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FORMULATION AND EVALUATION OF THERMALLY TRIGGERED MUCOADHESIVE IN SITU GEL OF TOPIRAMATE: β-CYCLODEXTRIN COMPLEX FOR NASAL DELIVERY

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ABSTRACT:

Nasal pathway achieved faster and greater level of drug absorption due to more surface area, the preventing of first pass metabolism and readily accessibility. Topiramate is a widely useful for the treatment of epilepsy. It is useful for various types of partial-onset and generalized-onset seizures, and is therefore considered a broad-spectrum agent. The aim of present research work was to increase the solubility of Topiramate by making its inclusion complex with β-cyclodextrin (β-CD) complex and to develop its thermally triggered mucoadhesive in situ gel (TTISG) as to overcome first-pass effect and consequently enhance its bioavailability. Formulation optimized by using central composite model total 18 formulations were obtained. The optimized formulation (F15) with a gelation temperature 29°C, gelation time 13 Second and drug release up to 90% after 5 hrs. As compared to marketed formulation it enhanced the bioavailability and as per the need of time is need to go for the further preclinical study to get the better exposure for the current research.

Keywords: Topiramate, in situ gel, Mucoadhesive, Inclusion Complex

INTRODUCTION:

Nasal drug delivery system is used for the treatment of local diseases, such as rhinitis and nasal congestion. Avoid drug degradation in the gastrointestinal tract,Avoid hepatic first-pass metabolism and rapid onset of action can be achieved.The bioavailabilty of larger drug molecules can be enhanced by means of absorption enhancer,The nasal bioavailability for smaller drug molecules is excellent,Drugs that are orally not absorbed can be transported to the systemic circulation by nasal drug delivery,Improved bioavailabilty. Mucoadhesion includes incorporation of adhesive molecules into certain kind of pharmaceutical dosage form planned to remain in close contact with the absorption tissue, releasing drug the drug near to the action site, thereby increasing its bioavailability and encouraging local or systemic effects. A nasal mucoadhesive in situ gel is liquid like before nasal administration and go through gelation upon contact with nasal mucosa is conferred via the use of Thermoreversible polymers.

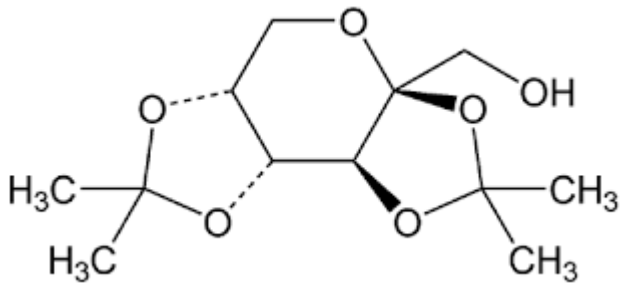


Fig. 1 Chemical structure of TPM API

Topiramate is antiepileptic drug used for the treatment of epilepsy. Half life is 19-23 hours. In patients with normal creatinine clearance, steady state concentration are reached within 4 days. The bioavailability of topiramate is about 80%[(1)].

As per the literature survey various researchers mostly focus on topiramate sustained release tablet[(3)], topiramate capsules[(4)], topiramate nanoemulsion[(5)], topiramate nanoparticles[(6)], topiramate transdermal patches[(7)] they have limitations are still do not achieve the particular bioavailability for the treatment of epilepsy. So, aim of present study to enhanced the bioavailability and to prevent first pass metabolism in the present work formulate thermally triggered mucoadhesive in situ nasal gel of topiramate with β-cyclodextrin complex by using 2^3 level central composite design.

MATERIALS AND METHODS

Materials

Topiramate was obtained as gift sample from Cipla Pharmaceutical, Kurkumbh, Pune. Poloxamer 407, Carbopol 934, Benzalkonium chloride were purchased from Analab fine chemicals, Mumbai. All solvents and chemicals used in this study were of analytical grade.

Preformulation Studies

Organoleptic Properties TPM:

The organoleptic properties such as appearance, color, odor of drug were evaluated by visual examination.

Determination of Melting Point:

Melting point of topiramate was determined by using capillary method.

Solubility Study:

The solubility of the drug was performed by placing of a drug in the conical flask by use of different solvents, which was then placed in a rotary shaker and was continuously shaken for 24 hours. After it is analysed the final drug.

FT-IR Spectroscopic Determination:

The Required quantity of drug was taken and mixed with potassium bromide and spectrum was recorded.

Calibration Curve of Topiramate:

10mg of drug was dissolved in 25ml of methanol and then volume made up to 100 ml with distilled water to get concentration100µg/ml. Stock solution was diluted further to get concentration range between 1µg/ml to 5µg/ml and absorbance was measured at 249nm. The standard calibration curve plotted of absorbance Vs Concentrations.

Drug Polymer Compatibility Study:

A compatibility study was carried out with potential formulation drug and polymer. API and polymer were mixed in specific quantity and placed in sealed vials for 3 months at 40°C ± 2°/75%±5% RH and 25°C±2°C/75%±5% RH. The samples withdrawal from specific time period & used for physical examination as well as FTIR.

PREPARATION OF SOLID INCLUSION COMPLEX OF TOPIRAMATE AND β-CYCLODEXTRIN

The solid inclusion complex of Topiramate and β-cyclodextrin was prepared by kneading method. B-cyclodextrin was impregnated with adequate amount of ethanol (95%v/v) to convert it into a paste. Topiramate was then added to the above paste and kneaded throughly with a pestle for 15min, and dried at 50°C for 24 h. The resultant dry solid mass was powdered and passed through a 60-mesh sieve and stored in dessicator until use.

Characterization of Solid Inclusion Complex of TPM

Fourier Transformed-Infrared Spectroscopy

A compatibility study was carried out with potential formulation drug and excipients. API and excipients were mixed in specific quantity and placed in sealed vials for 3 months at 40°C ± 2°/75%±5% RH and 25°C±2°C/75%±5% RH. The samples withdrawal from specific time period & used for physical examination as well as FTIR.

OPTIMIZATION OF IN SITU NASAL GEL:

Formula is optimized by using 2^3 level central composite design where in the Drug Concentration (1-1.50%), Concentration of β- Cyclodextrin (1-1.50%), Concentration of Polymer 407 (15-20), Concentration of Carbopol 934 (0.5-2) were chosen as independent variables. Gelation temperature, Gelation time and % drug Release were taken as dependent variables. This designed suggested by 18 batches it is performed by using cold method.

Table.1 Optimization of In situ nasal gel

Formulation Code	Drug (%)	β-Cyclodextrin (%)	Poloxamer 407 (%)	Carbopol 934 (%)
F1	1.25291	1.24709	15.1	1.25
F2	1	1.5	15	2
F3	1.25214	1.24786	20	1.25
F4	1	1.5	17.5	1.46
F5	1.5	1	20	0.5
F6	1.5	1	17.5	1.46933
F7	1	1.5	20	0.5
F8	1	1.5	15	2
F9	1.5	1	20	0.5
F10	1.5	1	15	0.5
F11	1	1.5	15	2
F12	1	1.5	15	0.5
F13	1.5	1	20	2
F14	1	1.5	20	0.5
F15	1.5	1	15	2
F16	1.23997	1.26003	17.5	0.6725
F17	1.5	1.5	15	0.5
F18	1	1	20	2

PREPARATION OF THERMALLY TRIGGERED MUCOADHESIVE IN SITU NASAL GEL

For the preparation of in situ nasal gel, accurately weighed calculated amount of Poloxamer 407 was solubilized in cold water with continuous stirring using magnetic stirrer and stored overnight at 4°C until clear solution obtained. Specified amount of Topiramate and β- cyclodextrin complex, Carbopol 934 and Benzalkonium chloride were stirred in calculated amount of distilled water at room temperature. The above dispersions were slowly added to the poloxamer 407 solution with continuous agitation to form formulation and stored in refrigerator overnight to get clear sol form.

EVALUATION OF MUCOADHESIVE IN SITU NASAL GEL

Clarity:

The clarity of formulation was determined by visual inspection under black and white background by using clarity test apparatus and it was graded as follows, Turbid+, Clear++, Very clear(glassy): +++.

pH:

The pH of formulation was determined by using pH meter which was calibrated using solution of pH 5 and pH 7 before the measurement.

Viscosity:

The viscosity of formulation before and after gelation was measured by using Brookfield Viscometer coupled with S-18 spindle.

Gelation temperature:

The gelation temperature was determined by placing the test tube containing adequate amount of the prepared solutions, in water bath at 4°C. The temperature of water bath increased slowly at a constant rate of 1°C in every 2min. The temperature on the thermometer was identified as the gelation temperature.

Gelation Time:

The 2 ml of the prepared formulation to a test tube (10ml), with a diameter of 1.0 cm. after sealing the test tube was circulation water bath at 37°C. following each temperature setting, equilibration was allowed for 10min. then observe the state of the sample and to examine the gelation.

In vitro Drug Release:

The cellophane membrane was set up between the donar and receptor compartments. The receptor compartments was filled with phosphate buffer (pH 6.8) at 37°C. The solution was stirred at 100 rpm. Formulation was placed on cellophane membrane and the compartments were clamped together. One ml of the sample was withdrawn at predetermined time interval for 1hr, from receptor compartments and immediately replaced using phosphate buffer (pH 6.8). after filtering through 0.45µm filter and appropriate dilution, the sample were analyzed for drug content at 249nm.

RESULT AND DISCUSSION

PREFORMULATION STUDY:

Organoleptic Properties TPM

Topiramate is a crystalline powder, White in color and odorless.

Melting point determination

Melting point of TPM was found to be 125±0.5°C.

Solubility:

The Topiramate was practically insoluble in water, freely soluble in organic solvents such as Methanol, Acetone and Chloroform.

FT-IR study of Topiramate:

From the FTIR study characteristics of TPM, O-H Stretching at 3380 cm^{-1}, C-H Stretching at 2960 cm^{-1} and N-H Bending at 3380 cm^{-1}.

Calibration curve of Topiramate

ʎ max of Topiramate was found to be 249 nm. The regression coefficient was found to be 0.9994 and slope 0.0533.

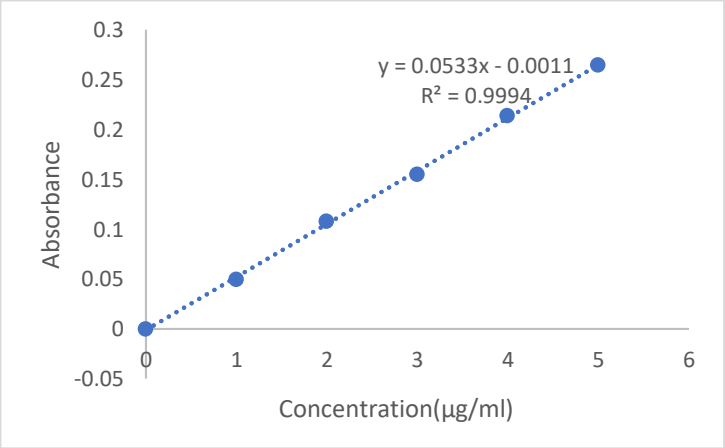


Fig. 2: Calibration curve of Topiramate

Drug polymer Compatibility Study

Table. 2: Drug-polymer compatibility data

Ingredient	Ratio	Temperature condition	Parameter	Initial	1 M	2 M	3 M
API	1	25°C±2°C/75%±5 % RH	Appearance	Solid white	As initial	As initial	As initial
			Color change	No	No	No	No
		40°C±2°C/75%±5 % RH	Appearance	Solid white	As initial	As initial	As initial
			Color change	No	No	No	No
API + Poloxamer 407	1:1	25°C±2°C/75%±5 % RH	Appearance	Solid white	As initial	As initial	As initial
			Color change	No	No	No	No
		40°C±2°C/75%±5 % RH	Appearance	Solid white	As initial	As initial	As initial
			Color change	No	No	No	No
API+ Carbopol 934	1:1	25°C±2°C/75%±5 % RH	Appearance	Solid white	As initial	As initial	As initial
			Color change	No	No	No	No
		40°C±2°C/75%±5 % RH	Appearance	Solid white	As initial	As initial	As initial
			Color change	No	No	No	No
Drug Compatibility data of solid inclusion complex							
API + β-cyclodextrin	1:1	25°C±2°C/75%±5 % RH	Appearance	Solid white	As initial	As initial	As initial
			Color change	No	No	No	No
		40°C±2°C/75%±5 % RH	Appearance	Solid white	As initial	As initial	As initial
			Color change	No	No	No	No
API+ β -cyclodextrin inclusion	1:1	25°C±2°C/75%±5 % RH	Appearance	Solid white	As initial	As initial	As initial
			Color change	No	No	No	No
		40°C±2°C/75%±5 % RH	Appearance	Solid white	As initial	As initial	As initial
			Color change	No	No	No	No

From the spectral analysis it was found that FTIR spectrum of Topiramate with β- Cyclodextrin showed all characteristics peaks in combination with no significant changes.

Table. 3: Optimization of Formulation Batch:

FORMULATION BATCHES	GELATION TEMP(°C)	GELATION TIME (SEC)	% DRUG RELEASE (%)
1	31	16	86.22
2	32	18	79.94
3	32	17	87.3
4	32	18	84.18
5	34	17	86.98
6	31	15	89
7	31	18	88.9
8	32	18	80.26
9	34	17	86.98
10	33	14	88.39
11	31	18	89.22
12	31	18	89.22
13	30	16	88.33
14	31	18	89
15	29	13	90
16	32	17	87.33
17	33	14	88.38
18	32	18	81.53

From all the trial batches F15 was found to be optimized batch, which showed the gelation temperature 29°C, gelation time 13 second and % drug release 90%.

VALIDATION OF EXPERIMENTAL DESIGN

Gelation Temperature

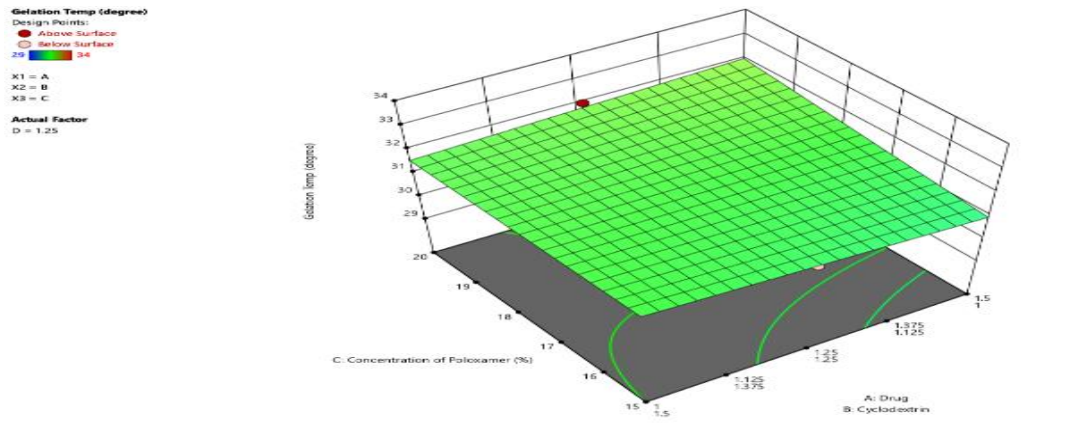
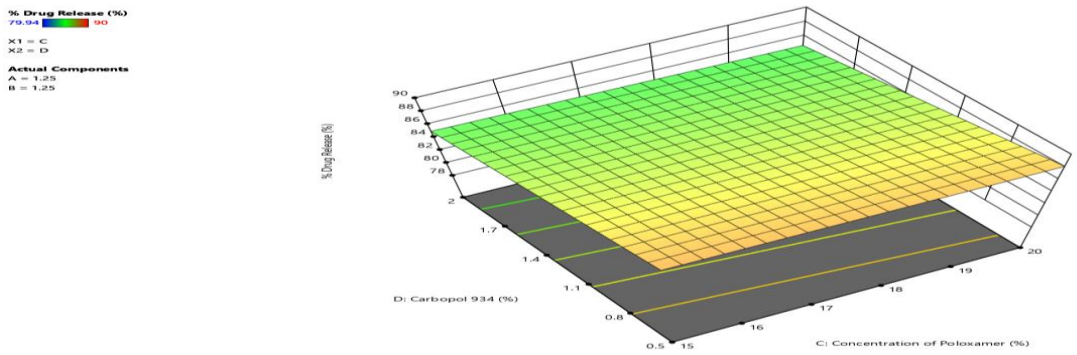


Fig. 3: 3D Surface graph for Effect of Concentration of Poloxamer and concentration of Solid inclusion complex on Gelation Temperature

Table. 4: statistics values of Gelation Temperature

Response	P- Value	F-Value	R^2 Value	Predicted R^2 Value	Remark
Gelation Temperature	0.0001	288.16	0.9917	0.9866	Significant

From 3D surface graph it was observed that when concentration of poloxamer and Drug: β-cyclodextrin increases then the gelation temperature increases.



Gelation Time

Fig. 4: 3D Surface graph for Effect of Concentration of Poloxamer and concentration of Carbopol 934 on Gelation Time

Table. 5: statistic values of Gelation time

Response	P- Value	F-Value	R^2 Value	Predicted R^2 Value	Remark
Gelation Temperature	0.0001	615.96	0.9961	0.9940	Significant

From 3D surface graph it was observed that when concentration of poloxamer and Drug: β-cyclodextrin increases then the gelation time increases.

% Drug Release

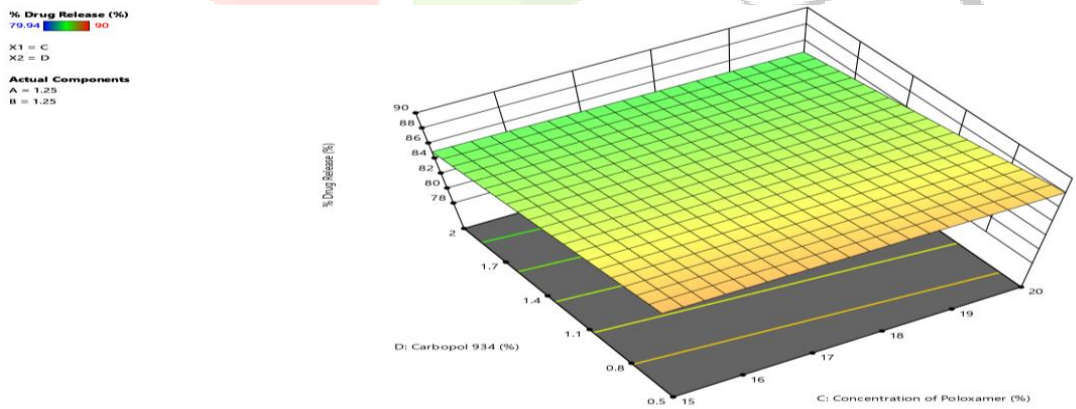


Fig. 5: 3D Surface Effect of Concentration of Poloxamer and Concentration of Carbopol 934 on % drug release

Table. 6: statistic values of % Drug release

Response	P- Value	F-Value	R^2 Value	Predicted R^2 Value	Remark
Gelation Temperature	0.0001	126.86	0.9814	0.9621	Significant

From 3D surface graph it was observed that when concentration of poloxamer and Drug: β-cyclodextrin increases then the percentage drug release increases. The gelation temperature was found in the range of 29-34. Gelation time was found in the range of 13-18. The percentage drug release was found in the range of 79-90%.

EVALUATION OF MUCOADHESIVE NASAL IN-SITU GEL:

Clarity: The clarity of formulation was determined by visual inspection under black and white background. The prepared formulation was found to be clear (++).

pH: pH of formulation was found to be 6.3±0.1. that is between physiological range of pH (within 5.70-6.78) of nasal mucosa.

Viscosity: Viscosity of F15 formulation was found to be 4ºC 43.80±0.3 and 32ºC 161±0.85

Gelation Temperature:

Gelation temperature of F15 formulation was found to be 29 ºC.

Gelation Time:

Gelation time of F15 formulation was found to be 13second.

In Vitro drug release:

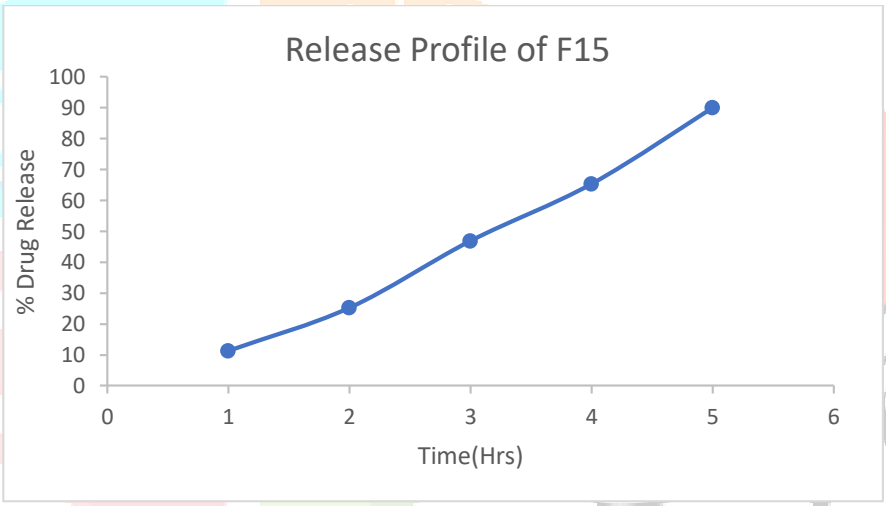


Fig. 6: Graph of % Drug Release

The drug release from this nasal in situ gel containing TPM up to 90%.

CONCLUSION:

Solubility of Topiramate was successfully increased by making its inclusion complex with β-cyclodextrin and was formulated as in situ gel. The nasal pathway has found to be useful in targeting drugs to the CNS. The high permeability, high vascularity and low enzymatic environment of nasal cavity as suitable for systemic delivery of drug molecule through nose. The optimized formulation containing inclusion complex of drug with β-CD achieved the target flux and had sufficient mucoadhesive property to ensure appropriate residence time at the site of application. The drug release from this nasal in situ gel containing Topiramate was found to be 90%, which would help to achieve longer action of Topiramate. Further preclinical study is necessary to get the better exposure for the current research.

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