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Research Article

Development and Characterization of Thermoreversible *In-situ* Gel Containing Curcumin Nanoparticles for Nasal Delivery: Design, *Ex-Vivo* Study

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Abstract

The present study aimed to develop and evaluate thermoreversible in situ nasal gel containing Curcumin nanoparticles. Curcumin nanoparticles were prepared by the ionic gelation method. These formulations were evaluated for entrapment efficiency, particle size, zeta potential, and *In vitro* drug release. Particle size and zeta potential of F1 formulation were found to be 299 nm, 0.1 mV, and entrapment efficiency was found to be87.2%. From the formulations, F1 shows maximum amount of drug released in a sustained manner for a prolonged period time. Hence F1formulation was selected as optimized and further used for thermoreversible in situ nasal gel by using 2×2 factorial designs. The thermoreversible nasal gel was evaluated for the gelation temperature (33˚C), viscosity (10550cps) and spreadability (17.29±0.3 gm*cm/sec). Further, the prepared gel (F1G3) was evaluated for *ex vivo* permeation study for12 hours and it shows maximum amount of drug release in a controlled manner. The % CDR of thermoreversible in situ gel formulation F1G3 was found to be 86.27% which follow the Higuchi model. The 'n' value of the formulation was found to be more than 0.5. This indicate that the release approximates the non-fickain diffusion mechanism.

Keywords: Curcumin nanoparticles, Carbopol 934, PF127, Thermoreversible in situ gel, Cold method, Nasal delivery.

INTRODUCTION

The history of nasal drug delivery dates back to earlier topical applications of drugs intended for local effects. The early 1980s saw the introduction of the nasal route as a promising systemic delivery alternative to other conventional drug delivery routes. The nasal route is easily accessible, convenient, and reliable with a porous endothelial membrane and a highly vascularized epithelium that provides a rapid absorption of compounds in to the systemic circulation, avoiding the hepatic first-pass elimination.[1] In the past decade, the nasal route for drug delivery has established itself as an important alternative to the parenteral route. The nasal route provides a higher degree of patient compliance and makes the patient more tractable. Moreover, drugs can be painlessly self-administered by the patient, which adds to the popularity of this route.[2]

In recent times, interest in the intranasal route to target drugs to brain and cerebrospinal fluid circumventing the blood-brain barrier has gained impetus. Intranasal formulations of drugs for the treatment of Parkinson's disease Alzheimer's disease and psychosis, have been developed and their therapeutic effectiveness over conventional oral formulations has been demonstrated. Comprehensive studies have shown the role of the olfactory pathway in the transport of nasally administered drugs to the Central nervous system (CNS).[3] Nanoparticle therapeutics is an emerging modality for the treatment of Parkinson's disease as it offers targeted delivery and enhances the therapeutic efficacy and/or bioavailability of neurotherapeutics.[4]

In situ gelling stimuli-sensitive hydrogels exhibit sol-to-gel phase transitions in response to external physical or chemical stimuli such as temperature, pH, ionic strength, light, electromagnetic radiation, and biomolecules which have received increasing attention for their great potential in drug delivery systems. They have many advantages, such as a sustained drug release behavior, easy administration procedure and improved patient compliance, not containing organic solvent, less systemic toxicity, site-specificity, reduced frequency of administration, and ability to deliver both hydrophilic and hydrophobic drugs.[5] Temperature is the most widely used stimulus in environmentally responsive polymer systems. Thermosensitive hydrogels show gelation by temperature change which are liquid at room temperature and undergo gelation when in contact with body fluids. Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) triblock co-polymers named poloxamers are one of the synthetic polymers that have unique thermosensitive gelling properties, excellent water solubility, low toxicity and irritation, good drug release properties and compatibility with other chemicals.[6]

Although the hydrogels that are prepared by poloxamers have various advantages, they exhibit weak mechanical strength and bio-adhesive properties. To improve these properties, bioadhesive polymers such as polyacrylates (Carbopol®), cellulose derivatives (e.g., hydroxypropyl methylcellulose,

hydroxypropyl cellulose, methylcellulose, and carboxymethyl cellulose), and natural polymers (e.g., chitosan, alginate) can be combined with them. [7, 8] In the present investigation, an attempt has been made to develop a delivery system directly from nose to brain, to improve bioavailability and avoid degradation. Curcumin nanoparticles were incorporated into a thermo-reversible gel by using 2^2 factorial design. The formulation of Curcumin nanoparticle in situ gel(CNP gel) were optimized for formulation parameters, such as gelling temperature, pH, *In vitro* release and *ex vivo* studies were carried out to account for the recovery of the drug by intranasal administration.

MATERIALS AND METHODS

Materials

The Curcumin was received as a gift sample from Natural Remedies Pvt Ltd, Bangalore, India. sodium hydroxide and potassium dihydrogen phosphate were purchased from Thermo Fisher Scientific India Pvt. Ltd., Bangalore, India. Carbopol 934 was purchased from Rolex Chemical Industries,47 Babu Genu Road B K Society, Mumbai, India and PF127 was purchased from Sigma- Aldrich Chemical Pvt Ltd., Bangalore. The distilled water was produced in our research laboratory with a distillation unit.

METHODS

Preparation of Curcumin nanoparticles

Chitosan nanoparticles were formulated by ionic cross-linking of chitosan solution with Tripolyphosphate anions. Chitosan was dissolved in an aqueous solution of acetic acid (0.25%v/v) at different concentrations such as 1.0, 2.0, 3.0, and 4.0 mg/ml at room temperature under magnetic stirrer, 5 ml of (0.84%w/v) Tripolyphosphate aqueous solution was added dropwise using a syringe needle into 10 ml chitosan solution containing 10mg of Curcumin. pH6 was adjusted by adding 0.1 M NaOH. The stirring was carried about 30 min. The prepared nanoparticle suspensions were centrifuged at 12000X g for 30 min using a C24 centrifuge(Table 1). The formation of the particles was a result of the interaction between the negative groups of the TPP and the positively charged amino groups of chitosan.[9]

Table 1: Composition of Curcumin loaded nanoparticles

CODE	DRUG CARRIER RATIO	DRUG (mg)	POLYMER (mg)	ACETIC ACID (%v/v)	TPP (ml)
F1	1:1	10	10	0.25	5
F2	1:2	10	20	0.25	5
F3	1:3	10	30	0.25	5
F4	1:4	10	40	0.25	5

Characterization of Nanoparticles

Nanoparticles were characterized for different parameters such as morphology, particle size, and drug entrapment efficiency, and *In vitro* release studies.[10]

In vitro drug release study

In vitro drug release study was carried out by using a dialysis tube with an artificial membrane. The prepared curcumin nanoparticles were re-dispersed in 5 ml of phosphate buffer pH 6.4 and subjected to dialysis by immersing the dialysis tube in the receptor compartment containing 150 ml of phosphate buffer pH 6.4. The receptor medium was agitated continuously using a magnetic stirrer and the temperature was maintained at 37 ± 1˚C. 5ml sample of receptor compartment was taken at various intervals of time throughout 12 h and each time 5 ml fresh buffer was replaced. The amount of drug released was determined spectrometrically at 424 nm.[11]

Preparation of nasal in situ gel containing Curcumin nanoparticles

Carbopol-poloxamer gel of Curcumin was prepared by the cold method. Carbopol 934 (0.5%-1% w/v) was initially dissolved in deionized water using a magnetic stirrer. Following complete dissolution, the solution was cooled in an ice bath, PF127 (18-20%w/v) was then added slowly with continuous stirring. The mixture was kept in fridge at 4˚C for 24 h to ensure complete wetting and removal of entrapped air bubbles. The calculated amount of Curcumin nanoparticles was slowly added to the prepared polymer solution making 1%, and 2% w/w was then added to the polymer solution while stirring in ice cold water bath(Table 2). All samples were then transferred into amber bottles and stored in the refrigerator.[12]

Table 2: Composition of thermoreversible in situ gel(%w/w)

Formulation code	Nanoparticles	Carbopol 934 %w/w	PF127 %w/w	Distilled water
F1G1	1:1	0.5 (-)	18 (-)	QS
F1G2	1:1	1 (+)	18 (-)	QS
F1G3	1:1	0.5 (-)	20 (+)	QS
F1G4	1:1	1 (+)	20 (+)	QS

Experimental design:

In this study, 2×2factorial design was carried out to optimize the thermoreversible in situ nasal gel. The concentration of Carbopol 934 (X1) and concentration ofPF127 (X2)were selected as the independent variables at 2 levels. The levels were selected based on preliminary studies. The dependent variables selected were *In vitro* drug release at 12 h (Z1), and gelation temperature (Z2) (Table 3). The polynomial equations and response surface plots giving the effect of variables on the responses were generated.

Table 3: Factors and Levels with their real values

FACTORS	Low Level (-)	High Level (+)
Carbopol 934	0.5 %	1 %
PF127	18 %	20 %

Evaluation of Prepared *in situ* gel

Determination of pH

One ml of the prepared gels was transferred to a 10 ml volumetric flask, and the solution was diluted with distilled water. The pH of the resulting solution was determined using a digital pH meter.

Viscosity

The viscosity of the in-situ gel systems was determined using a Brookfield viscometer coupled with an S-94 spindle (Brookfield Engineering Laboratories Inc., MA, USA). The prepared gel formulations were transferred to the beaker. The spindle was lowered perpendicularly into the gel at l00 rpm and temperature was maintained at 37±0.5 °C. The viscosity was determined during the cooling of the system.[13]

Spreadability

The formulated gel was determined for its spreadability after 48 hours of preparation, it was measured by spreading one gram of gel in between two plates made up of glass for 1 minute. Weight of 125 g was kept on the upper glass plate to evenly distribute the gel. The mathematical formula was expressed as

$$S = M \times L / T$$

Where,
M = weight tied to the upper slide
L = length of glass slides
T = time taken to separate the slides [14]

Gelation temperature

The gelation temperature was determined using the test-tube inverting method. A volume of 2ml of the in-situ gel was placed in a test tube, which was then immersed in a water bath at 15˚C. Then the water bath temperature was gradually increasing, samples were examined every 2 minutes, and the gelation temperature was recorded when the gel stopped flowing upon test tube inversion at 90˚.[15]

In Vitro Drug Release Study

An *In vitro* drug release study of formulated in situ gels was carried out on the Franz diffusion cell. Franz diffusion membrane was used as a diffusion membrane. The diffusion cell was filled with phosphate buffer pH 6.4, diffusion membrane was mounted on the cell. The temperature was maintained at 34-37°C. At predetermined time points, 1 ml samples were withdrawn from the acceptor compartment, replacing the sampled volume with phosphate buffer pH 6.4, after each sampling, for a period of 12 h. The samples withdrawn were filtered and used for analysis. Blank samples were run simultaneously throughout the experiment to check for any interference. The amount of diffused drug was determined at 424 nm using on UV visible spectrophotometer, Shimadzu UV 1800.[16]

Ex vivo drug permeation study

Ex vivo permeation study was conducted using a dialysis bag containing 150 ml of phosphate buffer (pH 6.4 0.1 M) using an excised goat nasal mucosa. The goat's nose was obtained from a local slaughterhouse within 15 min after the goat was sacrificed. After removing the skin, the nose was stored on ice-cold phosphate buffer (pH 6.4, 0.05 M). The septum was fully exposed, and nasal mucosa was carefully removed using forceps and surgical scissors. The freshly excised nasal mucosa was mounted on the diffusion cell, and gel containing an equivalent dose of 50 mg Curcumin nanoparticles was placed on it. Throughout the study, the buffer solution in the chamber was maintained at 37±1° by connecting the dialysis bag to the water bath. At predetermined time intervals, 1 ml of the samples was withdrawn at a pre-determined time interval and replaced with an equal amount of phosphate buffer. The samples were appropriately diluted and filtered and absorbances were measured spectrophotometrically at 424 nm using a Jasco V-550 UV/Vis Spectrophotometer (Tokyo, Japan), taking phosphate buffer (pH 6.4) as the blank. [17-18]

RESULTS AND DISCUSSION

Physicochemical Characterization of Nanoparticles

Nanoparticles prepared by ionic gelation technique were found to be discrete and through SEM analysis (Fig. 1), where the mean size distribution was found to be 299 nm and 483.The drug entrapment efficiency of nanoparticles prepared by ionic gelation technique containing drug: polymer in various ratios of 1:1, 1:2, 1:3, and 1:4 was found to be 87.2%, 84.1%,81.5%, and 76.9% respectively(Table 4) and thus, there was a steady increase in the entrapment efficiency by decreasing the polymer concentration in the formulation. The high entrapment efficiency is likely due to electrostatic interactions between the drug and the polymer. The *In vitro* drug release studies were carried out for all formulation in phosphate buffer pH 6.4. All batches showed sustained release over 12 h shown in Fig 2.

Table 4: Characterization of Curcumin nanoparticles.

Sl.No	Batch code	Drug: carrier ratio	Invitro drug release	Entrapment efficiency (%)	Particle size(nm)
1	F1	1:1	81.8%	87.2±0.23	299±5.04
2	F2	1:2	76.3%	84.1±0.56	344±4.2
3	F3	1:3	72.2%	81.5±0.58	389±8.9
4	F4	1:4	69.1%	76.9±0.42	483±10.5

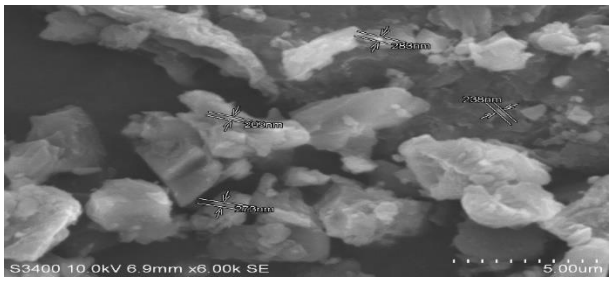

Figure 1: SEM of Formulation F1

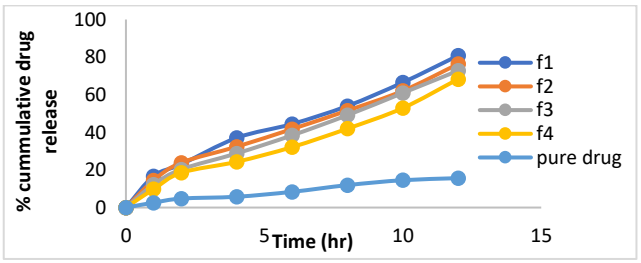

Figure 2: *In vitro* drug release profile of nanoparticles formulation F1-F4

Evaluation of Curcumin *in situ* gel

Optimization

A total of 4 trial formulations were proposed by the 2×2 factorial design for 2 independent variables Concentration of Carbopol 934 (X1) and concentration ofPF127 (X2)), which were varied at two different levels (high, low). The effect of these independent variables on gelation temperature and cumulative drug release after 12 h (%) was investigated. According to the 2×2 factorial design, various trial formulations of nasal in situ gel containing Curcumin nanoparticles were prepared by Cold method. An overview of the experimental trials and observed responses is presented in (Table 6).

pH

It is known that the normal physiological pH of nasal mucosa is 5.5-6.5 however the nasal mucosa can tolerate solutions within the pH range of 3-10. The pH of all gel formulations was found to be in a range of 6.1 to 6.5 which is between the physiological ranges of pH of the nasal mucosa (Table 5).

Viscosity Studies

Viscosity measurement of the formulations at 4˚C and 37˚C temperatures showed that there was an increase in viscosity with an increase in temperature. This indicated the formation of the temperature-induced gel structure of poloxamer(Table 5).

Spreadability

The spreadability studies results shown in Table 4 revealed that spreadability decreases when the polymer concentration of in-situ gel formulation increases. The spreadability of all prepared in-situ gel formulations was found to be in the range of 12.70-21.04gm*cm/sec.(Table 5)

Table 5: pH, Viscosity, and Spreadability of in situ nasal gel

Formulation code	pH	Viscosity (Cps) at 37˚C	Spreadability gm*cm/sec
F1G1	6.1	10750	14.25±0.1
F1G2	6.3	11400	15.00±0.2
F1G3	6.4	10550	19.29±0.3
F1G4	6.5	11650	16.41±0.2

Gelation temperature

The gelation temperature (T) is an important parameter for in-situ forming of hydrogels. The performance criteria of the nasal-delivery formulations are imposed by the physiological temperature of the nasal cavity (30–35°C) and by the mucociliary clearance time (half-life 21), which correspondingly specify the temperature range and time limits for the sol-gel transition. (Table 6)

***In Vitro* drug release**

The *Invitro* drug release studies were carried out for all formulated nasal in situ gels containing Curcumin nanoparticles in phosphate buffer pH 6.4. All batches showed sustained release over 12 h. The cumulative drug release from these nasal in situ gel containing Curcumin nanoparticles was within the range of 84.82% to 93.97% a sustained drug release from nasal in situ gel. The bio-adhesive polymer retarded the drug release from the nasal gel, the retarding effect thereby delaying the release process. (Table6&Figure5)

Table 6: Gelation temperature and % drug release of in situ nasal gel

Formulation code	Gelation Temperature (˚C)	*Invitro* drug release (%)
F1G1	52±0.9˚C	90.84%
F1G2	50±1˚C	84.82%
F1G3	33±1˚C	93.97%
F1G4	31±0.2˚C	86.83%

The result of ANOVA, as shown in Table6, indicated that all models were significant (P<0.05) for all response parameters investigated. In addition, Design-Expert 8.0.0 software generates contour and three-dimensional response surface plots for gelation temperature and drug release are presented in Fig3 and4 respectively.

Table 7: Summary of ANOVA for the response parameter of % drug release.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	50.20	2	25.10	1822.92	0.0166	Significant
A-% drug release	6.90	1	6.90	501.45	0.0284	
B-Gelation temperature	50.20	1	50.20	3645.63	0.0105	
Residual	0.0138	1	0.0138			
Cor Total	50.21	3				

X1 represents the concentration of Carbopol 934 and X2 representsPF127 respectively. X1&X2are the interaction effects. S and NS indicate significant and non-significant, respectively d.f. indicates the degree of freedom.

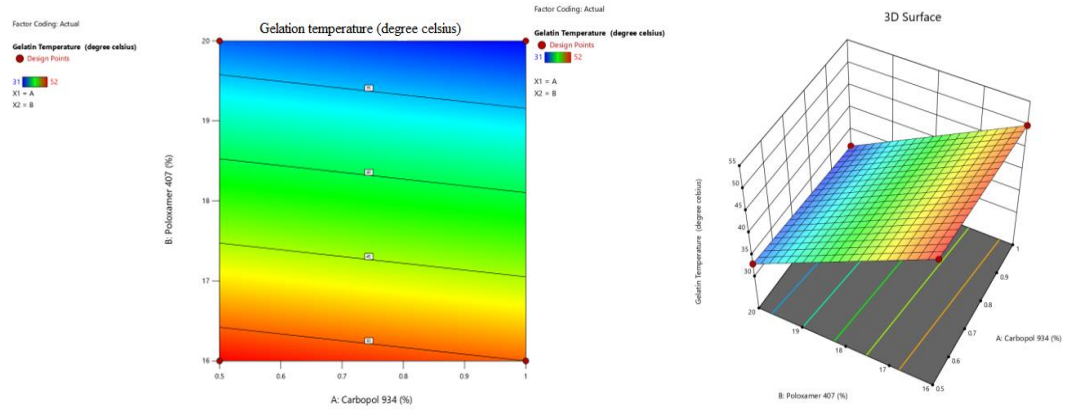

Figure 3: Contour and three-dimensional response surface plots for Gelation temperature

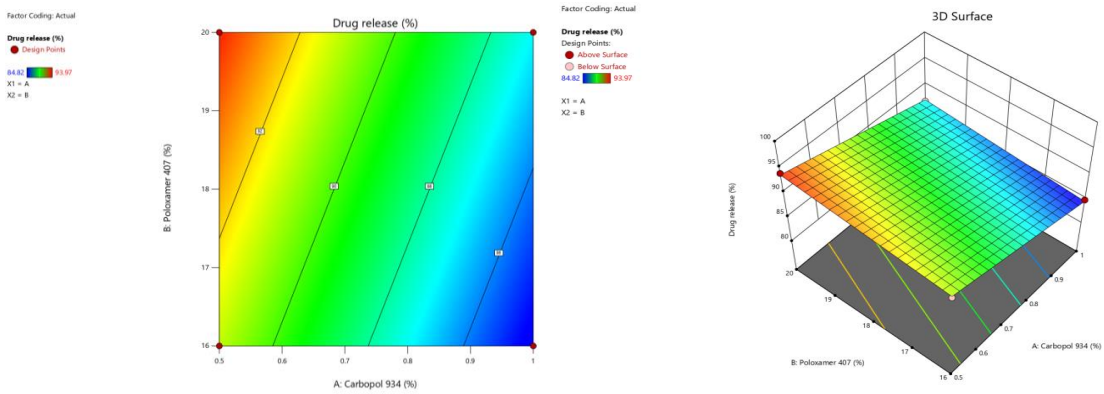

Figure 4: Contour and three-dimensional response surface plots for % drug release

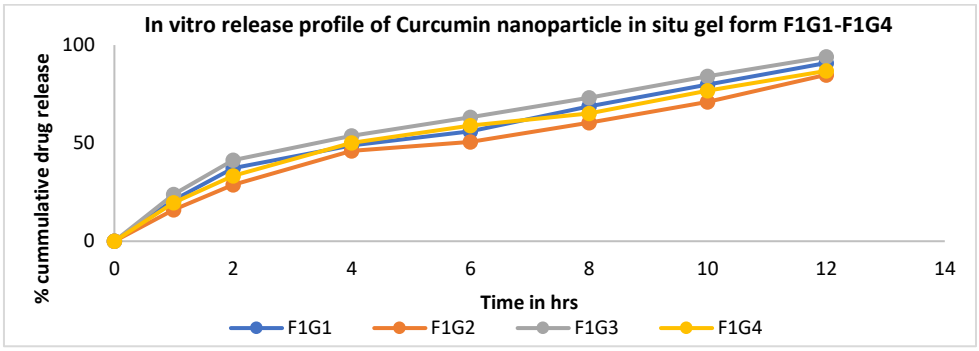

Figure 5: *In vitro* drug release of nasal in situ gel of Curcumin nanoparticles in phosphate buffer pH 6.4

Table 8: Results of curve fitting of the *Invitro* release data for in situ nasal gel

Formulation code	%CDR	Zero-order	First order	Higuchi	Peppas	n values
F1G1	90.85	0.9417	0.9467	0.9902	0.6045	1.14
F1G2	84.83	0.9535	0.9516	0.9825	0.657	1.17
F1G3	93.97	0.9216	0.9427	0.9953	0.5815	1.13
F1G4	86.84	0.9329	0.9721	0.9938	0.6185	1.15

From the above results we can conclude that F1G3 formulation is optimized because, it shows suitable nasal pH, desirable nasal temperature and spreadability. *In vitro* drug release shows more drug release compare to other formulations due to increase in the concentration of Carbopol 934 drug release will be decreased. So F1G3 formulation is selected for the *ex vivo* permeation study.

Ex vivo drug permeation study

Ex vivo drug permeation study was carried out only for optimized formulation (F1G3) using the nasal mucosa of a goat. The cumulative drug release from these nasal in situ gel containing Curcumin nanoparticles was 86.27%showing controlled drug release for a prolonged period. (Fig 6)

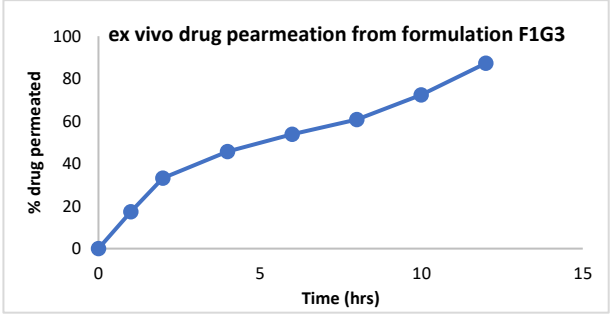

Figure 6: *Ex vivo* drug permeation of Curcumin nanoparticles in situ nasal gel in phosphate buffer pH 6.4

Table 9: Release kinetic profile of F1G3 formulation

Time	Log time	Square root time	%CDR	Log %CDR	% Drug remaining	Log %cum drug remaining
0	0	0	0	0	100	2
1	0	1	17.41	1.2408	82.5892	1.9169
2	0.3011	1.4142	33.25	1.5219	66.7411	1.8243
4	0.6021	2	45.75	1.6604	54.2411	1.7343
6	0.7782	2.4494	53.79	1.7307	46.2054	1.6646
8	0.9031	2.8284	60.71	1.7832	39.2857	1.5942
10	1	3.1623	72.32	1.8592	27.6785	1.4421
12	1.0792	3.4641	87.27	1.9408	12.7232	1.1045

Table 10: Results of curve fitting of the *ex vivo* release data from nasal in situ gel (F1G3)

MODELS	F1G3
Zero-order(r^2)	0.9451
First order(r^2)	0.9391
Higuchi(r^2)	0.9828
Peppas(r^2)	0.6324
'n' value	1.15

CONCLUSION

The present study represents a thermoreversible in situ nasal gel containing Curcumin nanoparticles developed using the cold method. Formulation F1was selected as an optimum formulation based on drug entrapment efficiency, particle size, morphology, zeta potential, and *In vitro* release of nanoparticles. Curcumin nanoparticle in situ gel was successfully developed by using Poloxamer 407and Carbopol 934 with the help of a 2×2 factorial design. Formulation (F1G3) was found to be optimized due to its desirable gelation temperature (33°C), desirable nasal pH (6.4), and *In vitro* drug release (93.97%) and *ex vivo* permeation studies suggested that Carbopol not only acts as a mucoadhesive agent but also as a penetration enhancer whereas poloxamer acts as thermoreversible polymer leading to the controlled release of a drug for a prolonged time. In conclusion, intranasal gel of curcumin nanoparticles could be a better alternative to existing conventional dosage forms to improve drug bioavailability and patient compliance.

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