure 3: FTIR report of excipients (glycerylmonooleate + Poloxamer+HPMC+Eudragit RL-100) used in the formulations.

The FTIR graph of the excipient Eudragit RL-100 and HPMC is presented in Figure 4 and 5 respectively. The literatures stated that a reduction of the peak intensity, the appearance of an absorption peak or the appearance of new peaks indicate the existence of interactions between the excipient and the API.

From the analysis of these graphs it was found that C=O stretching vibration of acid 1655-1685; C=O stretching vibration of ketones 1690-1725; C=C stretching the vibration of the aromatic ring 3000-3100; OH vibration 3300-3400. Collectively, the results clearly indicated the compatibility exist between the selected drug ibuprofen and the different excipients used in the formulation of cubosome and transdermal patch.

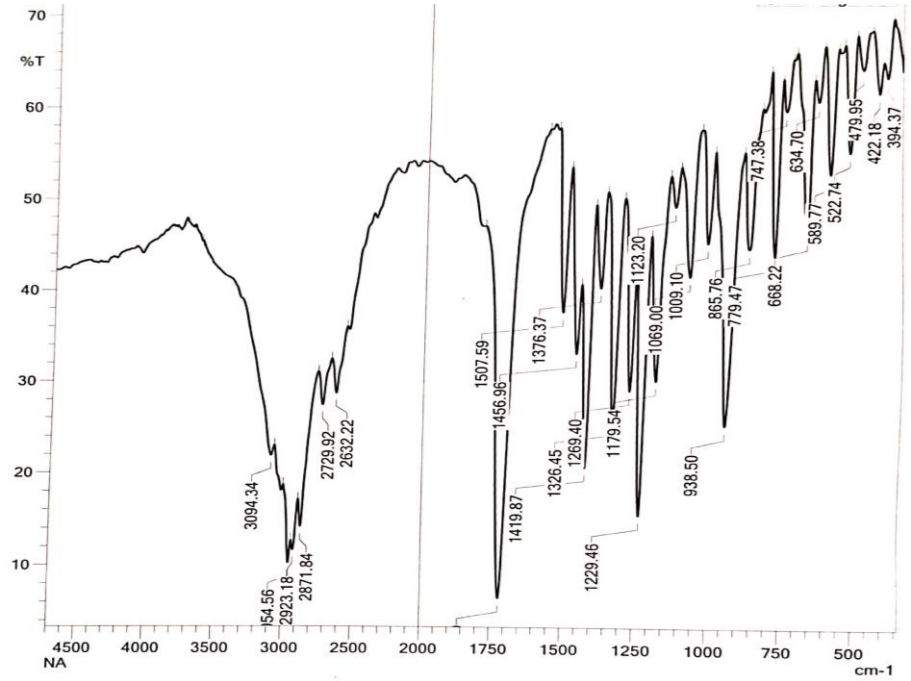

Figure 4: FTIR report of drug with the excipient Eudragit RL-100.

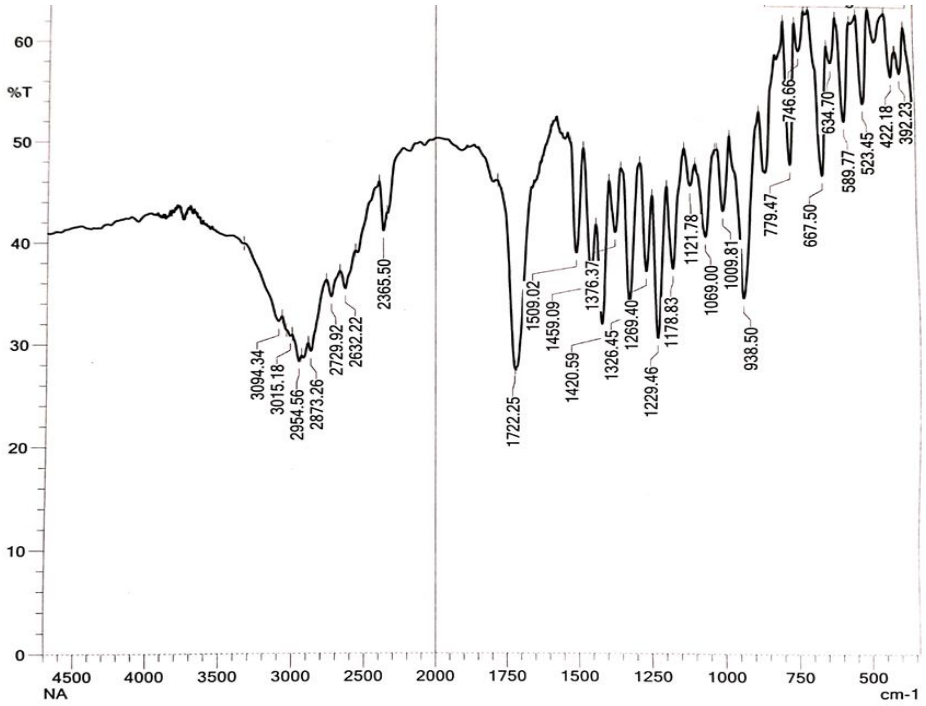

Figure 5: FTIR report of drug with the excipient HPMC.

Ibuprofen cubosomes prepared by top-down technique was evaluated for morphological characters by SEM revealed the cuboidal geometry of the granules in the formulations. Also the results revealed no aggregation among the particles and the particle surface was smooth without surface deformations and visible pinholes.

The results of drug content and entrapment efficiency, particle size, zeta potential and polydispersity index analysis of prepared cubosomes is shown in Table 4. The formulations with the code of C3, C6, C8, and C9 revealed significant results in all the parameters evaluated. In case of particle size analysis, the result showed that the particle size range of all the formulations (C1 – C9) are within the nanometre range of 150-500nm and the average particle size was found to be 198.6nm. The results of zeta potential analysis clearly indicated that there is no aggregation in the formulations prepared.

Table 4: Analysis of different parameters of prepared cubosomes.

Formulation code	Drug content (%)*	Entrapment efficiency (%)*	Particle size (nm)*	Poly dispersity Index (PDI)*	Zeta potential (–mV)
C1	91.21±1.0	85.00±1.89	172.5±.0.71	0.305±0.04	–23.1±0.21
C2	91.78±1.1	86.63±1.51	216.1±0.42	0.321±0.06	–23.7±0.14
C3	94.79±0.6	88.33±0.98	163.2±0.30	0.243±0.06	–27.3±0.18
C4	89.71±0.8	76.66±1.39	255.4±0.16	0.423±0.02	–24.7±0.31
C5	90.82±1.3	78.78±1.01	225.7±0.24	0.345±0.03	–22.4±0.15
C6	95.37±1.2	93.39±0.67	157.3±0.25	0.226±0.05	–28.5±0.12
C7	88.25±0.7	83.25±0.75	235.1±0.43	0.371±0.02	–24.5±0.12
C8	92.41±0.5	87.34±1.25	210.5±0.26	0.295±0.01	–26.1±0.15
C9	96.72±1.1	91.65±1.03	152.3±0.40	0.210±0.05	–29.5±0.14

*mean±standard deviation (SD), n=3.

Based on the results obtained in the evaluation of drug content, entrapment efficiency, particle size, PDI and zeta potential of prepared cubosomes (C1–C9), four out of nine formulations namely, C3, C6, C8 and C9 were selected for *in vitro* drug release evaluation which was done by Franz diffusion cell method. The results obtained in this evaluation is presented in Table 5 & Figure 6. A significant percentage drug release (95.13%) was found in the C9 formulation. Next to that the formulation C6 showed 90.71% and C3 formulation showed 88.71% drug release. The C8 formulation showed a score of 85.20%.

Table 5: Percentage drug release found in the *in vitro* evaluation of cubosomes.

Time (h)	C3	C6	C8	C9
1	5.53	6.02	5.42	8.15
2	7.50	8.17	6.15	10.12
3	11.66	15.31	10.30	25.40
4	23.43	24.60	19.25	29.70
5	27.50	35.72	26.41	35.66
6	31.25	42.30	30.12	47.85
7	39.65	48.50	37.33	57.60
8	43.31	52.15	42.10	63.14
9	48.27	56.20	48.20	67.20
10	53.70	62.16	51.40	71.52
11	61.48	68.45	59.23	76.40
12	73.30	79.13	67.45	83.10
24	88.71	90.71	85.20	95.13

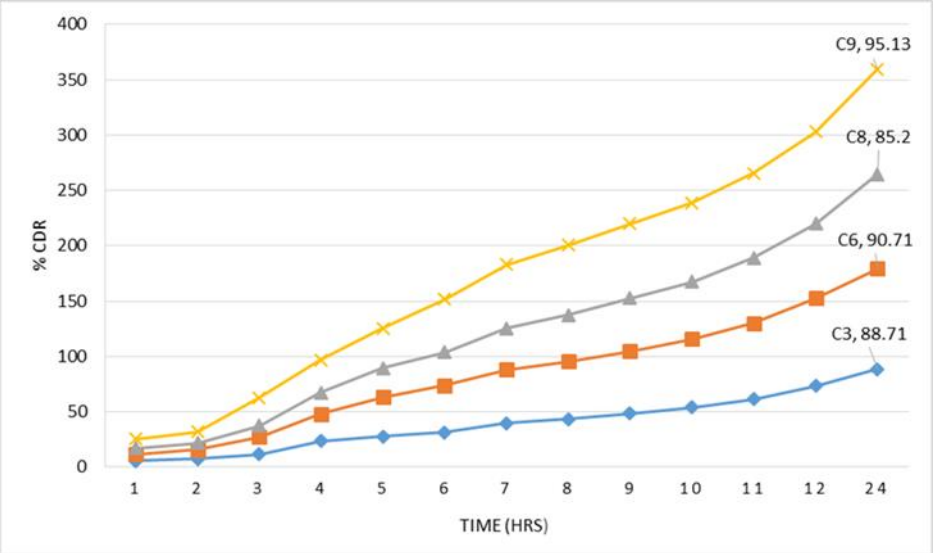

Figure 6: Percentage release of ibuprofen from the cubosome formulations in phosphate buffer saline.

In the evaluation of drug release kinetics of cubosome formulations C3, C6, C8 and C9, the zero order, first order, Hixon-Crowell's, Higuchi and Korsmeyer-Peppas release model were focused.

Various drug release parameters analysed for the cubosome formulation C3, C6, C8 and C9 is tabulated in Table 6–9 & Figure 7–10. The statistical kinetic values (R^2 and the slope) obtained in the evaluation of C3 formulation is presented in Table 10.

Table 6: *In vitro* drug release parameters for cubosome formulation C3.

Time (h)	% CDR	Log % CDR remaining	Cube root of % drug remaining	Log % CDR	Square root time	Log of time
1	5.53	1.9752	4.5544	0.7427	1	0
2	7.50	1.9661	4.5225	0.8750	1.4142	0.3010
3	11.66	1.9464	4.4563	1.0666	1.7320	0.4771
4	23.43	1.8840	4.2463	1.3697	2	0.6020
5	27.50	1.8603	4.1697	1.4393	2.2360	0.6989
6	31.25	1.8372	4.0966	1.4948	2.4494	0.7781
7	39.65	1.7806	3.9224	1.5982	2.6457	0.8450
8	43.31	1.7535	3.8415	1.5982	2.8284	0.9030
9	48.27	1.7137	3.7260	1.6836	3	0.9542
10	53.70	1.6653	3.5908	1.7299	3.1622	1
11	61.48	1.5856	3.3772	1.7887	3.3166	1.0413
12	73.30	1.4265	2.9888	1.8651	3.4641	1.0791
24	88.71	1.0526	2.2433	1.9479	4.8989	1.3802

Table 7: *In vitro* drug release parameters for cubosome formulation C6.

Time (h)	% CDR	Log % CDR remaining	Cube root of % drug remaining	Log % CDR	Square root time	Log of time
1	6.02	1.9730	4.5465	0.7795	1	0
2	8.17	1.9629	4.5115	0.9122	1.4142	0.3010
3	15.31	1.9278	4.3914	1.1849	1.7320	0.4771
4	24.60	1.8773	4.2246	1.3909	2	0.6020
5	35.72	1.8080	4.0058	1.5529	2.2360	0.6989
6	42.30	1.7596	3.8641	1.6263	2.4494	0.7781
7	48.50	1.7118	3.7205	1.6857	2.6457	0.8450
8	52.15	1.6798	3.6304	1.7172	2.8284	0.9030
9	56.20	1.6414	3.5249	1.7497	3	0.9542
10	62.16	1.5779	3.3572	1.7935	3.1622	1
11	68.45	1.4989	3.1598	1.8353	3.3166	1.0413
12	79.13	1.3195	2.7532	1.8983	3.4641	1.0791
24	90.71	0.9680	2.1021	1.9576	4.8989	1.3802

Table 8: *In vitro* drug release parameters for cubosome formulation C8.

Time (h)	% CDR	Log % CDR remaining	Cube root of % drug remaining	Log % CDR	Square root time	Log of time
1	5.42	1.9758	4.5564	0.7333	1	0
2	6.15	1.9724	4.5444	0.7888	1.4142	0.3010
3	10.30	1.9527	4.4764	1.0128	1.7320	0.4771
4	19.25	1.9071	4.3222	1.2844	2	0.6020
5	26.41	1.8668	4.1905	1.4217	2.2360	0.6989
6	30.12	1.8443	4.1189	1.4788	2.4494	0.7781
7	37.33	1.7970	3.9720	1.5720	2.6457	0.8450
8	42.10	1.7626	3.8686	1.6242	2.8284	0.9030
9	48.20	1.7143	3.7277	1.6830	3	0.9542
10	51.40	1.6866	3.6493	1.7109	3.1622	1
11	59.23	1.6103	3.4417	1.7725	3.3166	1.0413
12	67.45	1.5125	3.1928	1.8289	3.4641	1.0791
24	85.20	1.1702	2.4552	1.9304	4.8989	1.3802

Table 9: In vitro drug release parameters for cubosome formulation C9.

Time (h)	% CDR	Log % CDR remaining	Cube root of % drug remaining	Log % CDR	Square root time	Log of time
1	8.15	1.9618	4.4519	0.9111	1	0
2	10.12	1.9536	4.4794	1.0051	1.4142	0.3010
3	25.40	1.8727	4.2096	1.4048	1.7320	0.4771
4	29.70	1.8469	4.1200	1.4727	2	0.6020
5	35.66	1.8084	4.0083	1.5521	2.2360	0.6989
6	47.85	1.7172	3.7360	1.6798	2.4494	0.7781
7	57.60	1.6273	3.4870	1.7604	2.6457	0.8450
8	63.14	1.5665	3.3280	1.8003	2.8284	0.9030
9	67.20	1.5158	3.2010	1.8273	3	0.9542
10	71.52	1.4545	3.0538	1.8544	3.1622	1
11	76.40	1.3729	2.8683	1.8830	3.3166	1.0413
12	83.10	1.2278	2.5662	1.9196	3.4641	1.0791
24	95.13	0.6875	1.6950	1.9783	4.8989	1.3802

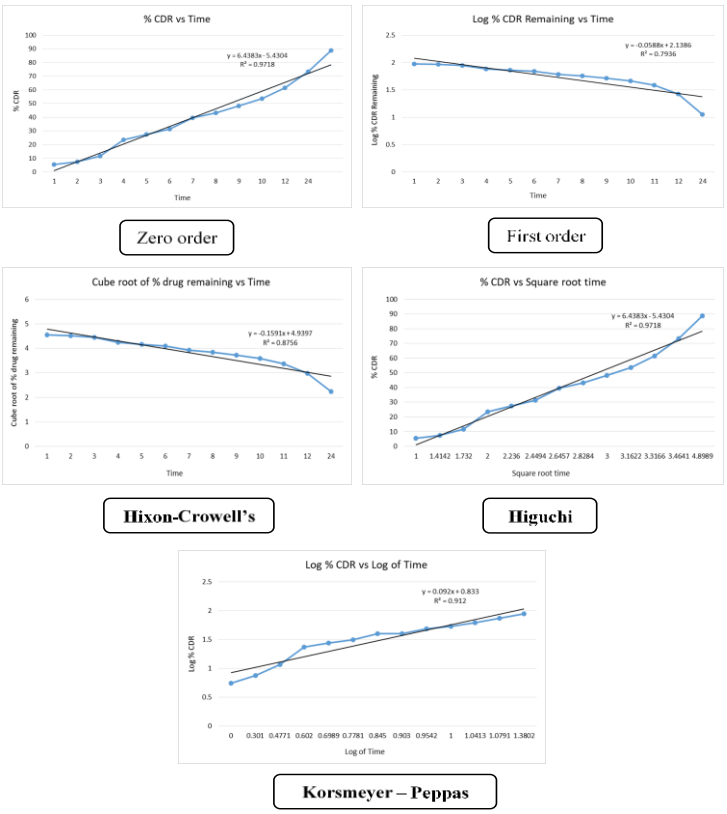

Figure 7: The release kinetics of C3 formulation according to different models.

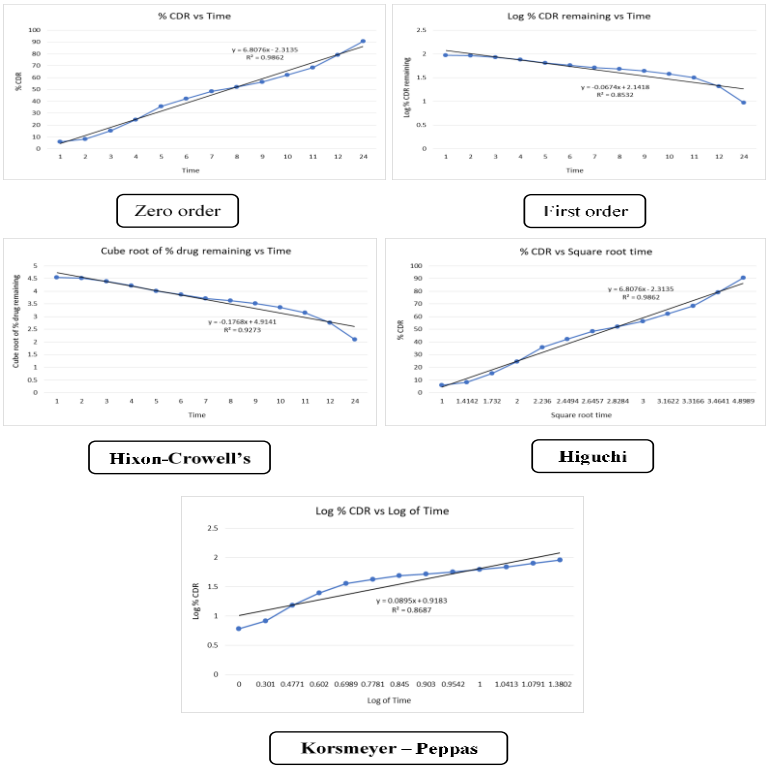

Figure 8: The release kinetics of C6 formulation according to different models.

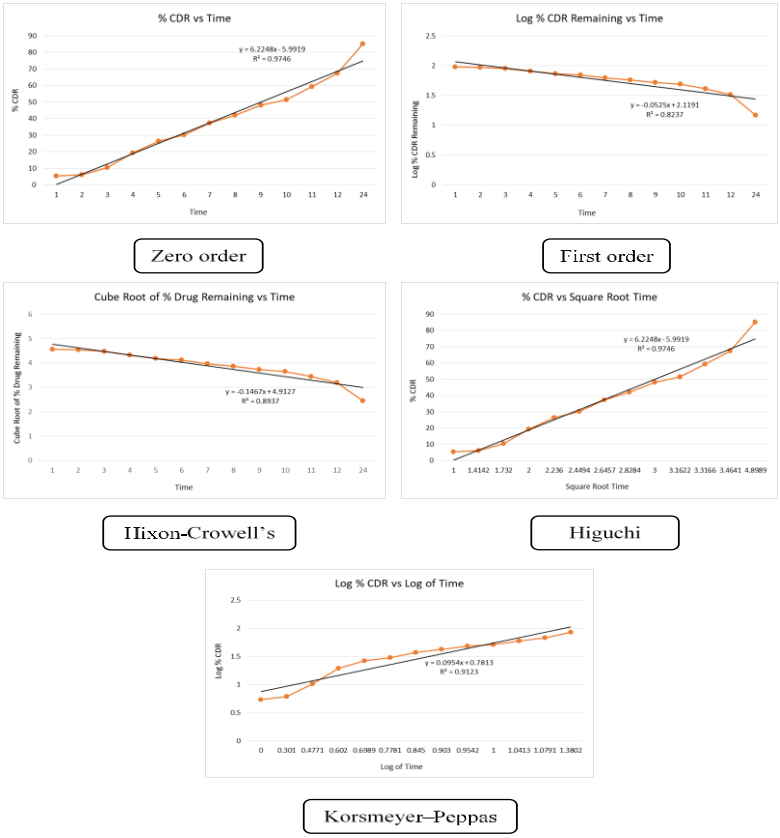

Figure 9: Release kinetics of C8 formulation according to different models.

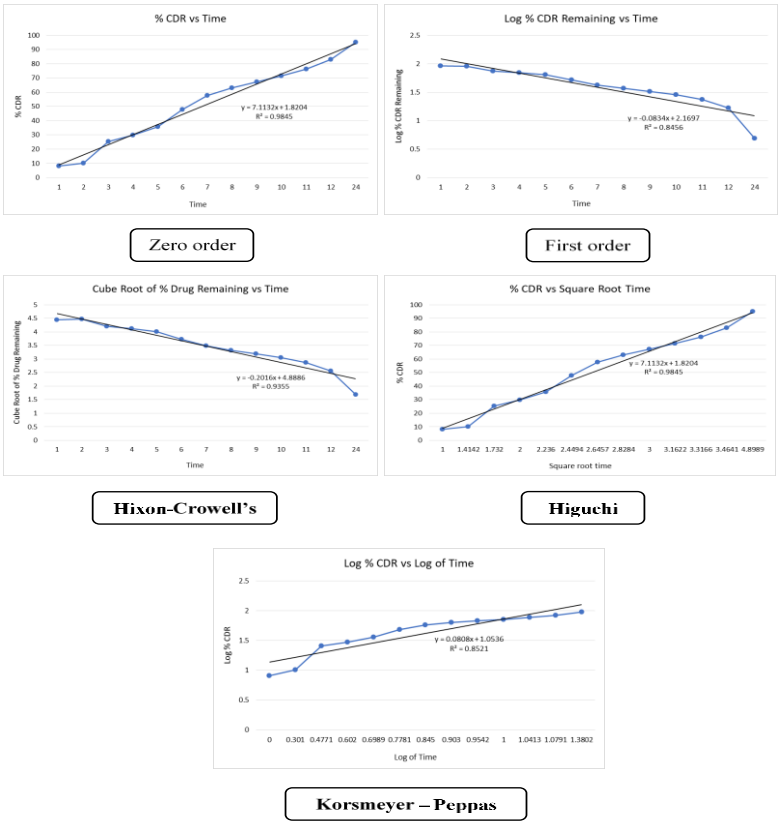

Figure 10: Release kinetics of C9 formulation according to different models.

Table 10: Statistical kinetic values of cubosome formulations.

Release kinetic models	Formulations							
	C3		C6		C8		C9	
	R^2	Slope	R^2	Slope	R^2	Slope	R^2	Slope
Zero order	0.971	6.438	0.986	6.807	0.974	6.224	0.984	7.113
First order	0.793	– 0.058	0.853	– 0.067	0.823	– 0.052	0.845	– 0.083
Hixon- Crowell	0.875	– 0.159	0.927	– 0.176	0.893	– 0.146	0.935	– 0.201
Higuchi	0.971	6.438	0.986	6.807	0.974	6.224	0.984	7.113
Korsmeyer-Peppas	0.912	0.092	0.868	0.089	0.912	0.095	0.852	0.080

Analysis of release data indicated that the formulation C6 and C9 were best fit towards Zero order and Higuchi model with R^2 value of 0.986 and 0.984 respectively in both models. Next to that the formulation C8 and C3 showed better results in both the above models. The C8 formulation showed the R^2 value of 0.974 in Zero order and Higuchi model and the C3 formulation showed the R^2 value of 0.971 in Zero order and Higuchi model. Obeying the Zero order indicated that a constant release of drug from the prepared cubosome formulations and complying with Higuchi model indicated that the drug was released from the cubosome formulation by diffusion process. Previous literatures[12] indicated that the drug release mechanism from cubosomes is based on the principle of drug diffusion, where the concentration gradient of the drug across the cubosomes is the driving force of the diffusion. Therefore, the drug release rate from cubosomes is generally coincidental with the Higuchi or Fick diffusion equation.

Notably, in the preparation of cubosomes, three different concentration of glyceryl monooleate, 2%, 4% and 6%w/v and the poloxmer 407, 0.5%, 1% and 1.5%w/v were used. Out of 9 cubosome formulations, the formulations contain the highest concentration (6%w/v) of glyceryl monooleate. In case of poloxmer 407, the C3 formulation contains 0.5%w/v, the C6 formulation contains 1% and the C9 formulation contains 1.5%w/v concentration of poloxmer 407 (Table 1). From the results, it was clear that the increase in the concentration of these additives facilitate the release of drug from the formulations.

CONCLUSION

In the present study, the pre-formulation study done initially confirmed the physicochemical quality of drug substance ibuprofen used in this study. Results of drug-excipient compatibility study revealed the compatibility exist between the drug ibuprofen and the excipients used in the formulation of cubosome. After the pre-

formulation studies, 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. The zero order, first order, Hixon-Crowell's, Higuchi and Korsmeyer-Peppas release model were focused in the drug release kinetics evaluation. Morphological characterization of all the cubosome formulations revealed no aggregation among the particles and the particle surface was smooth without surface deformations and visible pinholes. Based on the results of drug content, entrapment efficiency, particle size, zeta potential and polydispersity index (PDI) analysis, the formulations namely C3, C6, C8, and C9 were selected for *in vitro* drug release evaluation. Analysis of release data indicated that the selected formulation were best fit towards Zero order and Higuchi model which indicated that a constant release of drug from the prepared cubosome formulations and complying with Higuchi model indicated that the drug was released from the cubosome formulation by diffusion process. Particularly, the formulations C3, C6 and C9 were showed significant results overall that can be seen in all the parameters subjected to evaluation. Further research such as loading these cubosome formulations in transdermal patches and their evaluations may leads to successful development of a novel sustained release drug delivery system in the future.

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