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Original Article

IN SITU GEL FORMULATION OF POTASSIUM NITRATE: A NOVEL APPROACH TO TREAT DENTIN HYPERSENSITIVITY

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ABSTRACT

Objective: The objective of the present study was to develop an *in situ* gelling formulation of potassium nitrate for the treatment of dentin hypersensitivity (DH).

Methods: Formulation was optimized using 3^2 full factorial design, wherein the concentration of two gelling agents, poloxamer 407 and chitosan (90% deacetylation) were the independent variables and formulation viscosity and gelation time were dependent variables. The trial formulations were evaluated for pH, spreadability, drug content, adherence time, and *in vitro* drug release, apart from viscosity and gelation time.

Results: The optimized formulation containing 22% of poloxamer 407 and 0.5 % of chitosan exhibited a gelation time of less than 150 s, a viscosity of about 2450 cps, and thermoreversible sol-gel transition behavior. The novel *in situ* gel showed a pH of 4.58, and spreadability as 5.55 g. cm/s and adherence time 4.3 h. The formulation could sustain the drug release over a period of 4 h and it was found to be 81.83±1.03%. Accelerated stability studies conducted over 3 mo duration ensured good physical and chemical stability of the formulation.

Conclusion: The optimized *in situ* gel formulation of potassium nitrate in the sol state is expected to allow easy and site-specific administration on the sensitive tooth. Upon application, the temperature-sensitive sol would get converted to a gel that would improve its retention time on the sensitive tooth and extend the duration of therapeutic action by sustaining the drug release.

Keywords: Dentin hypersensitivity, Thermoreversible sol-gel, Potassium nitrate, Poloxamer, Chitosan

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INTRODUCTION

Dentin hypersensitivity (DH) is a condition associated with sharp, short pain when exposed dentin responds to particular stimuli like cold, hot, sweet, and sour. This condition is attributed to various factors and reasons like tooth decay, dental erosion, crack in the tooth, gingival recession, periodontal infection, excessive use of tooth whitening products, and so on [1]. The condition is more common among the adults in the age group of 20 to 49 y, with the highest prevalence in ages 30 to 39 y. Females are more prone to DH than the males [2, 3]. The major mechanisms of DH that have been proposed in the literature include direct innervation theory, odontoblast receptor theory, and hydrodynamic theory. The most widely accepted Bra¨nnstro¨m's hydrodynamic theory suggests that external stimuli cause movement of the dentin fluid in the tubules, resulting in pressure changes across the dentin. This stimulates intra-dental nerve response signals that are ultimately perceived as pain by the brain [4].

The treatment modalities for DH include at-home treatments and in-office treatments. At-home treatments involve the use of toothpastes, powders, mouthwashes, and gargles. In-office treatments are performed by professional dentists, that include filling treatments, laser treatments, and even tooth extraction [5]. Large number of actives are effective in reducing or even eliminating the symptoms of DH. Based on the mechanism of action, the actives used for desensitizing are broadly classified as nerve desensitizers (e. g.-potassium nitrate); protein precipitators (e. g.-glutaraldehyde, zinc chloride, silver nitrate) and dentinal tubules plugging agents (e. g.–sodium fluoride, stannous fluoride, potassium oxalate, calcium phosphate etc.)

Potassium-containing salts such as potassium nitrate, potassium chloride or potassium citrate are one of the most preferred actives in a variety of formulations meant for treating the DH. Potassium salts act by diffusing along the dentinal tubules and disturbing nerve transmission by interfering with the depolarization process. Lack of nerve transmission in response to the excitatory stimuli prevents the pain sensation and relieves the symptoms of DH [6].

The existing formulations for at-home treatment of DH, such as toothpastes and mouthwashes, have several limitations, like lack of sufficient retention time on the dental surface. When washed off, their effect recedes significantly. Also, these formulations are not site-specific and are applied to all the teeth, whereas the DH may be associated with only one or a few teeth [1, 2]. A few gel formulations are available in the market. However, owing to the higher viscosity and semisolid consistency, the gel application could be difficult and may incur wastage. These problems can be overcome by the development of an *in situ* gelling formulation, which is administered as a liquid/sol and undergoes a phase transition to a gel upon exposure to the physiological environment [7]. A liquid formulation would thus be easy to apply even to the difficult-to-access areas in the oral cavity with the aid of a special applicator nozzle. Transition of the sol to a viscous gel upon application would allow the formulation to adhere well to the tooth surface and prolong the contact time of the drug at the target site. This is expected to enhance the efficacy of the formulation, shorten the duration of the overall treatment regime, and provide a site-specific action.

Considering the aforementioned merits of an *in situ* gelling formulation, the aim of the current work was to design and optimize a thermosensitive sol-gel system for the treatment of DH [8]. To our knowledge, such a work has not been reported so far in the literature.

MATERIALS AND METHODS

Materials

Poloxamer 407 was obtained as a gift sample from BASF, Mumbai, India. Xylitol was obtained as a gift sample from ACG Worldwide, Mumbai. Potassium nitrate, chitosan (90% deacetylation), methyl paraben and propyl paraben, clove oil, and glacial acetic acid were of analytical grade. They were purchased from Analab Finechem, Pune, India.

Methods

Selection of gelling agents

Placebo formulations with varying concentrations of poloxamer 407 alone and in combination with other polymers like chitosan [9] and xanthan gum [10] were prepared and evaluated for consistency and thermoresponsive gelling behavior (table 1).

Table 1: Preliminary trials for polymer selection

Ingredients (% w/w)	P1	P2	P3	P4	P5	P6	P7	P8
Poloxamer 407	20	26	20	20	20	20	20	20
Chitosan (90%)	-	-	0.3	0.5	0.7	-	-	-
Xanthan gum	-	-	-	-	-	0.5	1.0	1.5
1% Glacial acetic acid solution	-	-	10	10	10	-	-	-
Purified water q. s	100	100	100	100	100	100	100	100

In case of trials P1and P2, poloxamer was accurately weighed and dispersed in cold (4-6 °C) purified water under agitation. The clear solution was obtained by keeping the suspension in the refrigerator for 1-2 h.

In case of trials P3-P5, chitosan solutions were prepared in 1% v/v of glacial acetic acid solution. These solutions were mixed with poloxamer 407 solution prepared in afore mentioned manner.

Varying concentrations of xanthan gum were used in combination with poloxamer in the trials P6 to P8. The gum was dispersed in purified water with constant stirring to form a slurry. This slurry was then mixed with previously prepared poloxamer 407 solution.

Preparation of *in situ* gelling formulations of potassium nitrate

In the present work *in situ* gel of poloxamer 407 and chitosan was prepared as previously reported by Gratieri *et al.* [11] Chitosan was accurately weighed and dispersed in 1% v/v of glacial acetic acid solution. The dispersion was kept aside for 10–15 min. Methyl and propylparaben were dissolved in a sufficient amount of purified water with the aid of heating at 80 °C. To this solution, weighed quantities of xylitol, sodium saccharin, and potassium nitrate were added and dissolved. The chitosan solution and drug solution were mixed together, poloxamer 407 was added to the solution and refrigerated (2-8 °C) until the polymer dissolved completely. The formulation was allowed to attain room temperature. Clove oil was then added to the prepared formulation and the weight was then made up to 100 g by adding purified water. The formulation was filled in double lacquered collapsible aluminum tubes.

Optimization studies

Design Expert software version 10 (Stat-Ease Inc., Mineapolis, MN, USA) was employed to optimize the *in situ* gelling formulation [12]. A 3^2 randomized full factorial design was employed in the present study. In this design, two factors were evaluated, each at three levels and experimental trials were performed for all ten possible combinations suggested by the software (table 3). The concentration of chitosan (X_1) and concentration of poloxamer 407 (X_2) were chosen as factors. Viscosity and gelation time were considered as responses or dependent variables. Viscosity in the range of 2200-2500 cps in the gel state and gelation time of NMT 150 s were laid down as the constraints on the response variables. Each factor was studied at 3 different levels (-1, 0,+1) viz. X_1 (concentration of poloxamer 407) each at 18% w/w, 20 %w/w, 22% w/w; whereas X_2 (concentration of chitosan) each at 0.025%w/w, 0.26%w/w, 0.5 %w/w.

Table 2: Composition of *in situ* gelling formulations of potassium nitrate

Ingredients (% w/w)	X1	X2	X3	X4
Potassium nitrate	5	5	5	5
Poloxamer 407	20	20	20	20
Chitosan (90%)	0.3	0.3	0.3	0.3
Methyl paraben	0.18	0.18	0.18	0.18
Propyl paraben	0.02	0.02	0.02	0.02
Xylitol	5	5	10	10
Glacial acetic acid solution	10	10	10	10
Clove oil	0.1	0.25	0.1	0.25
Purified water q. s	100	100	100	100

Table 3: Trial runs for the optimization of *in situ* gelling formulation of potassium nitrate

Polymers (%w/w)	F1	F2	F3	F4	F5	F6	F7	F8	F_9	F_{10}
Potassium nitrate	5	5	5	5	5	5	5	5	5	5
Chitosan	0.50	0.26	0.50	0.26	0.025	0.26	0.26	0.50	0.025	0.025
Poloxamer 407	22	20	18	22	18	18	20	20	20	22
Xylitol	5	5	5	5	5	5	5	5	5	5
Methyl paraben	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Propyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Glacial acetic acid (1 % v/v)	10	10	10	10	10	10	10	10	10	10
Clove Oil	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Purified water q. s	100	100	100	100	100	100	100	100	100	100

Evaluation of *in situ* gelling formulations

Appearance

The formulations were evaluated for appearance by visual observation against the black and white background.

pH determination

pH of the formulations was determined using a digital pH meter. (EQ-614, Equip-Tronics, India)

Gelation temperature and time

It was determined by using the method described by Miller and Donovan technique [13]. The test tube containing about 2 g of the formulation was immersed in the water bath. The temperature of the water bath was increased slowly and left to equilibrate for 5 min at each new setting and gelation temperature and time were recorded for the transformation of sol into gel.

Viscosity

The viscosity of the formulations was measured using Brookfield digital viscometer (Brookfield Engineering Laboratories, USA, Model LVDVE). Spindle no.62 was used at 50 RPM to monitor the viscosity of formulations in sol state at room temperature. The preparations were then allowed to convert to gel by heating them till 37 °C on a water bath and the resulting gels were subjected to viscosity studies using spindle no.63 at 20 RPM [14].

Spreadability

About 1 g of formulation in the gel form was placed at the center of the glass plate (10 x10 cm). Another glass plate was mounted over it carefully. Standard weight of 1 kg was placed on the plate (avoiding sliding of the plate) [15]. The diameter of the gel in cm was measured after 30 min. The spreadability parameter was calculated using the formula–

$$S = M * l/t$$

where,

S = spreadability

M = weight applied on upper slide

t = time taken

l = diameter of gel spread on plate

The spreadability of each formulation was determined in triplicate.

Adherence time

Human extracted molars obtained from a dental clinic were used for this study. They were pre-washed with hydrogen peroxide solution and placed in a petri dish. The dish was filled with phosphate buffer pH 6.8 and maintained on water bath thermostatically controlled at 37 °C. The *in situ* gelling formulations were applied to the dental surface with the help of a micropipette and observed for gelation time. The buffer was intermittently added over the tooth surface to mimic the oral cavity conditions. The observation of the teeth was continued till the gel disappeared from the tooth surface. The time of adherence was noted for all the formulations.

Drug content

About 1 g of formulation (equivalent to 50 mg of potassium nitrate) was weighed accurately and added to 25 ml of simulated salivary fluid (SSF). The mixture was stirred on magnetic stirrer to dissolve the drug. The volume was made up to 100 ml with SSF. The aliquot of 1 ml of the above solution was diluted to 10 ml with SSF. The absorbance of the sample solution was determined at 301 nm against SSF as blank using UV visible spectrophotometer (UV-1700, Schimadzu Corp., Japan) Drug content was determined in triplicate.

***In vitro* drug release studies**

The prepared formulations were subjected to *in vitro* release studies using Franz diffusion cells. SSF was filled up to the brim in the receptor chamber of the cells and maintained at 37 °C with the help of a circulating water bath [14]. The receptor medium was continuously agitated at 100 RPM. Donor compartment comprised of about 1 g formulation spread evenly. Donor and receptor compartments were separated by cellophane membrane (molecular weight cut off-12000 Daltons). Aliquots of 3 ml were withdrawn at regular intervals (30, 60, 90, 120, 180, 240 min) and replaced by an equal volume of the fresh SSF. The drug content in samples was analyzed spectrophotometrically at 301 nm.

Accelerated stability studies

The formulation F1 (table 3) was prepared in bulk amount. It was filled in double lacquered aluminum collapsible tubes and subjected to stability studies as per the conditions mentioned in table 4. The samples were evaluated for spreadability, pH, gelation time and temperature, viscosity, and drug content.

Table 4: Test conditions for accelerated stability studies

S. No.	Parameters	Test conditions
1	Duration of study	3 mo
2	Temperature, RH conditions	40 °C±2 °C, 75±5% RH
3	Frequency of testing	Initial, 1 mo, 2 mo, 3 mo

RESULTS

Selection of the gelling agents

Placebo formulations using poloxamer 407 alone and incorporating combinations of poloxamer 407 with various polymers like chitosan and xanthan gum were prepared and evaluated visually for appearance and consistency at room temperature as well as at 37 °C Composition containing 20 % w/w poloxamer 407 showed inadequate gelling at 37 °C Composition P2 containing Poloxamer 407 at the concentration of 26 % w/w resulted in a firm and clear gel formation at body temperature. However, this composition at room temperature was quite viscous and that could compromise the ease of application to the affected tooth. Similarly, the combination of 20% poloxamer and xanthan gum at various concentrations (Compositions P3-P5) produced the sols of higher viscosity at room temperature. This defeated the purpose of developing the *in situ* gelling formulations and hence trials with xanthan gum were discontinued. Formulae P6-P8 prepared using a combination of 20% poloxamer 407 and chitosan exhibited lower viscosity at room temperature but desirable gel-like consistency at 37 °C. Our observation corroborated well with the studies conducted by Gratieri *et al.* [11] Hence this combination was chosen for further studies.

Preparation of *in situ* gelling formulations of potassium nitrate

In situ gelling formulations of potassium nitrate were prepared using 20% poloxamer 407 and 0.3% chitosan. Methyl and propylparaben were added as antimicrobial preservatives. Xylitol was used as a sweetener and clove oil as a flavouring agent in the formulations. Xylitol at 10% concentration imparted extra sweetness (X3 and X4), while at 5% contributed appropriate sweet taste. (X1 and X2) Clove oil in 0.1% w/w did not impart much flavor and aroma to the formulation (X1), while 0.25 % w/w gave pleasant flavor and taste to the preparation (X2). Hence 5 % w/w xylitol and 0.25 % w/w clove oil (X2) were selected as sweetener and flavoring agent, respectively.

Optimization studies

Optimization studies involved preparation of 10 trial formulations suggested by Design Expert Software Version 10. A 3P2P full factorial design adopted in order to optimize the formulation for viscosity and gelation time.

Effect of formulation variable on viscosity

The formulations prepared as per the trial runs given in table 3 showed viscosity in the range as 968–2410 cps (37 °C).

The responses of viscosity were fed in software. An equation for response Y1 i.e., viscosity, was produced as a function of independent variables viz. concentration of poloxamer 407 and concentration of chitosan.

$$Y_1 = 1179.20+1068.07 * X_1+140.16 * X_2$$

The result of multiple linear regression analysis showed that both the coefficients b1 and b2 bear a positive sign. Increment in the concentration of X_1 (Poloxamer 407) and X_2 (Chitosan) resulted in a linear increase in the viscosity.

The contour plot and response surface plot (fig. 1) confirmed the linearity of the model with no interactions between the independent variables. The model was found to be significant. ($p = 0.0227$).

Effect of formulation variables on gelation time

The responses of gelation time were fed in the software. An equation for response Y2 was produced as a function of independent variables and expressed as follows-

$$Y_2 = 130.2-152.28 * X_1-50.5 * X_2$$

The negative signs of both the coefficients indicated a linear decrease in the gelation time with an increase in the concentration of X_1 (poloxamer 407) and X_2 (chitosan). The model was found to be significant as the probability i.e. p was less than 0.05 ($p = 0.0001$).

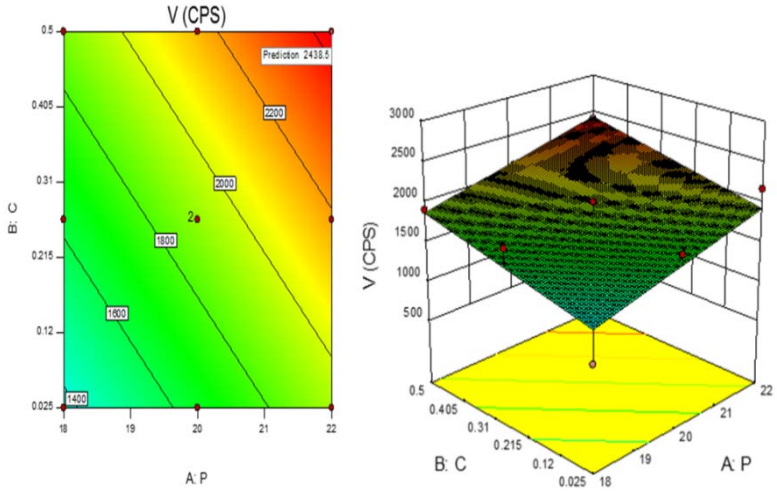

Fig. 1: Contour plot and surface response plot of viscosity as a response variable and Concentration of poloxamer 407 and chitosan as independent variables

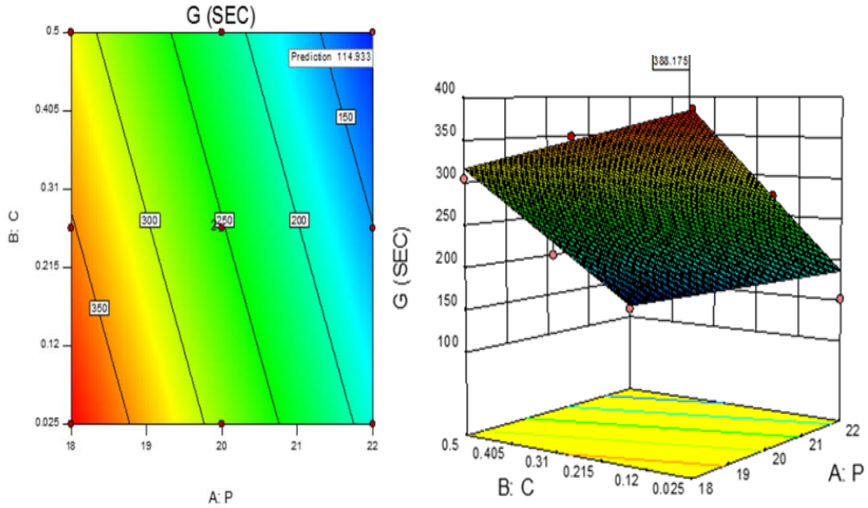

Fig. 2: Contour plots and surface response plots of gelation time (response variable) and concentration of poloxamer 407 and chitosan as independent variables

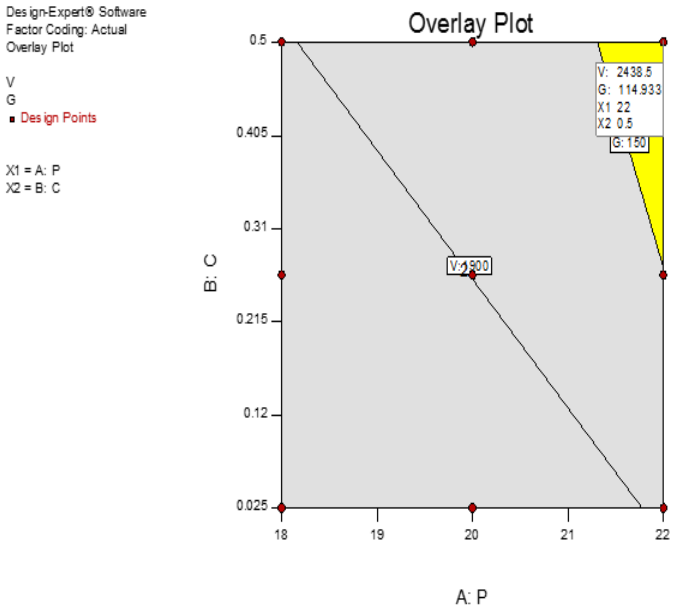

Fig. 3: Overlay plot of optimized formulation

Formulation of optimized formulation of *in situ* gel

After generating response surface plots, an optimization process was undertaken with desirable characteristics of responses to probe the optimal solution. An overlay plot was obtained by overlapping the contour plots of two responses. Yellow zone in fig. 3 indicates the design space fulfilling the criteria of (2200-2500 cps) viscosity and NMT 150 s of gelation time. The desirability function was utilized to find out the optimized formulation. Formula F1 showed the highest overall desirability function of 0.756. Therefore, formulation F1 was considered as the optimum formulation with a concentration of poloxamer 407 at 22% w/w and chitosan at 0.5% w/w; and the values of independent variables of this formula were considered to be optimum for the preparation of *in situ* gelling formulation.

Evaluation of formulations

The evaluation parameters of the trial formulations are summarized in table 5.

All the formulations had acceptable appearance, clarity, fragrance, and taste. The pH of the formulations was in the range of 4.5–4.79.

Table 5: Evaluation of *in situ* gelling formulations

Formulation no.	Viscosity (cps)		Gelation time (sec)	Adherence time (h)	Spreadability (g/cm. sec)
	4 °C-6 °C	37 °C			
F1	593±2.62	2410±1.24	110±0.47	4.30±0.1	4.55±0.2
F2	291±1.69	1789±2.16	162±1.02	4.10±0.1	4.98±0.1
F3	318±1.25	1913±1.63	205±0.47	3.70±0.1	4.34±0.2
F4	434±1.25	2008±2.21	185±0.94	4.30±0.1	5.25±0.4
F5	170±1.09	968±1.44	390±0.38	2.30±0.1	5.91±0.2
F6	212±1.32	1844±1.38	358±1.01	2.30±0.2	4.91±0.1
F7	294±2.04	1978±1.06	169±1.02	4.00±0.1	5.36±0.4
F8	253±1.07	1889±2.04	200±0.47	3.30±0.1	4.87±0.2
F9	196±1.25	1776±1.63	190±1.02	4.00±0.2	5.43±0.1
F10	470±1.31	2172±1.43	152±0.38	4.30±0.1	5.69±0.2

Note: All data is expressed as mean±SD, n=3

Gelation temperature

The gelation temperature of all the formulations was found to be in the range of 36 °C–37.8 °C. It is found to be satisfactory as the temperature inside the oral cavity is in the above-given range i.e., from 36.4 °C–37.5 °C.

Drug content

Drug content of all the trial batches was found to be in the range of 98–102%. This indicates the uniformity of drug content and non-interference of excipients in the estimation of the assay.

***In vitro* drug release studies**

The *in vitro* release profiles of the trial formulations are depicted in fig. 4 and 5.

The formulations could sustain the release of potassium nitrate up to 4 h. Preparations containing lower concentration of gelling agents (F5–F9) showed faster release initially up to 1.5 h in comparison with other formulations. This could be attributed to the lower viscosity of these formulations. At later time points, there was no significant difference between the drug release of the formulations.

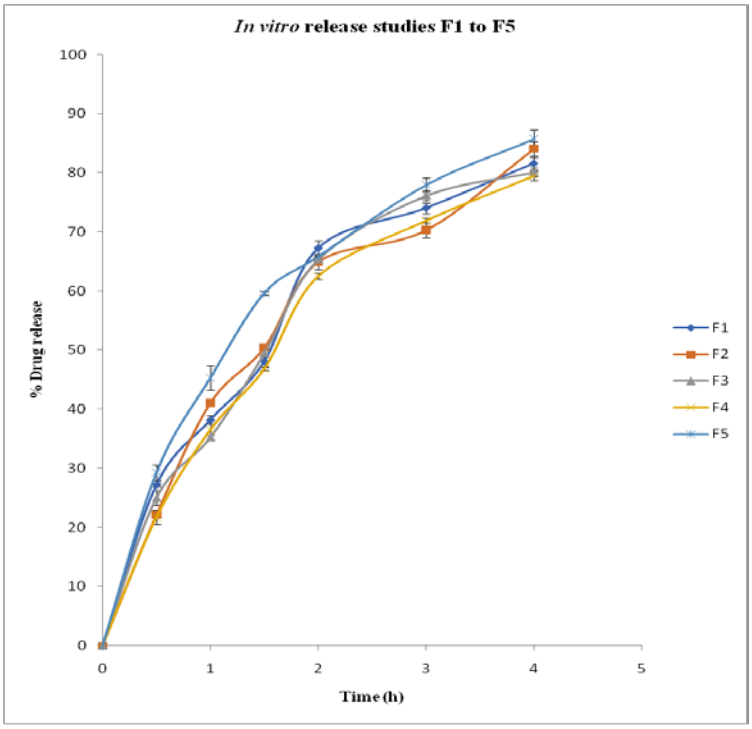

Fig. 4: *In vitro* release studies for formulations F1–F5, Note: All data is expressed as mean±SD, n=3

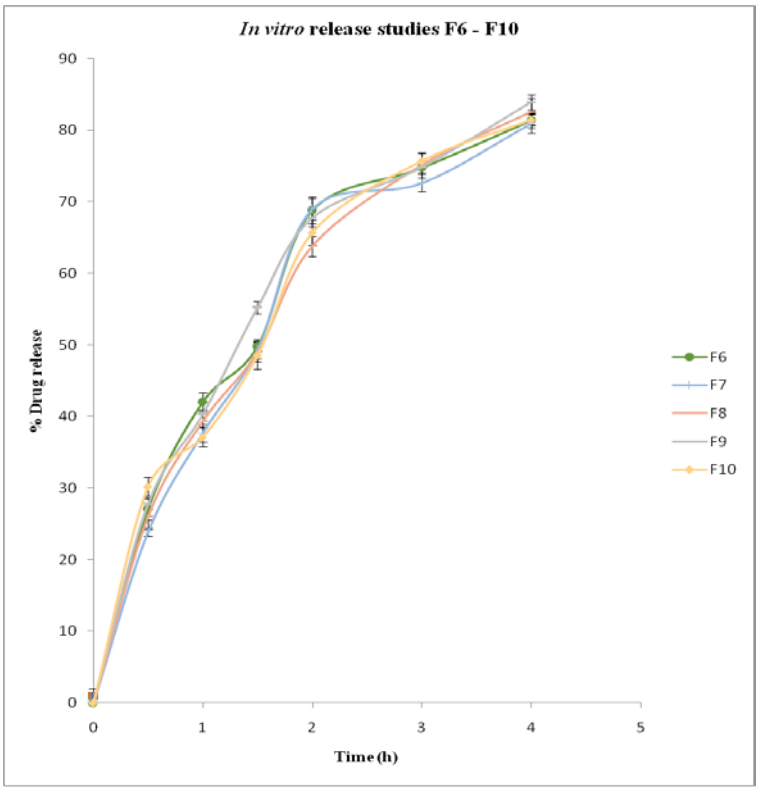

Fig. 5: *In vitro* release studies for formulations F6–F10, Note: All data is expressed as mean±SD, n=3

Accelerated stability studies

The formulation samples subjected to stability studies were clear in appearance, thick consistency with characteristic clove oil aroma, sweet with an astringent aftertaste. Since the samples were subjected to 40 °C storage temperature, they were in the state of gel, which upon subjecting to room temperature, converted to viscous solutions.

Table 6: Evaluation parameters of stability samples

S. No.	Initial	1 mo	2 mo	3 mo
pH	4.56±0.04	4.64±0.03	4.59±0.04	4.71±0.02
Viscosity (cps) at 37 °C	2449±1.15	2384±1.73	2330±1.5	2401±1.15
Gelation time (s)	110±0.5	105±1.0	111±1.52	110±1.52
Adherence time (h)	4.3±0.01	4.3±0.02	4.3±0.01	4.3±0.02
Spreadability (g. cm/s)	5.59±0.04	5.49±0.06	5.78±0.06	5.13±0.05
Drug Content (%)	99.73±1.02	97.89±0.57	99.20±1.05	98.37±0.82
% *in vitro* drug release at 4 h	81.83±1.03	81.19±1.21	80.69±1.30	80.57±1.23

Note: All data is expressed as mean±SD, n=3

As seen in table 6, the formulation after storage at accelerated conditions showed acceptable physical and chemical stability. The viscosity, gelation time, *in vitro* release profile of stability samples did not show any significant difference when compared to that of the initial sample. The optimized formulation was thus considered stable at the end of 3 mo study period.

DISCUSSION

Dentine hypersensitivity also called as cervical dentinal sensitivity or tooth sensitivity, is a common but significant clinical problem. It manifests as a brief, sharp pain arising from exposed dentin. It occurs typically in response to chemical, thermal, evaporative, or osmotic stimuli [4, 11]. Large number of diverse formulations with different desensitizing agents are employed in the treatment of dentin hypersensitivity [16]. Potassium, responsible for preventing nerve transmission, is the primary agent for at-home desensitizing toothpastes. Studies have reported that dentifrices containing potassium ions are effective in reducing sensitivity and the American Dental Association Council on Dental Therapeutics has granted its Seal of Acceptance to dentifrices containing 5% potassium nitrate (Council on Dental Therapeutics 1986) [17, 18]. Hence for the formulation potassium nitrate was used as an active ingredient of choice. Toothpastes, powders, mouthwashes and rinses, tooth gels are the commonly prescribed at-home remedies for DH [19]. Though popular, these formulations have their own limitations. Toothpastes and mouthwashes do not remain on dental surfaces for a long period of time. Once washed and rinsed, their effect recedes quickly. The action of these products is not site-specific. Majority of pastes and dentifrices contain a variety of abrasive agents which could further aggravate DH condition [2, 17, 20]. In order to overcome the shortcomings of the existing products, there is a need of a formulation which would be easy to apply, adhere on the tooth surface for long time and show its therapeutic effect specifically on the affected tooth. Hence the concept of *in situ* gel formulation was developed and studied in the current work.

Temperature, pH, and ion-sensitive *in situ* gelling systems have been explored in the field of drug delivery [21]. These are formulated for drug administration via ocular, transdermal, buccal, rectal, vaginal as well as injectable routes such as intramuscular and subcutaneous [22–24]. Temperature-induced *in situ* gelling system is an effective,

convenient platform for mucosal drug delivery. The sizable difference between room temperature and the physiological temperature can help in maintaining the formulation in sol state while on shelf and inducing gelation upon administration due to the higher physiological temperature. In the current work, we developed the temperature-sensitive *in situ* gelling formulation for the treatment of DH. Poloxamer, a widely used non-ionic polymer, is considered safe and acceptable for oral, parenteral, topical as well as ophthalmic administration [25]. It is a triblock copolymer composed of a central hydrophobic chain of polyoxypropylene (poly (propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly (ethylene oxide)) known for exhibiting the phenomenon of reverse thermal gelation under a certain concentration and temperature. Of various available grades, poloxamer 407 shows thermoreversible gelling behavior at physiologically relevant temperature. Aqueous solutions of about 20% and higher concentration of poloxamer 407 are liquid at room temperature (20-27 °C) and undergo gelation at around 35-37 °C [26]. At lower temperature, the polymer solution is in the sol state. Higher temperatures lead to dehydration of the hydrophobic polypropylene oxide repeat units and subsequent hydrophobic interactions among them. The three-dimensional network formed by the polymeric interactions trap water and results in gel formation. $T_{sol\text{-}gel}$ is concentration dependent and increases by a reduction of the poloxamer 407 concentration in an aqueous solution until a lower level is reached, at which point poloxamer 407 does not gel anymore [27].

Combination of poloxamer 407 and chitosan imparted consistency to the formulation that would allow easy administration and application to the sensitive tooth. Chitosan is a natural gelling agent and also has its application in dentistry as a re-mineralizing agent [28]. Its antimicrobial action helps in preventing dental caries [29]. Its mucoadhesive nature could aid in prolonged retention of the formulation in the oral cavity [30, 31]. Chitosan owing to these multiple functionalities was incorporated along with poloxamer 407 in the *in situ* gelling formulation of potassium nitrate. Since the formulation is expected to stay in the oral cavity for a significant time, its taste and appeal are the key aspects from the patient compliance point of view. By the addition of an appropriate sweetening agent and flavoring agent the acceptability in patients can be increased. Xylitol was chosen as a sweetener since, unlike sucrose, it does not lead to plaque formation. It also promotes mineralization activity on enamel and can be safely used in diabetic patients [32]. It has more dental benefits than any other polyols and sugars. Traditionally, clove oil has been successfully used for relief from toothache. Eugenol from clove oil is highly effective in providing analgesic and local anesthetic property [33]. Besides this, eugenol also has the characteristic aroma and taste. Dual advantage of clove oil thus justified its incorporation into the formulation.

Gels prepared were evaluated for parameters like appearance, pH, viscosity, adherence, spreadability, gelation temperature and time, drug content analysis and *in vitro* release study [34]. However, viscosity and gelation time were considered as the critical parameters amongst these. Hence, they were considered as responses in optimization studies [12]. Highly viscous gels on the tooth/molar surface could be irritating and cause discomfort, whereas thin gels would run off the tooth surface. The preliminary trials taken earlier indicated 2200-2500 cps as an optimum viscosity and hence was chosen as the constraint for this response. Gelation time determines how fast the gel is formed upon elevation of temperature. Too long a gelation time would lead to a lack of retention at the target site and would render the therapy ineffective. Hence, the constraint of NMT 150 s was laid down for this response. Design of experiments is considered to be a fast and effective approach in optimizing the formulations [35]. Application of 3^2 full factorial design using Design Expert software enabled in optimizing the formulation with the help of 10 trial runs. The optimized formulation, when subjected to accelerated stability studies for 3 mo demonstrated an acceptable physical and chemical stability.

CONCLUSION

The temperature-sensitive *in situ* gel formulation of potassium nitrate was developed and optimized for the viscosity and gelation time. The resulting formulation in the sol state is expected to offer the advantage of ease of application, specifically to sensitive teeth. Its conversion to the gel state upon application would offer better adherence and longer residence time on the sensitive teeth. Prolonged duration of action is expected to shorten the overall tenure of the therapy and provide faster relief from hypersensitivity. Clinical studies are warranted before this novel, scalable and translational technology can be commercialized for better management of dentin hypersensitivity.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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