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Development and Evaluation of Nanoemulsion of Carbamazepine for Intranasal Delivery

Madhavi Dwikuntla, Swathi Jakku, Anil Goud Kandhula, Krishnaveni Janapareddi*

Department of Pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana, India-506009

ABSTRACT

Carbamazepine is the drug used in the treatment of epilepsy. It exhibits low oral bioavailability because of first pass metabolism. In this present work, nano emulsion of Carbamazepine was developed for intra nasal administration and its pharmacodynamic activity was assessed. The phase titration method was used to create nano emulsions. The composition of the optimized formulation was oleic acid 10% as an oil phase, 65% of Smix, consisting of transcuto P and propylene glycol in 1:2 ratio, 24% of aqueous phase, and 1% of sodium deoxycholate as a permeation enhancer. The optimized formulation showed mean globule size of 109 ± 2.8 nm, PDI 0.234 ± 0.10 , zeta potential -25.6 ± 1.3 mV and drug content 98.4 ± 0.18 %. Ex vivo permeation studies on porcine nasal mucosa were carried out for nano emulsions and drug solution. The formulation containing sodium deoxycholate as permeation enhancer and formulation without permeation enhancer demonstrated significantly high permeability coefficient ($P < 0.0001$) when compared to drug solution. Antiepileptic activity was studied in male wister rats for optimized nano emulsions via nasal route compared with sterile drug solution administered by intravenous route. The optimized intranasal formulation demonstrated significantly higher activity in which all rats survived whereas only 50% rats survived in drug solution group given by I.V route.

Keywords: Nano emulsion, Intranasal delivery, Brain targeting, Epilepsy, Carbamazepine

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*Corresponding Author:

Dr. Krishnaveni Janapareddi

Associate Professor

University College of Pharmaceutical Sciences,

Warangal-506009, Telangana, India.

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1. Introduction

Epilepsy is a neurological disorder in which nerve cell activity in the brain becomes abnormal. Epilepsy is usually treated by medication and in some cases by surgery, devices, or dietary changes. Nasal route has been considered as a potential route to achieve faster and higher level of drug absorption. Nasal mucosa is permeable to many compounds due to rich vasculature and reaches CNS via olfactory and trigeminal nerve pathways. The nasal route circumvents hepatic first pass metabolism and degradation of drug associated with the oral drug delivery. Nano emulsions are a colloidal particulate system in the

submicron size globules act as carriers of drug molecules. Their size varies from 10 to 150 nm. It is a thermodynamically stable system due to the presence of high proportion of emulsifying agent. Marketed formulations of Carbamazepine are available as tablets and injection dosage forms. Major limitation of Carbamazepine tablets was delayed onset of action with higher latent period, in sufficient uptake in the brain leading to poor therapeutic benefit to patients. An intravenous access is not practical in an emergency situation when the patient is not in a hospital. There is need to develop alternative delivery

strategies of antiepileptic drug to localize drug in brain rapidly bypassing BBB[1]. Nasal administration of antiepileptic drugs in seizure emergencies by the surrounding people could dramatically improve patient condition before hospitalization. Several dosage forms have been used for intranasal delivery such as liquids, powders, gels, and suspensions[2]. Researchers investigated several methods for the enhancement of drug permeation through the nasal mucosa such as use of mucoadhesive polymers and absorption enhancers to prolong the contact time of drugs with the nasal mucosa [3].

2. Materials and Methods

Materials

Oleic acid, Polyethyleneglycol-400, Propylene glycol, Disodium hydrogen orthophosphate, Sodium hydroxide, Potassium dihydrogen orthophosphate were purchased from SD fine chem. Ltd. (Mumbai, India), Transcutol-P, Labra sol, Lauro glycol 90 were purchased from Gattefosse, France (Colorcon, Mumbai), Sodium deoxy cholate was purchased from Sigma Aldrich[4].

Methods

Calibration curves of Carbamazepine

Carbamazepine was accurately weighed and dissolved in phosphate buffer saline of pH 6.4 to obtain stock solution (1 mg/mL). Different concentrations (1 to 100µg/mL) of Carbamazepine were prepared from stock solution on dilution. The absorbance of the samples was measured at 288 nm and calibration curve of Carbamazepine was plotted.

Solubility Study

The solubility of Carbamazepine in various oils, surfactants, and co-surfactants was determined. About 2ml of each of the selected vehicle was taken in glass vial to which Carbamazepine was added in excess and mixed using a Cyclomixer to facilitate uniform dispersion. Then, the mixture was agitated in a gyratory shaker at room temperature for 24 hrs. After reaching equilibrium, samples were collected and centrifuged at 4000rpm for 10minutes. The supernatant was filtered through 0.45 µm filter and quantified by UV method after suitable dilution.

Construction of Pseudo Ternary phase diagram

Pseudo ternary phase diagrams were constructed between oil, Smix and water. The weight ratios of surfactant to co-surfactant was varied as 1:1, 2:1, 3:1, 1:2 and 1:3. The weight ratios of oil with surfactant mixture (Smix) were varied as 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1 and 9:1. To the oil and Smix mixture, small amounts of water were added drop wise. Following each addition, the mixture in test tubes was vortexed for 2 min. The point at which the mixture becomes turbid was considered as the end point of titration and the water quantity was noted. Phase diagrams were constructed using CHEMIX software version 7.00. The ratio of surfactant and co-surfactant mixture (Smix), at which maximum microemulsions region was obtained was selected for the preparation of nanoemulsion (5).

Preparation of Nanoemulsion (phase titration method):

A series of nano emulsions were prepared by varying proportions of oil (5-10%w/w), Smix (55-70%w/w), and water (25-40%) by water titration method. Drug was

dissolved in Oil, surfactant, and co-surfactant mixture by vertex mixing. Water was added to the homogeneous mixture and vortexed until a clear solution was obtained (6).

Characterization of Nanoemulsion

Phase separation and stability study of nano emulsion

100µL of nano emulsion formulation was added to a test tube and made up to 5ml with double distilled water and vortexed for 1 minute. The test tube was kept a side for 48 hours and observed for phase separation and precipitation of the drug, if any.

Globule size analysis

Formulation was diluted to 50 times using double distilled water and contents were mixed gently. The resultant nano emulsion was subjected to droplet size analysis. The size of globule was measured at 90° angle and at 25°C by Zetasizer (Nano ZS 90, Malvern).

Effect of dilution on droplet size

To evaluate the effect of dilution on droplet size, the formulations were subjected to different dilutions (1:100, 1:500 and 1:1000) and size of globule was measured.

Drug content determination

About 1 gram of the formulation (containing 10mg of Carbamazepine) was diluted to 10ml with methanol to produce 1mg/ml. Drug content was estimated after suitable dilutions with methanol using UV-Visible Spectrophotometer at 288 nm.

Entrapment efficiency

The formulation was taken in a dialysis sac and dialyzed against phosphate buffer of pH 6.4 at room temperature. The samples were withdrawn from the medium for 24 hrs at different intervals and analyzed for drug content using UV spectroscopy at λ_{max} of 288nm. The percentage of drug entrapped is calculated by using the following formula.

Percent Entrapment = $\frac{\text{total drug} - \text{free drug}}{\text{total drug}} \times 100$

In-vitro drug permeation study of nanoemulsions

In-vitro drug permeation studies were conducted using Franz diffusion cells. Initially, the dialysis membrane [DM 70, molecular weight cut off 12000-14000, Hi-media, Mumbai] was hydrated by soaking in distilled water for overnight at room temperature. It was placed on the receptor compartment of diffusion cell. Nanoemulsion formulation equivalent to 10mg of Carbamazepine was placed in donor compartment. Aliquots of samples were withdrawn from the receptor compartment at predetermined time intervals (0.25, 0.5, 1, 2, 3, 4, 5, 6 and 8hrs) and replaced with fresh medium. The samples were analyzed for drug content by UV method (7).

Ex-vivo permeation studies

Isolation of porcine nasal mucosa

On the day of experiment, the freshly excised nose of porcine was obtained from local slaughterhouse. The nasal mucosal membrane was identified, separated from the nasal cavity, and made free from adhered tissues. The specimens of nasal mucosa were dissected within 1 hour from the animal death and used immediately after isolation (8).

Ex-vivo permeation studies of nanoemulsion

The isolated porcine nasal mucosa was placed in Krebs ringer solution till the start of the experiment. The mucosa

was mounted between the donor and receptor compartments of a diffusion cell, with the mucosal side facing the donor compartment. Formulation was placed in donor compartment and phosphate buffer saline of pH 6.4 was placed in receiver compartment. Study was carried out at room temperature. Aliquots of samples were withdrawn from the receptor compartment at predetermined time intervals (0.25, 0.5, 1, 2, 3, 4, 5, 6 and 8hrs) and replaced with fresh medium. The samples were analyzed for drug release by UV method.

Steady state flux through nasal mucosa was calculated by plotting graph between the cumulative amount permeated through the porcine mucosa against time. The slope of the linear portion of the curve was determined by regression (9).

$$J_{ss} = m/A$$

Where,

J_{ss} = Steady state flux ($\mu\text{g}/\text{cm}^2/\text{hr}$) i. e, amount permeated per unit area and time at steady state

m = slope at steady state

A = surface area of diffusion cell

Physical stability (freeze-thawing)

Freeze thawing was employed to evaluate the physical stability of formulation. The formulations in Eppendorf tube was subjected to 5 freeze-thaw cycles, which include freezing at -20°C for 24 hours followed by thawing at 40°C for 24 hours. After completion of 5 freeze-thaw cycles, centrifugation was performed at 3000rpm for 5 minutes. The formulations were then observed for phase separation and precipitation of drug.

Differential Scanning Calorimetry (DSC)

Differential scanning Calorimetry (DSC) experiment was carried out to find out the purity of drug. About 15mg of drug was taken in the pierced DSC aluminum pan and crimped, scanned in the temperature range of 50 – 200°C . The heating rate was $10^\circ\text{C}/\text{min}$. Nitrogen served as purged gas. Empty aluminum pan was used as reference cell.

In vivo studies

The studies were conducted with prior approval of Institutional Animal Ethical Committee (IAEC/06/UCPSC / KU/ 2019) (10). Healthy male Wister rats weighing between 200 to 250 gms were used for assessment of antiepileptic activity by electric shock method. The rat was subjected to shock using 150 mA current for a period of 0.2 seconds to induce convulsion.

Animals

The animals are divided into four groups, each group containing 6 rats. Group-I was control (untreated), Group-II & III were treated with optimized nano emulsion and nano emulsion with permeation enhancer respectively by intranasal route and group-IV received sterile drug solution through tail vein. The carbamazepine dose was 2mg/kg for both intranasal and i.v routes (11).

Study design

The rats were anesthetized for a brief period of 3-4 minutes using chamber saturated with vapors of diethyl ether. The intranasal administration was carried out using rat nasal catheter of Impel Neuro Pharma (fig 1). The catheter tube is attached to the Hamilton syringe, which is loaded and pushed when ready for dosing. Carbamazepine was

administered at a dose of 2mg/kg to all groups except control. Five minutes after treatments, rats were subjected to electric shock using 150 mA current for a period of 0.2 seconds to induce convulsions and the duration of different phases, time for recovery were recorded. The duration of phases in treated groups was compared with placebo treated (control) group (12).

3. Results and Discussion

Solubility

The solubility of Carbamazepine in oils, surfactants, and co-surfactants at 37°C and the results were given in figure 2. The solubility of carbamazepine was high in transcutool p, oleic acid, PEG 400, propylene glycol (13).

Pseudo ternary phase diagrams

Pseudo-ternary phase diagrams were plotted at different ratios of surfactant (Transcutol P) co-surfactant (propylene glycol) shown in figure 3. Smix, at 1:2 ratio of Transcutol P and propylene glycol showed maximum nano emulsion region. (14).

Preparation of Nanoemulsion

Nano emulsions were prepared by phase titration method using transcutool P as surfactant, propylene glycol as co-surfactant in 1:2 ratio and oleic acid as oil. The compositions were given in the table 1.

Characterization of Nanoemulsion

Droplet size, poly dispersity index and zeta potential

The mean globule size, PDI and zeta potential of the transparent nano emulsions were determined, and the results were shown in table 2. The nano emulsions F5, F7, F8 showed globule sizes below 170 nm, were selected for further evaluation (15).

Phase separation and stability study of nano emulsion

Selected formulations (F5, F7 and F8) were observed for physical stability for 48 hrs. They were stable showing no phase separation or precipitation of the drug, retaining the mean globule size.

Determination of drug content and Entrapment efficiency

The drug content and entrapment efficiency of selected formulations were given in table 2. Drug content of all formulations was found to be between 92-98% and entrapment efficiency was found to be between 90-98%.

Stability of nano emulsion upon dilution

The selected formulations were subjected to different, and the mean droplet size and results were given in table 3. Upon dilution of 1000 times, size increased by 8-15% for all formulations.

Ex-vivo permeation studies and steady state flux of nano emulsions:

The Ex-vivo permeation studies were conducted on porcine nasal mucosa using Franz diffusion cell in order to determine the steady state flux of nano emulsion formulation. Ex-vivo permeation profiles of Carbamazepine formulations with permeation enhancer sodium deoxy cholate (F7S and F8S) and without permeation enhancer (F5, F7, F8 and Drug solution) were studied shown in fig.4 and steady state flux values in table 2 (16). Ex-vivo permeation studies revealed that all mentioned nano emulsion formulations showed significantly high steady state flux $P < 0.0001$ compared to drug solution (69.8

$\mu\text{g}/\text{cm}^2/\text{hr}$). F8 formulation showed high steady state flux ($P<0.0001$) ($324 \mu\text{g}/\text{cm}^2/\text{hr}$) than the F7 ($207 \mu\text{g}/\text{cm}^2/\text{hr}$) and F5 ($159 \mu\text{g}/\text{cm}^2/\text{hr}$). To improve the permeation of drug through the nasal mucosa sodium deoxy cholate (SDC) was employed as permeation enhancer in formulations F7S and F8S. Formulations with sodium deoxy cholate (F7S and F8S) showed 8% higher permeation than formulations without sodium deoxycholate (F7 and F8).

Pharmacodynamic activity of Carbamazepine

Maximal electro shock seizure induced convulsions were divided into five phases they are phase of tonic limb flexion, Tonic limb extension, Clonic convulsions, Stupor and Recovery or death. Immediately after tonic flexion, tonic phase (Extension phase) characterized by maximal extension of anterior and posterior legs could be observed. At the end of tonic phase, clonic phase characterized by paddling movement of the hind limb and shaking of body will be seen. During stupor phase which was observed after tonic and clonic phases rat remains silent without any movement. Abolition or decrease in the duration extension phase could be taken as an index of antiepileptic activity.

The duration of these phases was recorded. The F8S treated groups showed low intensity seizures of shorter duration and rapid recovery from seizures compared to rats treated with F8 and Carbamazepine solution (I.V). The duration of phases in treated groups was compared with placebo treated (control) and results were given in the table 3 (17). Carbamazepine formulation with SDC (F8S) showed reduction in Extension phase, 58.4% reduction in recovery time and all animals are alive when compared to control.

It was observed that F8S showed significantly high percentage reduction in recovery time at significantly $P<0.0001$ compared to drug solution group (i.v) and $P<0.5$ compared to F8. All six animals survived in nano emulsion (intra nasal) treated group. Whereas drug solution treated via i.v route 50% survived after 24hrs. Untreated control group rats died immediately after shock. The formulation F8S showed significantly high percentage reduction in recovery time $P<0.0001$ in comparison with drug solution(18).

Table.1. Compositions of Nano emulsions

Formulation code	Oliec acid(%w/w)	Smix (%w/w) Propylene glycol: transcutol p (1:2)	Aqueous phase(%w/w)	Visual observation
F1	5	50	45	Turbid
F2	10	52.5	37.5	Turbid
F3	10	55	35	Turbid
F4	5	60	35	Turbid
F5	5	65	15	Transparent
F6	7.5	65	27.5	Transparent
F7	5	62.5	33.5	Transparent
F8	10	65	25	Transparent
F9	5	65	30	Turbid
F10	4.5	60.5	35	Turbid
Formulations with 1% Sodium deoxy cholate as permeation enhancer				
F7S	5	62.5	33.5	Transparent
F8S	10	65	25	Transparent

Table.2. Globule size, PDI, Zeta potential, Drug content Efficiency and Entrapment Efficiency

Formulation code	Globule size (nm)	PDI $\pm$	Zeta potential (mV)	Drug content(%)	Entrapment Efficiency (%)	Steady state flux, Jss ($\mu\text{g}/\text{cm}^2/\text{hr}$)
F5	145 $\pm$ 0.31	0.223 $\pm$ 0.98	-33.6 $\pm$ 0.65	94 $\pm$ 0.5	99.3 $\pm$ 0.56	159.52 $\pm$ 0.5
F7	162 $\pm$ 0.34	0.180 $\pm$ 0.65	-33.1 $\pm$ 0.67	90.65 $\pm$ 0.25	99.46 $\pm$ 0.43	207 $\pm$ 0.14
F8	109 $\pm$ 0.26	0.234 $\pm$ 0.56	-25.6 $\pm$ 0.98	98.4 $\pm$ 0.18	99.34 $\pm$ 0.23	324 $\pm$ 0.21
F7S	165 $\pm$ 0.17	0.201 $\pm$ 0.45	-28.1 $\pm$ 0.34	92.03 $\pm$ 0.58	98.32 $\pm$ 0.45	345.5 $\pm$ 0.21
F8S	110 $\pm$ 0.16	0.223 $\pm$ 0.65	-22.4 $\pm$ 0.64	97.9 $\pm$ 0.92	99.29 $\pm$ 0.76	385 $\pm$ 0.5

Table.3: Ex-vivo permeation studies of Nano Emulsion

Time (Hrs)	Drug permeation (%) of Formulations			Drug permeation of formulations with permeation enhancer (SDC)		Drug solution
	F5	F7	F8	F7S	F8S	
0.25	7.75 $\pm$ 4.2	6.2 $\pm$ 4.3	6.00 $\pm$ 8.6	6.1	7.05 $\pm$ 4.9	10.72 $\pm$ 2.13
0.5	10.4 $\pm$ 2.3	12.24 $\pm$ 9.2	11.2 $\pm$ 5.6	13.02 $\pm$ 2.69	21.5 $\pm$ 1.9	17.4 $\pm$ 1.45
1	12.2 $\pm$ 1.9	20.35 $\pm$ 4.7	15.2 $\pm$ 4.3	20.42 $\pm$ 7.36	39.05 $\pm$ 5.8	18.3 $\pm$ 2.05

2	13.1±4.2	23.24±5.23	16.9±7.26	25.52±4.28	48.15±6.15	19.16±2.06
3	19.2±8.2	28.4±14.05	41.6±9.21	30.52±5.98	55.84±7.43	19.2±1.23
4	24.0±7.9	30.5±12.3	50.3±11.23	33.18±10.9	65.05±2.8	20.9±5.12
5	25.4±5.1	32.61±5.3	60.7±10	39.56±8.8	77.02±9.4	21.43±4.3
6	31.9±1.3	39.03±4.2	76±8.2	45.63±7.45	84.24±10.2	23.18±5.2
8	41.63±4.6	48.52±8.12	86.52±5.1***	56.74±3.69**	94.2±0.9****	26.04±15.06*

Note: ****p<0.0001; ***p<0.001; **p<0.01 statistically significant to drug solution.

Table.4. Antiepileptic activity of Carbamazepine by MES method, Duration of different phases and reduction at recovery time

Group No.	Treatment	Flexion (sec)	Extension (sec)	Convulsion (sec)	Stupor (sec)	Duration of seizure (sec)	% Mortality	Reduction in recovery time %
I	Control	6.2±1.05	9.82±0.62	13.92±2.12	283.85±8.01	313±22.95	100	
II	F8S (Intra nasal)	1.02±0.82	3.25±0.21 (66%)	6.09±0.8	120.77±2.6	130.43±12.3	0	58.4
III	F8 (Intra nasal)	1.42±0.42	4.2±0.62 (57%)	7.16±0.75	140.±10.57	152.78±1.03	0	51.43

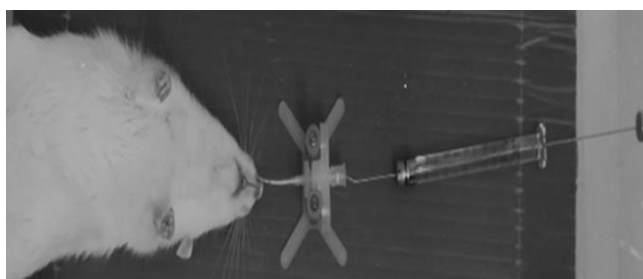


Fig.1. Rat nasal catheter of Impel Neuro Pharma

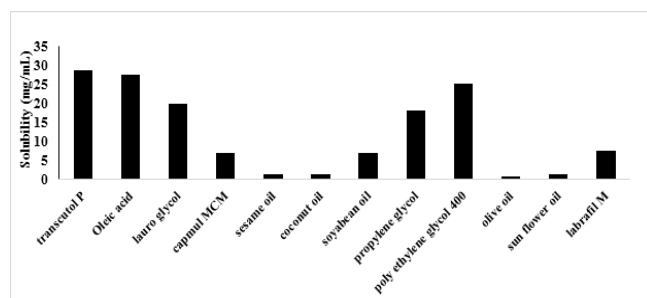


Fig.2. Solubility of Carbamazepine in oils, surfactants, and co-surfactants

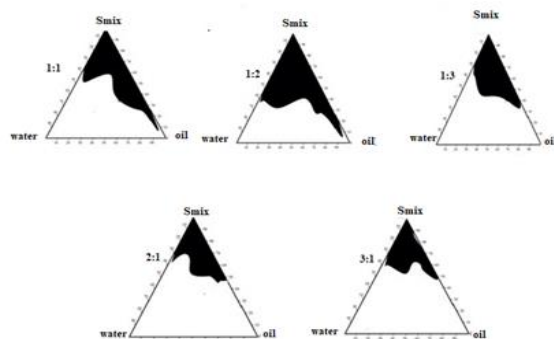


Fig.3. Pseudo-ternary phase diagrams of micro emulsions composed of oil (Oleic acid), surfactant mixture (Smix; propylene glycol: Transcutol P) and water. Shaded area represents the microemulsion region.

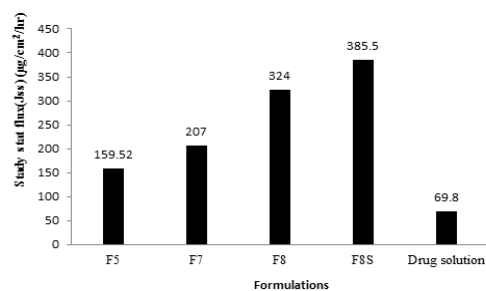


Fig.4. Steady state flux of formulation

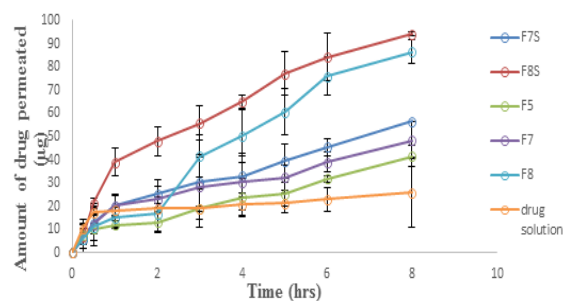


Fig.5. Ex-vivo permeation profiles

4. Conclusion

Carbamazepine has low bioavailability because of first pass metabolism. In the present study, nanoemulsion of Carbamazepine were developed for brain targeting via intra nasal route and evaluated for pharmacodynamic activity. The optimized nano emulsion (F8s) of carbamazepine showed significantly high steady state flux in exvivo permeation studies and showed significantly high anti-epileptic activity in male wister rats compared to I.V route.

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