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Formulation and Evaluation of Carbamazepine Cubosomal Transdermal Patch

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A B S T R A C T

Cubosomes, nanostructured lipid carriers, have attention in pharmaceutical research for their potential in efficient drug delivery systems. This study aimed to formulate optimized Carbamazepine cubosomes using Poloxamer107 as a stabilizing agent and GMO as the lipid component, intending to develop a transdermal patch for enhanced drug delivery. The cubosome formulations were systematically prepared via a bottom-up approach method, optimizing various parameters such as Poloxamer concentration, GMO ratio, and sonication time to achieve the desired characteristics. The dispersions of cubosomes were assessed for properties including zeta potential, particle size, drug loading capacity and polydispersity index. Subsequently, the optimized cubosome formulation was integrated into a transdermal patch matrix and characterized for its in-vitro drug release profile, drug kinetics using established methodologies. The results revealed that the formed cubosomes exhibited excellent stability, high drug loading capacity and uniform particle size distribution. The transdermal patch incorporating the optimized cubosome formulation demonstrated sustained drug release kinetics over an extended period. Short stability studies were performed on optimized formulation.

Keywords: Cubosomes, carbamazepine, *in-vitro* drug release profile, drug kinetics.

INTRODUCTION

Cubosomes are self-assembling nanoparticles composed of lipid molecules that are dispersed in water. They have a unique, well-structured cubic phase that has captured the interest of scientists across various domains, particularly in pharmaceutical and biomedical research. These nanocarriers are characterized by their unique bicontinuous cubic liquid crystalline structure, typically ranging from 10 to 500 nm in size. Composed of lipid layers that separate non-intersecting water channels, cubosomes possess remarkable properties suitable for drug delivery applications. They exhibit optical isotropy and viscosity, making them advantageous as drug carriers. Their structural configuration provides a large internal surface area (400 m2/g), enabling them to accommodate a wide range of drugs—hydrophilic, lipophilic, and amphiphilic while ensuring a high payload capacity. Cubosomes demonstrate biocompatibility, bio adhesion, non-toxicity, non-immunogenicity, and cost-effectiveness, making them an attractive platform for drug delivery systems. Studies have indicated their capability for sustained and prolonged drug release, as well as their potential in enhancing skin retention and transport of therapeutic agents due to similarities with the bicontinuous structures in human skin layers.

Carbamazepine, tricyclic antidepressants, possesses significant anticonvulsant and analgesic properties. Its anticonvulsant activity involves reducing polysynaptic responses and inhibiting post-tetanic potentiation. While the mechanism underlying its analgesic activity remains less understood, Carbamazepine is commonly prescribed for managing pain associated with trigeminal neuralgia. With a tricyclic chemical structure, Carbamazepine serves various roles, including being an anticonvulsant, analgesic, and sodium channel blocker. Cubosomal transdermal patches offer advantages such as enhanced skin retention, prolonged drug delivery, and the ability to encapsulate a wide range of drugs. This delivery system holds promise for effective and targeted administration of medications through the skin, ensuring sustained therapeutic benefits. The transdermal route of drug administration offers considerable advantages for both local and systemic drug delivery compared to conventional administration methods. This approach avoids hepatic first-pass metabolism, improving patient compliance. However, the highly organized structure of the stratum corneum presents a formidable barrier to drug permeation. Penetration enhancers play a pivotal role in overcoming this barrier by facilitating the delivery of poorly penetrating drugs, thereby expanding the scope of drugs amenable to transdermal delivery. The present study focused on formulating cubosomes loaded transdermal patch for sustained release of carbamazepine drug mainly in paediatric patients.

MATERIALS AND METHOD

MATERIALS

Chemicals: Glycerol Mono Oleate (GMO), Poloxamer 407, Carbamazepine, Deionized water, HPMC CPS 15, Ethyl Cellulose, Eudragit RL 100, Dichloro methane, Methanol, PEG 400.

Buffer: pH 7.4 phosphate buffer

Equipment: Digital Weighing Balance, Shimadzu UV Visible Spectrophotometer, Bruker Alpha FTIR Spectrophotometer, Hot water bath, Cyclomixer, Homogenizer, Vernier callipers, Sonicator, pH meter, Hot air oven, Zeta sizer, Centrifuge.

METHOD

Preformulation studies: Involve assessing a drug's characteristics such as its physical state, odour and colour.

FTIR studies: The Bruker alpha FT-IR spectrophotometer was utilized to obtain FT-IR spectra of pure drugs and drug-excipient mixtures.

Solubility studies: The solubility of Carbamazepine was assessed using a standard procedure involving various solvents, oils to determine its solubility profile. Quantifying solubility using analytical techniques like UV-Visible spectrophotometry.

Preparation of Phosphate Buffer of pH 7.4:

Dissolve 2.38g of disodium hydrogen phosphate, 0.19g of potassium dihydrogen phosphate and 8g of sodium chloride in sufficient water to produce 1000ml.

Determination of λ max : Solution of Carbamazepine containing the concentration 10 µg/ ml was prepared using pH 7.4 phosphate buffer and UV spectrum was taken using Shimadzu UV-1800 double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Standard calibration curve of Carbamazepine:

100mg of Carbamazepine was weighed accurately and dissolved in pH 7.4 phosphate buffer, which resulted in 1000 µg/ml. Then from the stock solution 100 µg/ml solution was prepared from this 2, 4, 6, 8, 10 µg/ml were prepared. The absorbance of the above dilutions were measured using UV-spectrophotometer at 214 nm using 7.4 pH phosphate buffer as blank. Graph is plotted by taking concentration on X-axis and absorbance on Y-axis.

Preparation of carbamazepine cubosomes:

The bottom-up methodology was employed, wherein nanostructure building blocks were initially generated and subsequently assembled into the final substance. This represents a recently developed approach for the generation of cubosomes, facilitating their synthesis and crystallization from molecular precursors. Subsequent investigations opted for the sonication technique due to its efficacy in achieving maximum entrapment efficiency and minimizing particle size. The cubosomal formulation comprised Glyceryl Mono Oleate (GMO) and Poloxamer 407. GMO concentrations ranged from 6% to 9.5%, while Poloxamer 407 varied from 0.5% to 3.5%, resulting in ten distinct batches. The process involved the gentle melting of GMO at 70°C in a water bath, followed by dropwise injection into preheated Poloxamer 407 solutions at 70°C. Simultaneously, 50mg of the drug was introduced, and distilled water was gradually added to achieve a final volume of 50mL. Mechanical stirring at 1500 rpm continued for 45 minutes, after which the solutions were sonicated for 15 minutes at a maximum power of 120 W. The resulting cubosome dispersions exhibited a milky white appearance following a 48-hour equilibration period subsequent to cooling to ambient temperature given in table1.

Preparation of cubosomes loaded transdermal patch:

A transdermal patch was developed using the solvent evaporation method. Initially, Hydroxypropyl methylcellulose and Eudragit RL was dissolved in ethanol and dichloro methane solvent system and stirred on a magnetic stirrer until it achieved a semi-solid consistency. Subsequently, the drug in the form of cubosomal dispersion, was incorporated into the solution and stirred continuously. Polyethylene glycol (PEG) 400 was gradually added drop by drop as a plasticizer. The resulting mixture was then poured into a Petri dish, and an inverted funnel was placed on top of it. Following this, it was allowed to dry for 24 hours to yield a patch. Finally, the patches were extracted using a sharp knife inserted along the edge of the patch and stored for further examination given in table 2.

Table 1 Formulation of cubosomes

S.no	Formulation code	Drug (mg)	GMO (grams)	Poloxamer 407(mg)	GMO: Poloxamer ratio	Water (ml) Up to 50
1	CF1	500	2.37	125	9.5 :0.5	50
2	CF2	500	2.25	250	9:1	50
3	CF3	500	2.313	187.5	9.25: 0.75	50
4	CF4	500	2.187	312.5	8.75: 1.25	50

5	**CF5**	**500**	**2.125**	**375**	**8.5: 1.5**	**50**
6	**CF6**	**500**	**2**	**500**	**8: 2**	**50**
7	**CF7**	**500**	**1.87**	**625**	**7.5:2.5**	**50**
8	**CF8**	**500**	**1.75**	**750**	**7: 3**	**50**
9	**CF9**	**500**	**1.68**	**812.5**	**6.75: 3.25**	**50**
10	**CF10**	**500**	**1.62**	**875**	**6.5: 3.5**	**50**

Table 2 Formulation of cubosomal Transdermal patch

S.NO	FORMULATION CODE	Cubosomal formulation (ml)	HPMC CPS 15(mg)	Eudragit RL (mg)	SOLVENT SYSTEM (Dichloro Methane: Ethanol)
1	**F1**	**CF1-12.2ml**	**150**	**150**	**1:1**
2	**F2**	**CF2-11.8ml**	**150**	**150**	**1:1**
3	**F3**	**CF3-12.1ml**	**150**	**150**	**1:1**
4	**F4**	**CF4- 12.2ml**	**150**	**150**	**1:1**

EVALUATION OF CUBOSOMES:

Particle size and Polydispersity index: The assessment of cubosome particle size and polydispersity index was conducted employing a computerized zeta sizer apparatus, specifically the Malvern zeta Sizer. The measurements were carried out at a temperature of 25°C through the dynamic light scattering methodology.

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 Zeta-sizer. The samples were stored in a polystyrene cuvette, and the zeta potential was measured using a zeta dip cell. Zeta potential for a stable formulation is found to be ±30mV.

Entrapment efficiency: The entrapment efficacy of the formulated cubosomal mixture was assessed utilizing the centrifugation technique. The cubosomes underwent centrifugation at room temperature for 30 minutes, with a rotational speed of 5000 rpm. The supernatant, containing the medication not encapsulated within the cubosomes, was separated and subjected to analysis against a phosphate buffer using a UV spectrophotometer at λ_{max} 214nm (pH 7.4). The entrapment efficiency was determined by calculating the amount of drug encapsulated in cubosomes through the specified 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 in the cubosomal formulation was assessed by blending the formulation with methanol, subjecting it to sonication for 10 minutes to achieve a clear solution, and subsequently filtering it. The resulting filtrate was then analyzed for drug content using a UV spectrophotometer at the wavelength maximum (λ max) of 214 nm.

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

***In-vitro release study*:** The release study employed a dialysis membrane, where the cubosomal formulation was positioned and the ends securely sealed. Subsequently, this assembly was immersed in a beaker containing phosphate buffer at pH 7.4. Sampling occurred at specified intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 hours), with an equivalent volume of buffer promptly replenished to maintain sink conditions. Analysis of the materials was conducted using a UV spectrometer at a wavelength of λmax 214 nm. The collected data points were then graphically represented.

EVALUATION OF TRANSDERMAL PATCHES

Physical appearance: Prepared patches were visually inspected for colour, clarity, flexibility and smoothness.

Thickness uniformity: Thickness of the patch was determined by using screw gauge.

Folding Endurance: The folding durability of the prepared patches was meticulously assessed 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: The patch was precisely weighed and placed in desiccators for a duration of 24 hours. Subsequently, the patches were reweighed, and the percentage of moisture absorption was determined using the provided formula.

% Moisture content = $\frac{\text{Initial weight – Final weight X 100}}{\text{Initial weight}}$

Drug content: Small segments were cut from a circular patch and immersed in 100 ml of methanol. The mixture was stirred with a magnetic stirrer for 24 hours and then subjected to sonication for approximately 15 minutes. The resulting solution was filtered and analyzed using a UV Spectrophotometer at a wavelength of 214nm.

***In-vitro* Diffusion study:** *In-vitro* diffusion of transdermal patches loaded with cubosomes, Franz diffusion cells were employed. 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 at pH 7.4 and stirred continuously at 900 rpm using a magnetic stirrer to ensure uniformity. Small samples (aliquots) are collected over a 24-hour period and subjected to UV analysis at 214 nm 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: The first order mode, zero order model, Higuchi, and Korsemeyer-Peppas kinetic models were used to fit the release data of the selected formulations.

Stability studies: Stability testing is conducted by exposing the cubosomal transdermal patches to temperatures and humidity conditions, such as 4°C ± 0.2°C, 25°C ± 2°C.

RESULTS AND DISSCUSION

Preformulation studies: In this specific study, the organoleptic characteristics of Pure Drug were evaluated. As per the findings, Pure Drug is a white solid that has no odour

FTIR studies: There is no interaction between drug , drug-excipients and optimized formulation in table 4 .

λ max of Carbamazepine: UV spectrum analysis of Carbamazepine revealed that the drug has a maximum absorbance at 214 nm shown in fig.

Standard Calibration Curve of Carbamazepine: Regression coefficient obtained is 0.9995, indicating high level of accuracy and precision in the measurements and shows a linear relationship between concentration and absorbance obeys Beer- Lambert's law as shown in fig

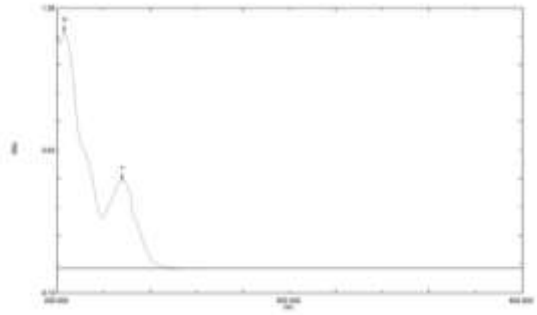

Fig.1 Absorption Spectrum of Carbamazepine

Concentration(ug/ml)	Absorbance(nm)WL 214*
2	0.240±0.001
4	0.452±0.002
6	0.647±0.001
8	0.876±0.002
10	1.081±0.001

Table.3 Calibration curve of Carbamazepine
*mean ±standard deviation (SD), n=3

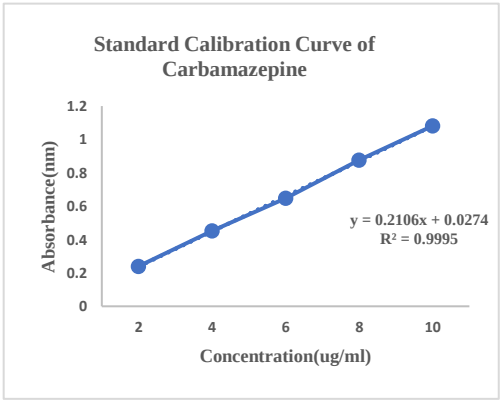

Fig.2 Standard calibration curve of carbamazepine

Functional Groups	Peak of functional group of pure drug (cm^{-1})	Peak of optimized formulation (cm^{-1})
O-H	**3466**	**3430**
C=O	**1677**	**1643**
C-H	**3023**	**3009**
C=C	**1594**	**1599**
C-N	**1309**	**1308**
N-H	**3315**	**3340**

Table 4 FTIR interpretation of drug and optimised formulation

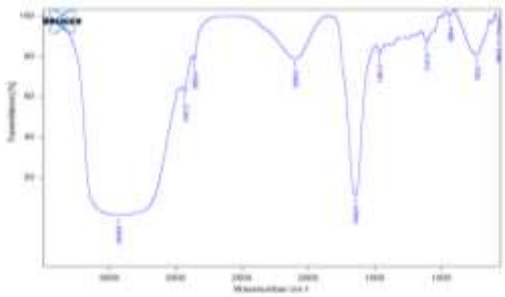

Fig.3 FTIR Spectrum of Carbamazepine

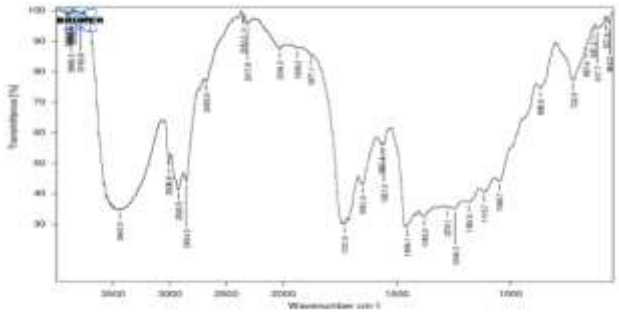

Fig.4 FTIR Spectrum of Carbamazepine+ GMO

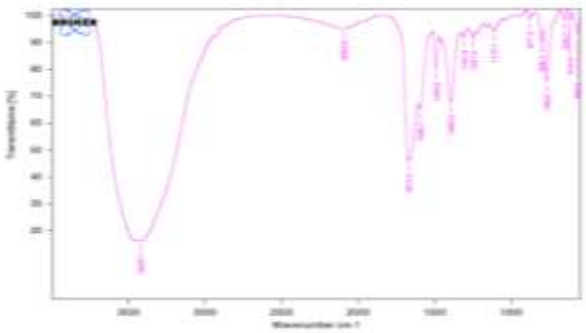

Fig.5 FTIR Spectrum of optimized formulation.

Table 5 Solubility studies of carbamazepine drug in various oils

S. No	Ingredients (OILS)	Solubility in mg/ml*
1	PEG-400	98±0.12
2	PEG-200	123.2±0.17
3	CAPRYOL 90	34.6±0.15
4	LABRAFAC PG	1.3 ± 0.8
5	CASTOR OIL	26.4±0.12
6	GMO	180±0.18

*mean ±standard deviation (SD), n=3

Table 6 Solubility studies of carbamazepine drug in various solvents

S. No	Solvents	Solubility (mg/ml) *
1	Ethanol	77.76 ±1.46
2	0.1N HCL	76.30± 1.75
3	Methanol	98.02 ±1.35
4	Chloroform	66.8 ± 1.41
5	Distilled water	29.76 ±2.23

*mean ±standard deviation (SD), n=3

The particle size range of all formulations are within the nano-meter range. The particle size was found to be in the range of 165 – 362nm and PDI was found to be in the range of 0.234 – 0.687. The results are shown in table 7.

The zetapotential results 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 (CF2) was observed to be better stable than other formulations. The results are shown in table 7. 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. The entrapment efficiency for all batches varied between 60% and 85%. The CF2 formulation demonstrated the highest entrapped efficiency. The pH levels of the formulated carbamazepine cubosomes ranged from 6.92 to 7.08, falling within the physiologically acceptable range for topical products.

CF2 formulation exhibited maximum entrapment efficiency and the results are shown in table 7. CF2 has the greater content of drug in it 98.95±0.04 and it is suitable for further studies. The results are shown in table 7. 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. Sustained drug delivery of the drug was provided since it produced a maximum of 45.81% of release at the end of 24 hours. High entrapment of the lipophilic drug in the lipid matrix attributed to the sustained release. CF2 achieved the highest release and it is considered for further studies. The resulted formulation code CF-2 was considered as the optimized formulation. The average vesicle size of optimized formulation (CF2) observed as 225 nm, zeta potential observed as -29.6mV and %EE was found as 85%.

Table.7 Evaluation of Cubosomal Dispersion formulations

Formulations	Size(nm) *	PDI*	Zeta Potential (-mV) *	Drug content (%) *	Entrapment Efficiency (%) *	pH*
CF1	**276±0.12**	**0.482±0.01**	**-28.3±0.18**	**96.05±0.04**	**82±0.81**	**6.98±0.02**
CF2	**225.1±0.23**	**0.390±0.02**	**-29.6±0.21**	**98.95±0.04**	**85±0.67**	**7.02±0.01**
CF3	**221.6±0.35**	**0.312±0.04**	**-26±0.32**	**97.65±0.06**	**83±0.79**	**6.92±0.01**
CF4	**357±0.54**	**0.600±0.02**	**-23±0.14**	**97.50±0.05**	**82±0.74**	**7.01±0.01**
CF5	**327.3±0.24**	**0.322±0.06**	**-24±0.12**	**96.37±0.07**	**73±0.68**	**7.06±0.02**
CF6	**319.3±0.42**	**0.366±0.01**	**-26±0.16**	**94.13±0.09**	**69± 0.45**	**6.98±0.01**
CF7	**217.3±0.53**	**0.687±0.01**	**-27±0.13**	**90.78±0.08**	**71±0.64**	**7.01±0.01**
CF8	**280.2±0.64**	**0.234±0.04**	**-24.9±0.18**	**89.10±0.09**	**67± 0.73**	**7.04±0.01**
CF9	**190.6±0.61**	**0.446±0.01**	**-24±0.14**	**90.35±0.09**	**65± 0.81**	**7.02±0.02**
CF10	**165.5±0.19**	**0.288±0.02**	**-23±0.12**	**88.69±0.07**	**70± 0.67**	**6.98±0.01**

*mean ±standard deviation (SD), n=3

Table 8 *In-vitro* Drug release studies of cubosomal dispersion formulations

Time(hr)	%CDR*									
	CF1	**CF2**	**CF3**	**CF4**	**CF5**	**CF6**	**CF7**	**CF8**	**CF9**	**CF10**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	**12.32±0.12**	**12.21±0.13**	**12.8±0.14**	**14.78±0.24**	**11.3±0.18**	**15.3±0.23**	**13.31±0.21**	**10.52±0.19**	**16.8±0.21**	**15.41±0.26**
2	**29.7±0.15**	**22.12±0.12**	**25.85±0.15**	**30.98±0.21**	**29.1±0.21**	**31.78±0.21**	**24.8±0.22**	**22.8±0.16**	**23.12±0.23**	**25.82±0.25**
4	**38.9±0.17**	**35.8±0.17**	**37.2±0.12**	**43.8±0.23**	**45.8±0.23**	**50.31±0.19**	**37.45±0.19**	**41.87±0.23**	**39.82±0.21**	**38.78±0.21**
6	**49.8±0.13**	**40.61±0.11**	**48.8±0.12**	**50.2±0.27**	**63.8±0.19**	**62.81±0.20**	**48.12±0.26**	**59.98±0.26**	**51.8±0.19**	**55.31±0.23**
8	**60.4±0.14**	**46.8±0.14**	**53.7±0.13**	**59.3±0.25**	**70.18±0.25**	**77.8±0.21**	**63.87±0.21**	**75.81±0.21**	**68.2±0.21**	**65.8±0.24**
12	**64.12±0.15**	**54.31±0.13**	**58.38±0.10**	**65.4±0.21**	**78.8±0.26**	**85.81±0.26**	**81.17±0.27**	**81.17±0.25**	**88.4±0.23**	**81.45±0.22**
24	**68.31±0.11**	**59.45±0.12**	**63.7±0.24**	**69.12±0.19**	**86.3±0.24**	**87.4±0.23**	**85.31±0.19**	**89.1±0.22**	**93.12±0.27**	**87.1±0.18**

*mean ±standard deviation (SD), n=3

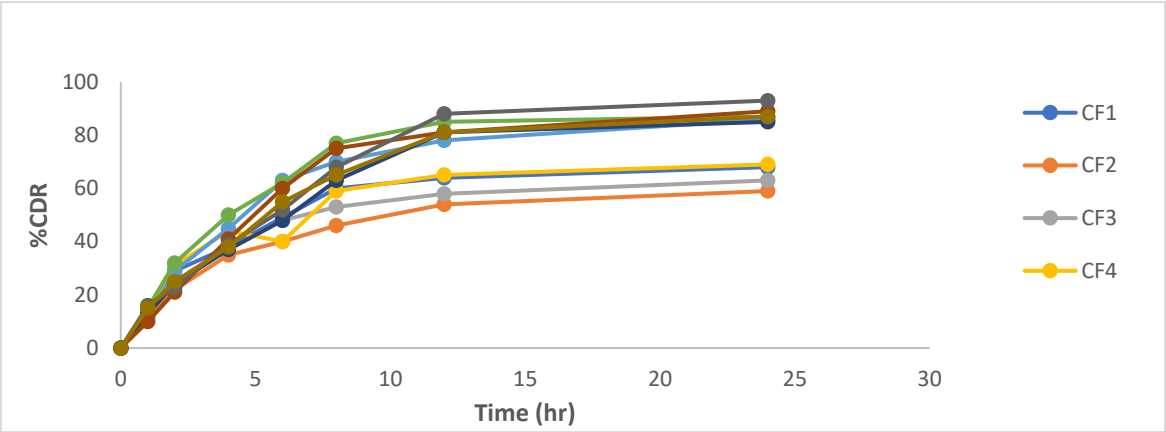

Fig.6 *In-vitro* release studies of cubosomal dispersion formulations

Evaluation of Cubosomal Transdermal patches

Physical appearance: Cubosomal transdermal patch white in colour, smooth and flexible.

Thickness uniformity: A measuring calipers 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 0.08mm.

Folding endurance: By measuring the formulated patch by folding reveals that it has the ability of 220 times to withstand folding without breaking or visible damage of cracks. The results indicate satisfactory good strength and flexibility.

Folding endurance = 385.

Drug content: Drug content was calculated as 94 % 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 48.95% 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 10 and the graph is shown in fig.

Kinetic study: The Zero Order kinetic plots were found to be fairly linear as indicated by their highest regression values (0.9901) for patch. This value indicates that the release was based on diffusion mechanism.

Table 9 Evaluation of Cubosomal Transdermal Patch Formulations

Patch formulations	weight (mg)*	Thickness (mm)*	Folding endurance*
F1	0.091±0.001	1.3±0.011	370±0.2
F2	0.089±0.002	1.4±0.023	392±0.4
F3	0.087±0.002	1.5±0.013	390±0.2
F4	0.084±0.001	1.4±0.014	387±0.6

*mean ±standard deviation (SD), n=3

Table 10 *In-vitro* Drug release studies of Cubosomal Transdermal Patch Formulations

Time(hr)	% CDR			
	F1	F2	F3	F4
0	0	0	0	0
1	13.42±0.1	11.21±0.2	11.8±0.3	15.3±0.2
2	22.72±0.2	16.12±0.3	21.12±0.4	21.78±0.3
4	38.49±0.2	24.62±0.4	29.82±0.2	28.31±0.2
6	45.18±0.3	32.31±0.2	36.28±0.4	35.2±0.1
8	54.14±0.3	40.18±0.3	43.81±0.2	43.3±0.2
12	61.12±0.4	45.35±0.4	49.28±0.2	48.4±0.3
24	65.31±0.2	48.95±0.2	56.41±0.4	60.12±0.4

*mean ±standard deviation (SD), n=3

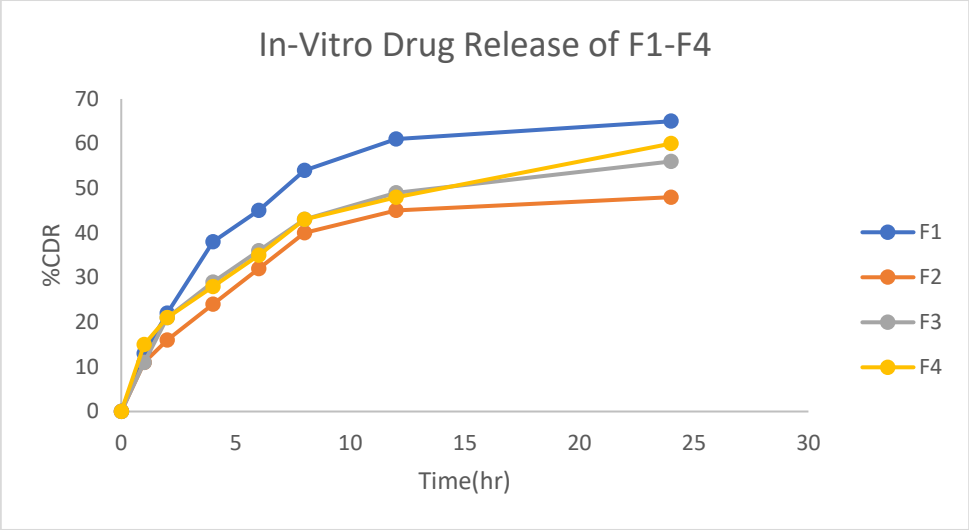

Fig.7 *In-vitro* Drug Release of F1-F4

Drug Release kinetic study of formulations (F1 to F4) was studied for different kinetic equations (zero order, first order, Higuchi, and Korsemeyer-Peppas equation). Optimized formulation indicates that R^2 values for the formulations F2 were found to be high for the zero order and higuchi model.

Table.11 Drug release kinetics of optimized formulation F2

TIME	%CDR	Log % CDR	SQRT	Log T	DR	LOG %DR
0	0	0	0	0	100	2
1	11.21	1.049605613	1	0	88.79	1.948364056
2	16.12	1.207365037	1.414213562	0.301029996	83.88	1.923658422
4	24.62	1.391288049	2	0.602059991	75.38	1.877256133
6	32.31	1.509336958	2.449489743	0.77815125	67.69	1.830524514
8	40.18	1.604009932	2.828427125	0.903089987	59.82	1.776846409
12	55.35	1.743117625	3.464101615	1.079181246	44.65	1.649821463
24	98.95	1.995415799	4.898979486	1.380211242	1.05	0.021189299

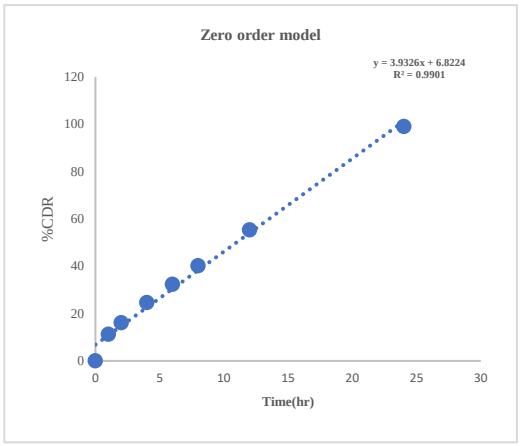

Fig.8 Zero order kinetics (F2)

Fig.9 First order kinetics (F2)

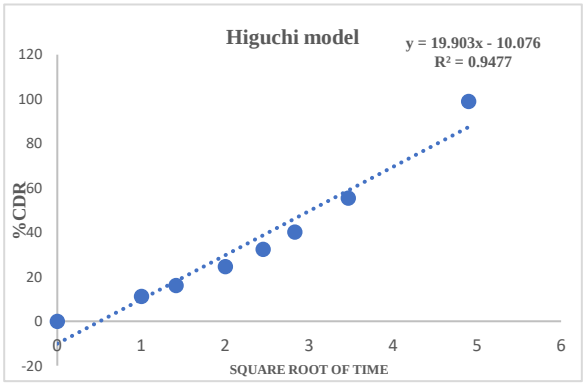

Fig.10 Higuchi Model

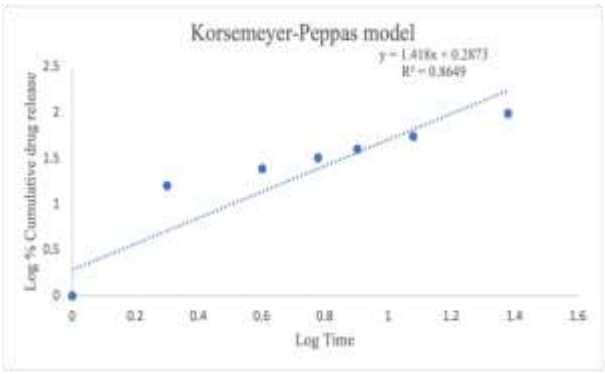

Fig.11 Korsemeyer-Peppas Model

Table.12 R-Square values of different models

Parameter	Zero order	First order	Higuchi	Korsemeyer- peppas
Regression values (R^2)	0.9901	0.8764	0.9477	0.8649
Slope	3.9326	0.0782	19.909	1.418
Intercept	6.8224	2.1857	10.076	0.2873

Table.13 Stability Studies of Optimized Cubosomal Formulation f2 for 1,2,3 months at temperatures 4℃ and 25℃ respectively

Characteristic	Time (months)					
	1 month		2 months		3 months	
Temperature(ºC) *	4.0 ±0.2℃	25 ± 2℃	4.0 ±0.2℃	25± 2℃	4.0 ±0.2℃	25 ± 2℃
Average vesicle size (nm) *	222±0.1	221±0.2	222.8±0.1	221.3±0.2	222.4±0.2	221.1±0.1
% EE*	82±0.21	85.3±0.54	80.1±0.26	85.1±0.36	79.12±0.42	85±0.52
Drug content (%) *	98.95±0.52	98.9±0.42	90.12±0.26	98.01±0.28	88.7±0.32	98±0.26

*mean ±standard deviation (SD), n=3

Table.14 Stability Studies of optimized cubosomal patch for 1,2,3 months at temperatures 25℃

S. No.	Parameters	Initial	1 month	2 months	3 months
1	**Average weight(mg)** *	170.02±0.42	169.89±0.25	169.85±0.62	169.79±0.12
2	**Thickness(mm)** *	0.84±0.01	0.82±0.03	0.82±0.04	0.80±0.03
3	***Invitro* Drug Release (%CDR)** *	48.95± 0.2	48.79±0.24	47.13±0.12	46.98±0.52

*mean ±standard deviation (SD), n=3

CONCLUSION:

The aforementioned research findings indicate that the utilization of cubosomal formulations led to enhanced solubility and permeability of the drug carbamazepine. Given the inherent challenges associated with the drug's low solubility and permeability, the adoption of cubosomes proved to be a successful strategy, significantly augmenting the drug's solubility and permeability. Among the formulations tested, CF2 emerged as the optimal preparation based on criteria such as particle size, polydispersity index, entrapment efficacy, drug content, zeta potential, and *in-vitro* release study. Consequently, CF2 was selected for the development of transdermal patches.

The transdermal patches formulated with the optimized composition demonstrated comparable efficacy to cubosomes and exhibited superior performance compared to cubosomal dispersion. This suggests that administering carbamazepine in the form of a cubosomal patch enhances its therapeutic effectiveness in the treatment of epilepsy. Future research endeavors may involve conducting further in vivo investigations to gain a more comprehensive understanding of the formulations and their associated properties.

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