WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 9, 716-730. Research Article ISSN 2277 – 7105

THERMOSENSITIVE GELS CONTAINING CARBAMAZEPINE MICROSPHERES FOR INTRANASAL BRAIN TARGETING

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Article Received on
23 Aug 2014,

Revised on 17 Sept 2014,
Accepted on 12 Oct 2014

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ABSTRACT:

Context: Carbamazepine, derived from tricyclic antidepressant drugs is one of the most widely used antiepileptic drugs. It is characterized by a considerable hepatic first-pass effect owing to the enzymatic auto-induction of its own metabolism. **Objective:** The objective of the present investigation was to prepare thermo-sensitive gels containing Carbamazepine microspheres for intranasal brain targeting to prolong the drug release and enhance the bioavailability. **Materials and Methods:** Carbamazepine loaded chitosan microspheres were prepared by emulsion cross-linking method by varying the drug: polymer ratio and evaluated. Microsphere embedded gel was prepared using Pluronic F127 and Pluronic F68 using the optimized microsphere formulation and evaluated for *in vitro* permeation and *ex vivo* permeation. **Results:** Microsphere formulation containing drug and polymer in the ratio 1:4 was found to be optimized. 17% PF-127 and 1% PF-68 were found to be promising gel vehicles. The microspheres in the viscous media showed a prolonged release, in comparison to the microspheres alone. Histopathological studies proved that the optimized formulation does not produce any toxic effect on the microscopic structure of nasal mucosa during *ex vivo* permeation studies. **Conclusion:** Formulated thermo-sensitive gel can prove to be a promising formulation for the safe and effective intranasal delivery and subsequent brain targeting of Carbamazepine.

KEY WORDS: Thermo-sensitive Gel, Carbamazepine, Chitosan, Pluronic F127, Pluronic F68, Intranasal brain delivery.

INTRODUCTION

Drug delivery by the nasal route has received a lot of attention recently because of its advantages such as rapid absorption, avoidance of first-pass elimination and so on [1]. Direct transport of drugs to the brain circumventing the brain barrier, following intranasal administration provides a unique feature and better option to target brain. The presence of mucoadhesive microspheres in the gel vehicle administered through nasal route can achieve a dual purpose of prolonged drug release and enhanced bioavailability [2].

Carbamazepine(CBZ) is a drug widely used as antiepileptic agent, in the therapy of psychomotor seizures and trigeminal neuralgia; it is traditionally given by oral administration but due to its poor water solubility (about 170 mg/l at 24 °C). It is characterized by slow and irregular gastrointestinal absorption. Many reports were focused on improving its dissolution characteristics. Furthermore this drug is characterized by a considerable hepatic first-pass effect owing to the enzymatic auto-induction of its own metabolism. This latter characteristic besides the need of a therapeutic prompt action make CBZ a promising candidate for the development of a nasal formulation [3]. It is well absorbed from gastrointestinal tract having 80% bioavailability and 76 % protein binding and is metabolized in liver by CYP3A4 to active epoxide form (10-11 epoxy Carbamazepine). Initially its plasma *half life* is 20- 40 hours but, decreases to 10-15 hours on chronic medication due to auto-induction [4,5].

The oral bioavailability of the drug is 80% but the present study is for brain targeting so the oral bioavailability would not be of consideration. Secondly, CBZ undergoes metabolism in the liver by CYP3A4 following oral delivery .The dose required for nasal route is less compared to oral route, it gives faster onset and longer duration of action. Hence, the present study is focused on nasal delivery of CBZ by formulating in thermo-sensitive gel.

Microsphere technology is one of the specialized systems becoming popular for designing nasal products, as it provides prolonged contact with the nasal mucosa and thus enhances absorption and bioavailability. This is particularly relevant to overcome certain limitations of the nasal route, i.e rapid mucocilliary clearance that determines limited drug delivery through the nasal route, especially in the delivery of drugs with high molecular weight and hydrophilic properties .To be safe, the particle size should be controlled and optimized in the range of 6–15 µm, so as to minimize the deposition of the particles in the anterior part of nasal cavity and also to the lungs. One strategy to overcome the clearance is to formulate a gel which increases the contact time in the nasal mucosa. Microspheres embedded hydrogel

showed a sustained release of drug, as well as additional properties such as thermo-sensitivity and biocompatibility due to the presence of both chitosan and Pluronics moieties [6].

Pluronics (PF-127 and PF-68) have been selected since they are thermoreversible polymers with the property of forming a solution at low temperatures (4–5 °C) and gel at body temperature (37 °C). This property makes them an interesting material to work with, especially in case of controlled release formulations. Chitosan, a linear polysaccharide produced by a process of deacetylation from chitin, is one such material that has been shown to be mucoadhesive. Chitosan may be a good option in nasal delivery as it binds to the nasal mucosal membrane with an increased retention time and it is a good absorption enhancer. Furthermore chitosan is an excipient able to enhance the dissolution rate of drug with low water solubility [7].

Present investigation is to develop thermo-sensitive gels containing Carbamazepine microspheres with an aim of increasing its therapeutic effectiveness for extended period of time thus reducing dose frequency and side effect. This system is potentially effective, safe and easy to administer than those presently in use.

MATERIALS AND METHODS

Materials

Carbamazepine was a gift sample from Amoli Organics, Mumbai. Chitosan was purchased from HiMedia, Mumbai. Pluronics (PF-127 and PF-68) were purchased from Sigma Chemical Co., (St. Louis, MO, USA). Glacial Acetic acid was purchased from New Modern Chemicals, Mumbai. Light liquid paraffin from Finer Chemicals, Ahmedabad and Span 80 and Sodium oleate from Loba Chemicals Pvt Ltd, Mumbai. Gluteraldehyde (25% v/v), petroleum ether, acetone, ethanol were from SD Fine Chemicals, Mumbai. All other chemicals and solvents were of analytical reagent grade and were used without further purification.

Compatibility studies

The compatibility studies were carried out at room temperature by Fourier transform infrared (FTIR) spectroscopy to determine the interaction of Carbamazepine with other excipients used in the formulation. The IR spectra of drug alone and in combination with pluronics (Pluronics F 127 and Pluronics F 68) and chitosan were taken. Physical mixtures of the drug with excipients in the ratio of 1:1 were prepared and the samples were analysed by Shimadzu IR SpectraAnalyzer (Shimadzu, Japan).

Preparation of Microspheres

The chitosan microspheres were prepared by emulsion crosslinking method. Chitosan solution (2%, w/v) was prepared in 4% aqueous glacial acetic acid by overnight stirring in a magnetic stirrer. The drug was dissolved in ethanol and mixed well in the polymer solution. 6 ml of the above resultant mixture was then injected through a syringe (# 23) into 40 ml of oil phase containing span 80 (7% v/v) and stirring was performed by mechanical stirrer at 1500 rpm to form w/o emulsion. Oil phase was light liquid paraffin. After 30 min of homogenization period 1.0 ml of glutaraldehyde 25% (v/v) was added to it stage by stage. It was then left for stabilization and cross-linking for a period of 3 h. Microspheres obtained were centrifuged at 4000 rpm. The sediment was then washed with petroleum ether and acetone thrice, and then dried in a hot air oven at 50 °C [2]. The composition of all the formulations is given in Table 1.

Evaluation of Microspheres

Shape and surface morphological analysis

The shape and surface morphology of the microspheres were studied with the aid of scanning electron microscope. Chitosan microspheres were fixed with carbon tape and mounted on metal stubs and then coated with platinum, keeping the acceleration voltage at 10 kV. Photographs were taken using Jeol JSM-6390 (Jeol, Japan) scanning electron microscope [2].

Drug Content

Accurately weighed microspheres equivalent to 100 mg of drug were suspended in 20 ml of methanol and sonicated for 3 minutes. The solution obtained was then filtered, diluted suitably and analyzed for drug content spectrophotometrically at 285 nm [8].

Encapsulation efficiency

Accurately weighed microspheres equivalent to 100 mg of drug were suspended in 20 ml of methanol and sonicated for 3 minutes. The solution obtained was then filtered, diluted suitably and analyzed for drug entrapment efficiency spectrophotometrically at 285 nm [8].

***In vitro* dissolution studies**

In vitro drug release studies were performed with a USP Type II dissolution using a modified form of the rotating basket method. Sample of microspheres equivalent to 10 mg of carbamazepine were tested in 900 ml of phosphate buffer (pH 6.4) to assure sink conditions. The rotational speed was set at 50 rpm and the temperature for the dissolution medium was

set at 37±5°C. Samples (10 ml) were withdrawn at predetermined time points (15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180) and for each withdrawal the volume was replaced with fresh medium. Samples were analyzed spectrophotometrically at 285 nm [8].

X-Ray Diffractometry

XRD powder diffraction method was applied to characterize the drug substance and the microspheres. The diffraction patterns of the Carbamazepine powder, blank microspheres and drug loaded microspheres were conducted with a X-ray powder diffractometer (Ultima N), using a copper Kα target with a nickel filter at 40 kV voltage, 30 mA current and at scanning speed of 0.02°/min over a 2θ range of 3–50° [2].

Differential Scanning Calorimetry

The thermo analytical examinations were carried out with a differential scanning calorimeter equipped with a thermal analysis data system (Perkin-Elmer DSC7 calorimeter, Perkin-Elmer Inc. Wellesley, MA, USA). Samples weighing 3–5 mg were heated in flat-bottomed sealed aluminium pans over a temperature range of 25–300 °C at a constant rate of 10 °C/min under nitrogen purge of (50 ml/min) using empty aluminium pan as reference [2].

Optimization Studies: Selection of Pluronic F127 concentration

The concentration of Pluronic F127 (PF127) was selected so as to obtain gel at minimum possible concentration below 34°C (Table 2). Vehicles with concentration varying from 16% w/v to 22% w/v were screened preliminarily to decide lowest possible concentration of PF127 in a formulation containing Carbamazepine microspheres that exhibited thermoreversible property below 34°C (temperature of the nasal cavity).

Suspension media preparation

PF-127 and PF-68 were solubilised in cold distilled water, with increasing quantities of PF-127 (16–22%, w/v) and PF-68 (1%, 2%, 3%w/v) along with 4% mannitol which acts as an isotonic agent, 0.05% glycerin, 0.1% sodium oleate, 0.05% benzalkonium chloride which is a preservative. These solutions were prepared in aseptic conditions, by dissolution in sterile water at 2 °C with overnight maturation at 4 °C. PF-127 and PF-68 vehicles were screened preliminarily to decide the lowest possible concentration ((when formulated after the addition of other ingredients) that exhibited thermo reversible property at 37 °C. The liquid was left at 4 °C until a clear solution was obtained [2]. The composition of the suspension media is given in Table 3.

Evaluation of the Prepared Formulation of Gels

Determination of pH

The pH of gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Determination of Viscosity

Rheology of gel formulations was studied by Brookefield digital viscometer (Model no: LVDV-II+P). The measurement was done in triplicate and average values were calculated.

***In vitro* permeation Study**

In vitro release of CBZ from the thermo-sensitive gel formulations was performed (in triplicate) using a Franz diffusion cell. The donor cell consisted of PBS (6.4). 1 g of the gel was transferred to the dialysis membrane (0.45 μm) of the vessel. At predetermined time intervals, 1 ml samples of the receptor fluid were taken and analyzed for CBZ spectrophotometrically at 285 nm, respectively. The medium was replaced after each sampling [9].

***Ex vivo* permeation studies**

Tissue preparation

The sheep nose was obtained from local slaughter house within 15 min after the sheep was sacrificed. After removing the skin, the nose was stored in ice cold phosphate buffer (pH 6.4). The septum was fully exposed and nasal mucosa was carefully removed using forceps, scapel and surgical scissors. The mucosal tissues were immediately immersed in formaldehyde solution. The freshly excised nasal mucosa was then used for the permeation studies.

Transnasal drug permeation studies

Tissue samples were inserted in Franz diffusion cells displaying a permeation area of 3.14 cm^2. 20 mL of phosphate buffer saline (PBS) pH 6.4 was added to the acceptor chamber. The temperature within the chambers was maintained at 37±5°C. Formulations equivalent to 100 mg of Carbamazepine were placed in the donor chamber. At predetermined time interval, 1mL samples were withdrawn from the receptor compartment, replacing the sampled volume with PBS pH 6.4 after each sampling, for a period of 3 hours. The samples withdrawn were filtered and analysed spectrophotometrically. The amount of permeated drug was determined using a UV-Vis. spectrophotometry at 285 nm [10].

Histopathological evaluation of nasal mucosa

Histopathological evaluation of sheep nasal tissue incubated in phosphate buffer solution PBS (pH 6.4) after collection was compared with tissue incubated in the diffusion chamber with gel formulation and was performed in a histopathology lab. Tissue was fixed in 10% buffered formalin (pH7.2), routinely processed and embedded in paraffin. Paraffin sections (7 µm) were cut on glass slides and stained with haematoxylin and eosin. Sections were examined under a light microscope, to detect any damage to the tissue during *in vitro* permeation by a pathologist blinded to the study [2].

Short term stability studies

Samples were stored in plastic container for 2 months at 4 ºC in freeze and at room temperature. After 30 and 60 days samples were visually observed for any sedimentation and subjected for pH, viscosity and *in vitro* release studies were carried out at every one month interval [9].

RESULTS AND DISCUSSION

Compatibility Studies

Compatibility studies of pure drug with excipients were carried out prior to the preparation of thermosensitive gel. I.R spectra of pure drug and combination of drug and excipients were obtained, which are shown in Table 4. All the characteristic peaks of Carbamazepine were present in spectra thus indicating compatibility between drug and polymers. It shows that there was no significant change in the chemical integrity of the drug.

Evaluation of the Chitosan microspheres

Surface Morphology and Particle Size Analysis

The particle size of all the formulations was found to be in the range of 10-500 µm. Formulation F-4 was selected as the optimized formulation as the particles size was between 10-30 µm and the surface was found to be smooth and spherical (Fig 1).

X-Ray Diffraction Analysis

The XRD patterns of optimized formulation (F4) are shown in Fig 2. XRD analysis suggests that the presence of the crystalline form of the carbamazepine was not observed in the drug-loaded chitosan microspheres, indicating that the drug was present as molecular dispersion in the polymer matrix.

Drug Content and Encapsulation Efficiency

The drug content of the formulations was found to be in the range of 7.9 to 8.88. The highest drug content was found in formulation F-5 (8.88). The encapsulation efficiency ranged from 79.82% to 88.86%. The encapsulation efficiency increased as the concentration of polymer (encapsulating material) was increased. The results of drug content and encapsulation efficiency are tabulated in Table 5.

***In vitro* Dissolution Study**

The rate of dissolution of CBZ powder was significantly low. The loading of CBZ into chitosan microspheres led to an improvement of its dissolution/release rate. The increase in the rate of dissolution was always remarkable as compared to the pure drug. About 73.98–86.46% of drug release was achieved in less than 3 h from chitosan microspheres (Fig 3). **Gavini** *et al* suggested that chitosan, a polymeric material is known for its properties of dissolution rate enhancer of drugs poorly soluble in water. The improvement of the dissolution rate of the drug from the microspheres can be also due to their small size and the cross-linking of polymer and drug that lead to the uniform dispersion of the drug into the polymeric network.

Differential Scanning Calorimetry

The DSC analysis was performed on the optimized formulation i.e. F-4 based upon the other evaluation tests carried out on microspheres. The DSC thermogram of the microsphere formulation is depicted in Fig 4. The DSC thermogram of carbamazepine exhibited a single sharp exothermic peak at 192.8°C corresponding to its melting transition temperature. This peak was not observed in the thermogram of the optimized drug loaded microspheres. The broadened and shifted peaks suggests that the drug was present as molecular dispersion in the polymer matrix.

Evaluation of Gel Containing Microspheres

Optimization Studies: Selection of Pluronic F127 concentration

Varying concentrations of Pluronic F127 (from 16% w/v to 22% w/v) were screened preliminarily to decide lowest possible concentration of PF127 that formed gel below 34°C (temperature of the nasal cavity). Thus, gelation range broadens with the concentration of the polymer and in presence of other excipients. From Table 3, it was found that only 17% PF 127 gels at 34.1 + 0.24 °C.. Thus, 17% PF 127 was selected for the further study.

Characterization of thermosensitive gel

pH of gels

pH of all the formulations (F-1 to F-3) was found to be between 5.23-6.19. The variation in pH was attributed to the concentration of Pluronic F68 in the formulations and the results are presented in Table 6.

Viscosity

Viscosity of the carbamazepine gels was determined using Brookefield digital viscometer (Model no: LVDV-II+P). The viscosity values were tabulated in Table 6. The viscosity was found to be 1047, 1186 and 1242 cps. The increase in viscosity of the formulations was directly proportional to polymer concentration.

***In vitro* diffusion study**

The permeation data obtained for Carbamazepine pure drug, formulations F1, F2 and F3 are shown in Table 7. The overall cumulative % drug permeated for F1 to F3 was found to be 59.29 %, 54.65 % and 51.06 % respectively. The amount of drug permeated across the nasal mucosa at the end of 3 hours was maximum i.e.59.29 % for F1. The lower drug release of formulations GF2 and GF3 as compared to GF1 may be attributed to the high polymer concentration in the former. With increase in the polymer concentration, the micelles formed are closely packed on gelation thus resisting the drug release to the external environment.

***Ex vivo* permeation study**

The *ex vivo* drug permeation study of the optimized formulation (GF-1) shows that 58.19% of the drug was permeated at the end of 3 hrs (Fig 5). The slower release of the drug can be attributed to the presence of polymers (PF127 and PF68) which resist the release of drug into the external environment from the gel matrix. Slower release is desirable so as to obtain sustained effect and to lower the dosing interval.

Histopathological evaluation of nasal mucosa

The microscopic observations indicate that the optimized formulation has no significant effect on the microscopic structure of mucosa. As shown in Figure 6, neither cell necrosis nor removal of the epithelium from the nasal mucosa was observed after permeation of GF-1. Thus, gel formulations seem to be safe with respect to nasal administration**.**

Stability studies

Stability studies of the optimized formulation GF1 were carried out according to the ICH guidelines. The accelerated stability studies were carried out at Room temperature/65% RH and 4°C/45% RH for the selected formulation up to 60 days. The formulation was analyzed for appearance, pH, viscosity and % drug release for up to 60 days at a time interval of 30 days. The formulation did not show much variation in any of the parameters. The results obtained were tabulated in Table 8 From these results it was concluded that, formulation GF1 was stable throughout the period and retained its original properties at 4 ± 2°C.

TABLE 1: Composition of Formulation

Formulation Ingredients	Formulation Code				
	F1	F2	F3	F4	F5
Carbamazepine	400	400	400	400	400
Chitosan	400	800	1200	1600	2000
Aqueous glacial acetic acid	4%	4%	4%	4%	4%
Ethanol	60mL	60mL	60mL	60mL	60mL
Light liquid paraffin	40mL	40mL	40mL	40mL	40mL
Span 80 (7% v/v)	2.8mL	2.8mL	2.8mL	2.8mL	2.8mL
Glutaraldehyde (25% v/v)	1.0mL	1.0mL	1.0mL	1.0mL	1.0mL
Petroleum ether	q.s.	q.s.	q.s.	q.s.	q.s.
Acetone	q.s.	q.s.	q.s.	q.s.	q.s.

TABLE 2: Optimization of PLURONIC F127

Concentration of Pluronic F127	Gelation temperature
16 % w/v	38 °C
17 % w/v	34.1°C
18 % w/v	33.2 °C
19 % w/v	32.6 °C
20 % w/v	28 °C
21 % w/v	26 °C
22 % w/v	24 °C

TABLE 3: Composition of Suspension media

Formulation Ingredients	Formulation Code		
	F1	F2	F3
Pluronic F127	17	17	17
Pluronic F68	1	2	3
Mannitol	4	4	4
Sodium Oleate	0.1	0.1	0.1
Glycerine	0.05	0.05	0.05
Benzalkonium Chloride	0.05	0.05	0.05
Water	q.s.	q.s.	q.s.

TABLE 4: Characteristic IR frequency ranges and their comparison with Pure Drug, Formulation and Mixtures

Functional Group	Reported Frequencies (cm^{-1})	Observed Frequencies (cm^{-1})			
		Pure drug	Drug + Chitosan	Drug + PF127	Drug + PF68
NH Stretching of NH_2	3000 – 3700	3466.08	3466.08	3466.08	3466.08
Aromatic C–H Stretching.	Aprox 3165	3163.26	3165.19	3157.47	3159.40
C= C ring Stretching	1400 – 1610	1396 – 1606.70	1382.96-1595.13	1348.24 – 1595.13	1384.89–1595.13
C – N (substituted amide)	1550-1640	1606.70	1629.85	1560.41	1604.77
C = O Stretching of $CONH_2$	1640-1690	1689.64	1649.85	1676.14	1651.07

TABLE 5: Drug Content and Encapsulation Efficiency of Formulations

Formulation	Drug content* (mg)	Encapsulation efficiency* (%)
F1	7.982±0.053	79.82±1.86
F2	8.283±0.052	82.83±1.93
F3	8.477±0.207	84.77±0.59
F4	8.563±0.122	85.63±0.28
F5	8.886±0.086	88.86±0.76

** Data are expressed as mean ± SD (n=3)*

TABLE 6: Viscosity and pH of the Formulations

Formulation	Viscosity* (cP)	pH*
GF1	1047±0.08	5.23±0.03
GF2	1186±0.05	5.23±0.08
GF3	1242±0.01	6.19±0.01

** Data are expressed as mean ± SD (n=3).*

TABLE 7: Comparative *in vitro* diffusion profile of Pure drug, GF1, GF2 and GF3

Time (min)	Pure drug	GF1	GF2	GF3
0	0	0	0	0
30	7.03	12.40	10.17	9.57
60	10.13	19.51	18.25	17.80
90	14.24	31.69	30.40	28.05
120	18.20	38.66	36.99	35.70
150	22.42	44.23	43.30	42.15
180	26.64	59.29	54.65	51.06

TABLE 8: Stability Studies of the best Formulation GF1

Evaluation Parameters	Optimized Formulation GF1				
	Initial	4± 2ºC		Room Temperature	
		30 Days	60 Days	30 Days	60 Days
% Drug Release	59.29	58.61	58.51	58.35	58.08
pH	5.23	5.23	5.21	5.19	5.17
Viscosity	620	624	629	1047	1052

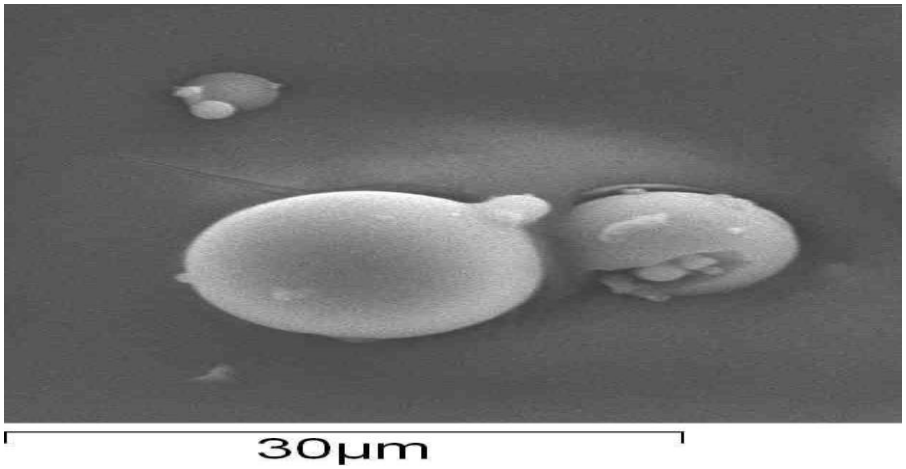


FIGURE 1: SEM Image of Optimized Formulation (F4)

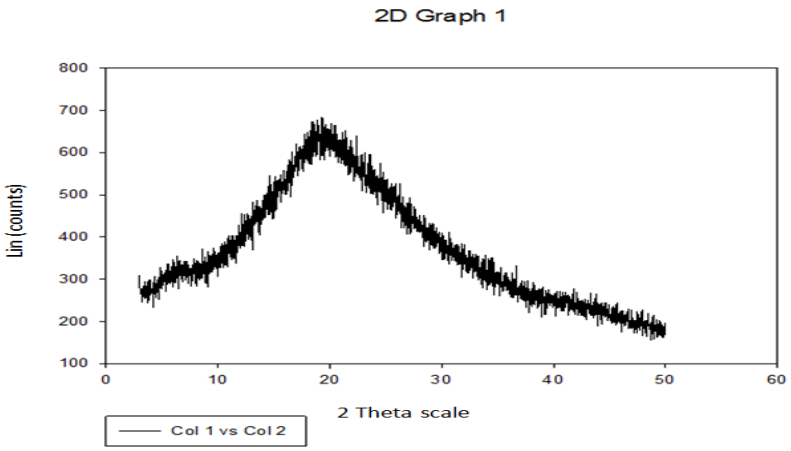


FIGURE 2: X-ray Diffraction Patterns of Optimized Formulation (F4)

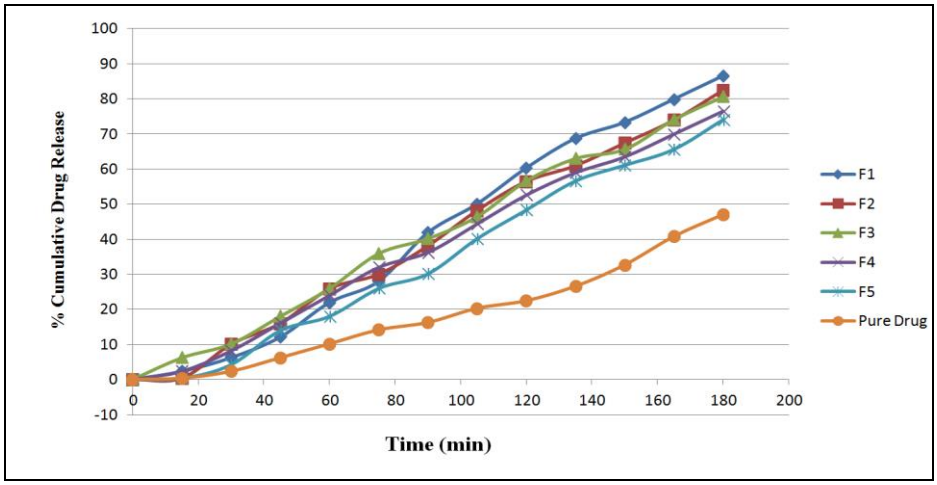
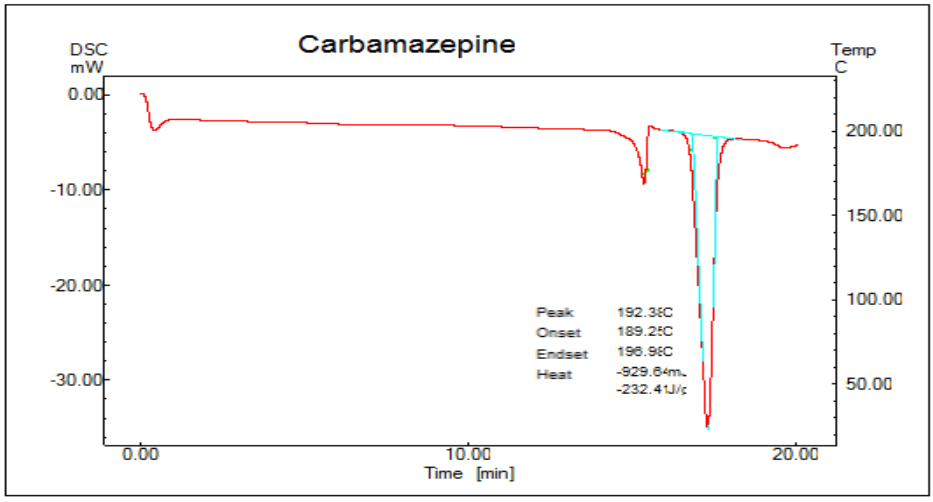
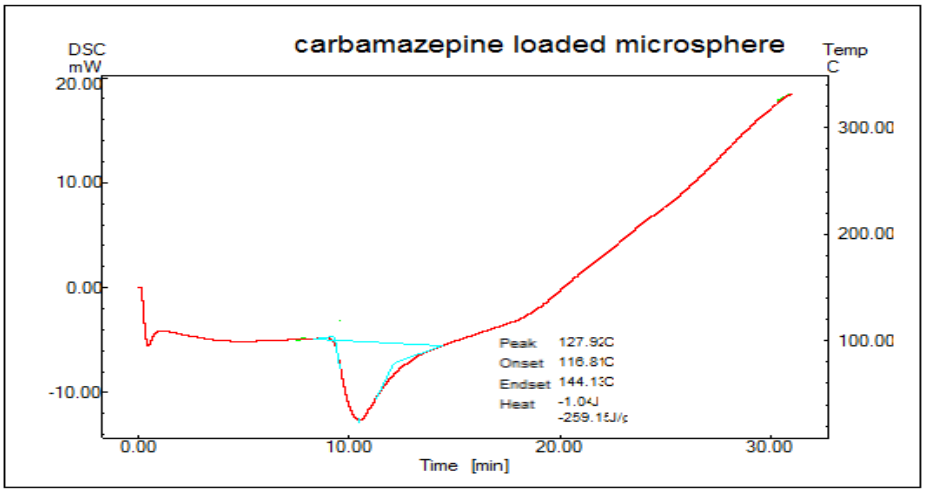


FIGURE 3: Comparative *In vitro* Dissolution Profile of Microspheres (F1-F5)



(a)



(b)

FIGURE 4: Differential Scanning Calorimetric studies (a) DSC thermogram of Pure drug and (b) DSC thermogram of Optimized formulation F4

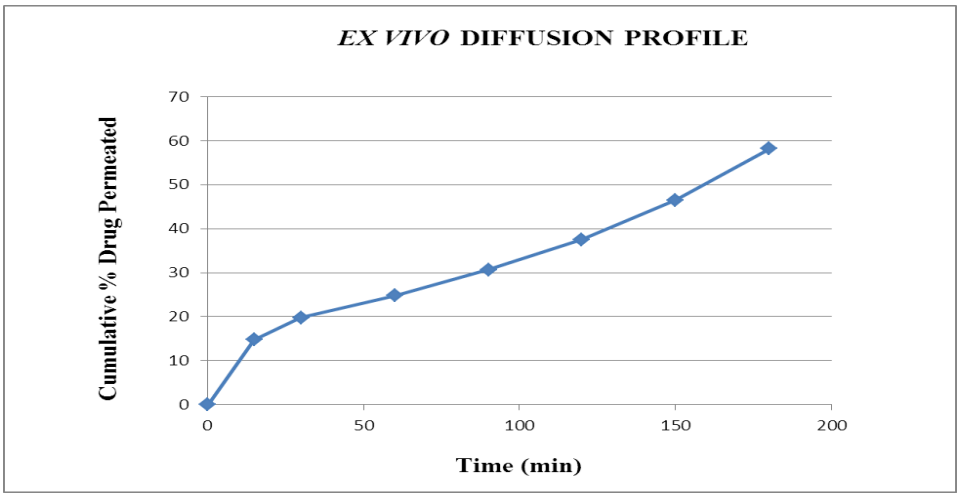


FIGURE 5: *Ex vivo* permeation (Formulation GF1) studies using Sheep Nasal Mucosa

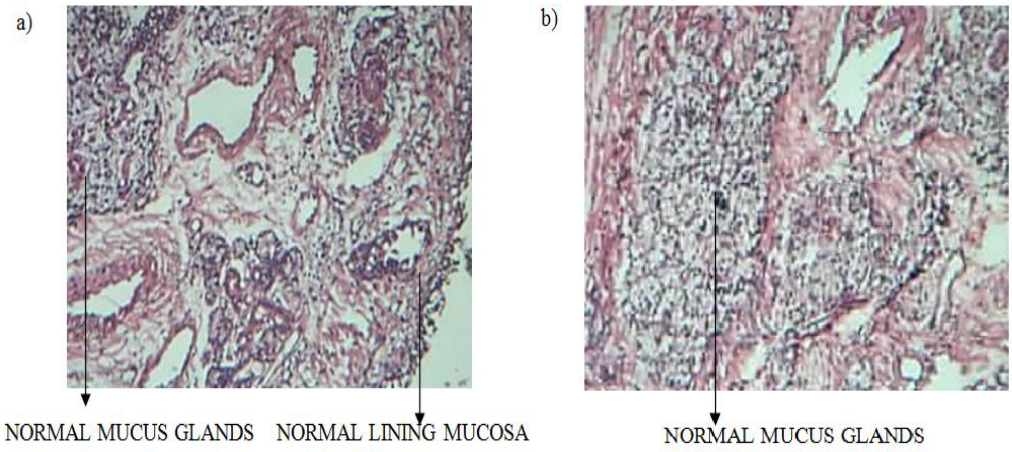


FIGURE 6: Histopathological studies: Nasal Mucosa treated with (a) PBS (Control) and with (b) Thermo-sensitive Gel containing Microspheres (Sample).

CONCLUSION

In the present study, an attempt was made to prepare a dispersion of Carbamazepine microspheres in thermosensitive pluronics based gel suspension for intranasal administration. Microspheres containing Carbamazepine and Chitosan in the ratio (1: 4) i.e. Formulation F4 was found to be optimized based on various parameters like particle shape and size, drug content, encapsulation efficiency and *in vitro* drug release. Gels were formulated with an optimized quantity of Pluronic F127 (17%) with varying concentrations of Pluronic F68 (1%, 2%, 3%). *In vitro* diffusion studies on the gel suggest that the gel containing 1% Pluronic F68 shows the maximum release at the end of 3 hours. *Ex vivo* permeation study using Sheep nasal mucosa of the optimized formulation GF1 shows that 58.19% drug was released at the end of 3 hours. Histopathological studies proved that the formulation does not cause any toxicity to the nasal mucosa. Thus, the formulated thermo-sensitive gel seems to be a promising formulation for the safe and effective intranasal delivery of Carbamazepine.

Declaration of interest

The authors declare that they have no competing interest.

REFERENCES

1. Illum L. "Nasal drug delivery-possibilities, problems and solutions". Journal of Controlled Release.2003; 87:187–98.
2. Jose S, Ansa CR, Cinu TA, Chacko AJ, Aleykutty NA, Ferreira SV et al "Thermosensitive gels containing Lorazepam microspheres for brain targeting".International journal of pharmaceutics.2013;441:516-26

3. Levy HR, Dreifuss FE, Mattson RH, Meldrum BS, Penry JK, Antiepileptic Drugs, 3rd ed. New York, Raven press; 1989: 447–555.
4. Tripathi KD. Essential of Medical Pharmacology. 6th ed. Sec 7. New Delhi: Jaypee Brother Medical Publishers; 2008.p.401
5. Carbmazepine [Internet]. 2012 [updated 2012 Mar 18; cited 2012 Feb 02]. Available from: http://en.wikipedia.org/wiki/Carbamazepine
6. Soane, RJ, Frier M, Perkins AC, Jones NS, Davis SS, Illum L " Evaluation of the clearance characteristics of
7. Ravi Kumar MNV, Muzzarelli RAA, Muzzarelli C, Sashiwa,H, Domb AJ et al " Chitosan chemistry and pharmaceutical perspectives". Chemistry Review. 2004; 104:6017-84.
8. Gavini E, Hegge AB, Rassu G, Sanna V, Testa C, Pirisino G, Karlsen J, et al. Nasal Administration of Carbamazepine using Chitosan Microspheres: *in vitro/in vivo* studies. Int J Pharm. 2006; 307: 9-15.
9. Majithiya RJ, Ghosh PK, Umrethia ML, Murthy RSR. Thermoreversible Mucoadhesive Gel for Nasal Delivery of Sumatriptan. AAPS Pharm Sci Tech. 2006; 7: E1-E7.
10. World Health Organization: WHO Technical Report Series; 2009. p.953-92.