ORIGINAL ARTICLE

Use of factorial design in formulation and evaluation of intrarectal *in situ* gel of sumatriptan

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ABSTRACT

The study's goal was to create an *in situ* intrarectal mucoadhesive gel of sumatriptan (SMT) combining mucoadhesive polymer (xyloglucan) and thermosensitive polymers (poloxamer 407 and poloxamer 188) to prolong rectal residence time for treatment of migraines. Nine SMT mucoadhesive rectal *in situ* gel (RIG) formulas were created by mixing poloxamer 407 (18%, 19%, or 20%) with poloxamer 188 (5%), a mucoadhesive polymer at various doses (0.1, 0.2, and 0.3) as well as SMT (25 mg/ml). The prepared suppositories underwent for mucoadhesive force, gelation temperature, and gelation time. When SMT and mucoadhesive polymer were added to the poloxamer mixture, the gelation temperature dropped; however, poloxamer 188 had the opposite effect. These polymers supported the prepared liquids' ability to adhere to mucous membranes and form a strong gel. The transition gelation temperature of the poloxamer solution rose as a result of the addition of poloxamer 188. The findings showed that the formula RIG5 which is composed of poloxamer 407 (19%), poloxamer 188 (5%), and xyloglucan (0.2%) had an ideal transition temperature of 36.33°C, gel strength of 44.66°C, mucoadhesive force of 6409°C, and *in vitro* drug release of 93.98% over an 8-hour period. In light of this, it can be said that SMT was successfully manufactured as RIG without causing any chemical reaction with its additives.

Key words: Cold method, *in situ gels,* poloxamer 188, poloxamer 407, sumatriptan, xyloglucan

INTRODUCTION

Sumatriptan (SMT) is a particular agonist for serotonin 5-hydroxytryptamine receptors (5-HTI) receptors. The usage of SMT is to treat bad migraine attacks as well as reducing other migraine symptoms such as phonophobia, photophobia, and nausea. SMT is given subcutaneously, nasally, and orally.[1] The Biopharmaceutics Classification System categorized it as a Class III medication (high water solubility and low bioavailability).[2]

Aqueous liquid *in situ* gels turn into gels under physiological circumstances. The production of *in situ* gels can be caused by a variety of processes, including pH changes, ionic crosslinking, and temperature changes.[3-5]

A traditional suppository is a solid medication that melts when it comes into contact with body heat. It is a good dose type for use with unconscious patients, newborns, and kids. One of their key advantages over oral

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dosages is that the drugs administered by suppositories do not experience the first pass effect in the liver and gastrointestinal tract (GIT) when positioned close to the outside orifice. In addition, compared to parenteral formulations, suppositories are less uncomfortable and more widely accepted. Conventional solid suppositories will cause patients to feel strange and uncomfortable. If the suppository is pushed further into the colon, the medication may experience the first pass effect.[6] Hence, *in situ* gels are easy to apply and offer patient comfort compared to traditional suppositories.[7]

The goal of this study was to formulate SMT as a rectal *in situ* gel (RIG) to avoid the first-pass effect and enhance patient compliance through simple administration, infrequent administration, and controlled drug release.

MATERIALS

SMT, poloxamer 407, and poloxamer 188 were imported from HyperChem (China). Xyloglucan was purchased from Richest (China). From Central Drug House in India, we bought sodium hydroxide and potassium dihydrogen phosphate. We extracted benzalkonium chloride from Pioneer (Iraq).

Preparation of rectal *in situ* gel containing sumatriptan

A cold approach was used to create the RIG for SMT.[8] With continual stirring in cold water, poloxamer 407 and poloxamer 188 were slowly added. At 4°C, this combination was kept overnight. The following day, SMT (25 mg/ml), xyloglucan (0.1%–0.3%), and preservative (benzalkonium chloride) were continuously agitated into the poloxamer mixture. In addition, the new combination was kept overnight at 4°C.[9]

Experimental design

In trial batches, the level of poloxamer and xyloglucan mainly affects the gel strength, gelation temperature, and drug release. With a constant concentration of poloxamer 188 (5% w/v), and varying concentrations of poloxamer 407, ranging from 18% to 20% w/v. Gelation investigations were carried out using phosphate buffer (pH 6.8) at 37°C to optimize the concentration.

A 3^2 full factorial design [Tables 1 and 2] outlines the dependable and independable variables of the design.[10] In Table 3, the 3^2 factorial design was used to project a total of nine trial formulations for the two independent variables, poloxamer (X1) and xyloglucan (X2), whose three levels were chosen to be 0.1% w/v, 0.2% w/v, and 0.3% w/v as low, medium, and high, respectively. As optimization responsive parameters in the formulation of RIG formulations, the impact of these independent variables on the gel strength (Y1), gelation temperature (Y2), and cumulative drug release after 8 h (%) (Y3) was examined. The formulation release (%), transition gelation temperature, and gel strength charts were created using Design-Expert 11 software: Design-Expert 11 is a software program developed by Stat-Ease, Inc., a company based in Minneapolis, Minnesota, United States.

Table 1: Various independent and dependent factors

Independent components	Dependent components
X1=Combination of poloxamer 407 and 188	Y1=Gel strength
X2=Xyloglucan	Y2=Gelation temperature
	Y3=Percentage drug release (after 8 h)

Table 2: Factors and levels with their real values

Factors	High degree (1)	Middle degree (0)	Low degree (−1)
Combination of poloxamer 407 and 188	18	19	20
Xyloglucan	0.1	0.2	0.3

Evaluation of rectal *in situ* gels

Drug content

With phosphate buffer, 0.5 ml of the RIG formulation (corresponding to 250 mg/mL SMT) was diluted to 10 ml (pH 6.8). With the same media, 1 ml of this solution was diluted once more to 10 ml. Then, spectrophotometric measurements of absorbance were made.[2]

Gel strength

For the formulations to gel, a sample of 5 g of RIG was placed in a 10 ml cylinder and immersed in a water bath at 371°C for 30 min. A 3.5 g mass was dropped onto the RIG's surface. The time it took for the mass to penetrate 0.5 cm into the gel was used to determine the gel's strength.[6]

Measurement of the sol–gel conversion temperature

In order to determine the transition gelation temperature, 2 cc of the iced formula were placed in a tube (10 ml). Parafilm was used to seal that tube. The tube was then placed in a water bath that was approximately 4°C in temperature. After every 10 min, the temperature of the water bath was gradually increased by 3°C. The temperature was lowered by 1°C every 10 min once it reached the region of the gelation temperature. The finding of solution gelation was the result of the ongoing temperature increase. To ensure that gelation had taken place and the meniscus of the mixture did not shift during slanting, the test tube was tilted at a 90° angle. As the changeover gelation temperature, that was noted.[11]

Mucoadhesive force determination

It is the formula's capacity for adherence to the rectal mucosa. The balancing technique was utilized, with a beaker

at one end of the balance and a vial filled with rat rectal mucosa that was 0.6 mm thick at the other. On the base of the vial was placed the rectal mucosa. The vials had been at that temperature of 35°C –37°C for 10 min before the treatment. The RIG was then diluted by 1 ml and placed in a watch glass beneath the vial. One minute was used as the first contact time between the vial and the gelling sample. The beaker was then gradually filled with water.[12,13] By weighing the amount of water needed to separate the RIG from the mucosa, equation was used to determine the mucoadhesive force:

$$\text{Detachment force } (\frac{dyne}{cm2}) = \frac{m \times g}{A}$$

Where A is the exposed rectal tissue area, which is 3.50 cm^2 in all preparations,[14] m is the needed weight (g), and g is the acceleration (980 cm/s^2) caused by gravity. Further research was done on the chosen RIG based on the aforementioned criteria.

In vitro drug release study

The United States Pharmacopeia (USP) paddle method was used to keep track of the drug release from the produced RIGs. The formulation was diluted by 1 ml and put in a cellophane bag. The bag was submerged in a tank containing 500 ml of phosphate buffer (pH 6.8) at 37°C as the dissolution media. One hundred revolutions per minute was the rotational speed. Four milliliters of aliquots were taken out and examined spectrophotometrically at 282 nm at predefined intervals.[15] *In vitro* release of the selected RIG formula was performed and compared to SMT aqueous solution (250 mg in 1 ml), which was inserted into the semipermeable bag to study the effect of the RIG component, the base, and the additives on the SMT release.

Drug-excipient compatibility studies by Fourier transform infrared

The Fourier transform infrared (FTIR) spectrometer captured the FTIR spectra of chosen RIG, SMT alone, and its excipients in the range of 4000 cm^{-1} and 400 cm^{-1}. The material was mixed with potassium bromide KBr (1:100) in a mortar before being compressed to a tiny disc by a hydraulic press with a 14-ton capacity.[16] Its purpose was to investigate any possible interaction between the medicine and the formulation's excipients.

RESULTS AND DISCUSSION

Optimization

The 3^2 factorial design for the combination of the two independent variables, poloxamer 407 and poloxamer 188 (X1), xyloglucan (X2), which were adjusted at three different levels, proposed a total of nine trial formulations, as shown in Table 4 (high, middle, and low). In the current study, the effect of these independent factors on the optimization response parameters of cumulative drug release after 8 h (%) and gel strength (%) in phosphate buffer pH 6.8 was examined. In order to fit these data, the Design-Expert 11 software generated the proper polynomial

Table 3: Composition of various mucoadhesive rectal *in situ* gel formulations

Composition	RIG1	RIG2	RIG3	RIG4	RIG5	RIG6	RIG7	RIG8	RIG9
SMT (mg)	250	250	250	250	250	250	250	250	250
Poloxamer 407(%w/v)	18	18	18	19	19	19	20	20	20
Poloxamer 188 (%w/v)	5	5	5	5	5	5	5	5	5
Xyloglucan (%w/v)	0.1	0.2	0.3	0.1	0.2	0.3	0.1	0.2	0.3
Benzalkonium chloride (%w/v)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Distilled water qs (mL)	10	10	10	10	10	10	10	10	10

RIG: Rectal *in situ* gels, SMT: Sumatriptan

Table 4: With observed response values, full factorial design

Run	Factor 1: Combination of poloxamer 407 and poloxamer 188 (X1) %	Factor 2: Xyloglucan (X2) %	Response 1: Gel strength (s)	Response 2: Gelation temperature (°C)	Response 3: Drug release (%)
1	18	0.1	31.3	44.5	97.67
2	18	0.2	36.3	40.5	95.88
3	18	0.3	39.9	37.66	88.03
4	19	0.1	36	38.66	95.5
5	19	0.2	44.66	36.33	93.98
6	19	0.3	47.7	34	89.98
7	20	0.1	38.33	37.66	90.25
8	20	0.2	45.33	32.66	88.8
9	20	0.3	51.33	29.33	80.75

model equations, which included both individual major factors and interaction factors.[17]

As shown in Table 5, the analysis of variance results showed that all models were significant ($P < 0.05$) for all response parameters examined.

In addition, Design-Expert 11 software generate contour and 3D response surface plots for gel strengths, transition gelation temperature, and drug release (%), are shown in Figures 1-3, respectively.

The optimized formula RIG5 showed gel strength of 44.66 + 0.02, gelation temperature of 36.33 + 0.11, and drug release of 93.98 + 0.26.

Table 5: Summary of ANOVA for the response parameters

Source	Sum of squares	df*	Mean square	*F*	*P*-probability >*F*
Gel strength					
Model	320.64	2	160.32	78.57	<0.0001 (significance)*
X1*	135.82	1	135.82	66.57	0.0002 (significance)
X2*	184.82	1	184.82	90.58	<0.0001 (significance)
Gelation temperature					
Model	0.0001	2	0.0000	42.32	0.0003 (significance)
X1	0.0000	1	0.0000	47.86	0.0005 (significance)
X2	0.0000	1	0.0000	36.78	0.0009 (significance)
Drug release					
Model	210.50	5	42.10	18.35	0.0186 (significance)
X1	54.96	1	54.96	23.96	0.0163 (significance)
X2	42.31	1	18.44	18.44	0.0232 (significance)

*X1 represents combination of poloxamer 407 and 188, X2 represents xyloglucan. df: Degree of freedom

Drug content

The results of RIG formulations were in the range of 98%–101% which are acceptable according to the USP,[18] indicating high content uniformity of them and suitability of the preparation method.

Mucoadhesive force determination

Table 6 shows the mucoadhesive power of the prepared formulas. It also shows that if the quantity of poloxamer 407 was increased, there would be an increase in the mucoadhesive power of the RIG. That result belonged to density increase and development of more compact lattice structure.[19]

Strong mucoadhesive force of the RIG prevents the drainage of the drug from the rectal, leads to prolonged retention, and increases absorption across mucosal tissues. However, too much mucoadhesive force (>10,000 dyne/cm^2) gel can damage the rectal mucosal membrane.[20]

In vitro drug release

All RIG formulations, including SMT, underwent *in vitro* drug release experiments in phosphate buffer pH 6.8. Every batch displayed a longer-than-8-h SMT release. These formulae had a cumulative drug release that ranged from 88.81% to 93.98%. It was clear that the type of bioadhesive employed as well as the poloxamer concentration had an impact on the release of SMT. The bioadhesive polymer slowed down the process of drug release from rectal gel. This effect of the bioadhesive polymers can be attributed to their ability to increase the viscosity of the final product as well as to crush or distort the extramicellar aqueous channels of poloxamer micelles through which the SMT diffuses.

Using the dialysis membrane, the proportion of SMT released from the control (SMT aqueous solution) was compared to that from RIG. In comparison to chosen RIG5, a faster release of the SMT solution was seen with a significant difference ($P < 0.05$). According to Figure 4, the percentage of drug release from pure drug solution is

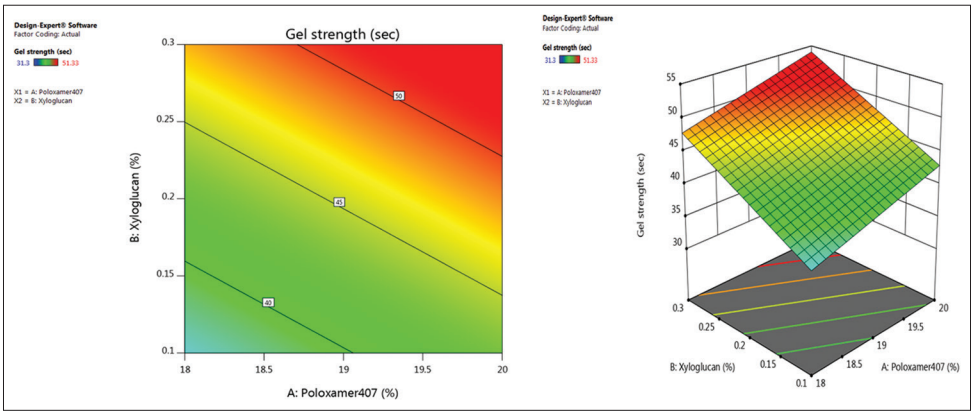

Figure 1: Gel strength contour and three-dimensional response surface plots

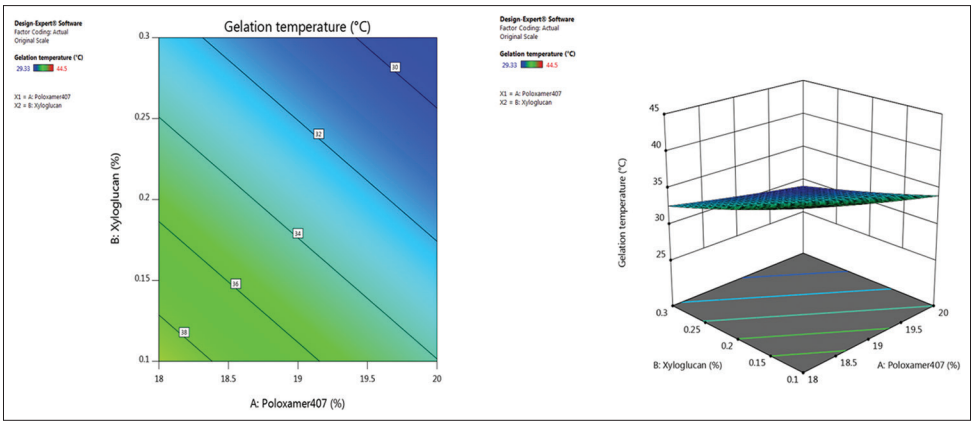

Figure 2: Plots of the contour and three-dimensional gelation temperature response surfaces

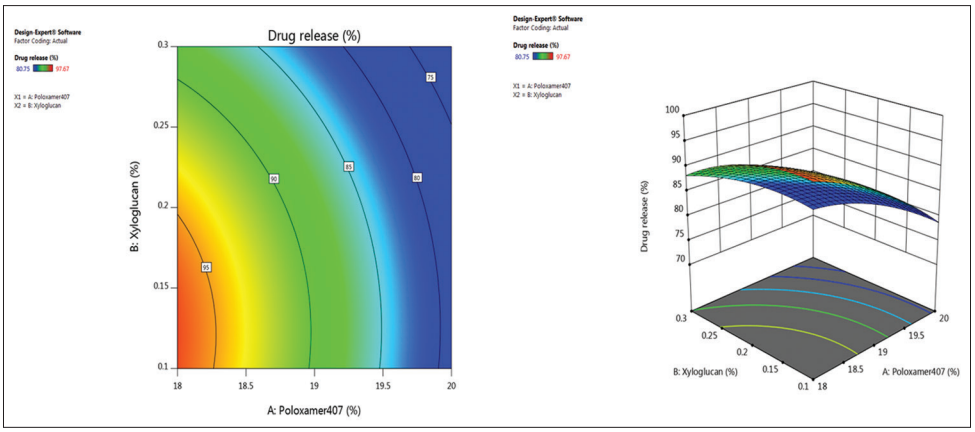

Figure 3: Plots for % drug release on a contour and three-dimensional response surface

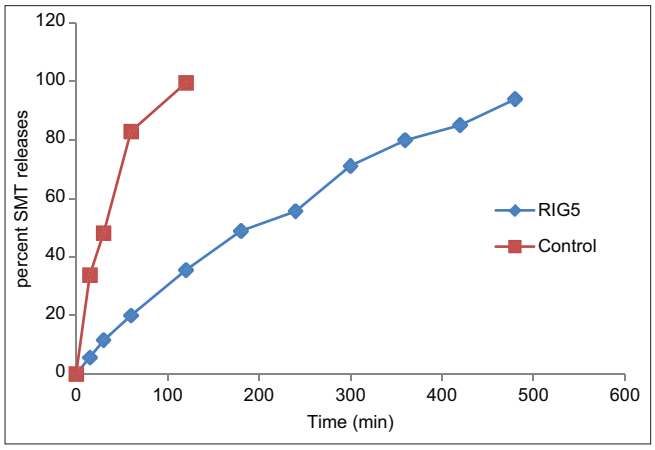

Figure 4: Effect of formulation elements on SMT release *in vitro*. SMT: Sumatriptan

99.33% in 2 h, while the percentage of drug release from RIG5 in 8 h is 93.98%.[21]

Drug-excipient compatibility studies by Fourier transform infrared

Figure 5 shows the characteristic peaks of SMT which were compared with reference FTIR spectrum.[17] FTIR of poloxamer 407 and poloxamer 188 shows peaks at 3483.44, 2881.65, and 1280.73 cm^{-1} for O-H stretching, aliphatic C-H stretching, and C-O stretching in C-O-C group, respectively. N-H str., C-N str., S = O str., and C-S str. were found to have distinctive SMT peaks in RIG5, respectively, at 3383.66 cm^{-1}, 1233.58 cm^{-1}, 1342.46 cm^{-1}, and 632.65 cm^{-1}. Therefore, there were no appreciable variations in the major bands of the medication, and SMT did not interact with other RIG5 additions.

Table 6: Detachment weight and mucoadhesive force of rectal *in situ* gel formulas

RIG	Mean±SD (*n*=3)	
	Detachment weight (g)	Mucoadhesive force (dyne/cm^2)
RIG1	14.6±2.51	4769±785.43
RIG2	17.5±1.51	5723±476.74
RIG3	20±1.71	6540±746.45
RIG4	16.6±1.51	5429±312.10
RIG5	19.62±2.31	6409±470.11
RIG6	29±2.51	14,063±533.14
RIG7	17.5±2.11	5723±377.22
RIG8	22.57±3.01	7372±444.20
RIG9	31.5±3.11	10,290±812.10

RIG: Rectal *in situ* gels, SD: Standard deviation

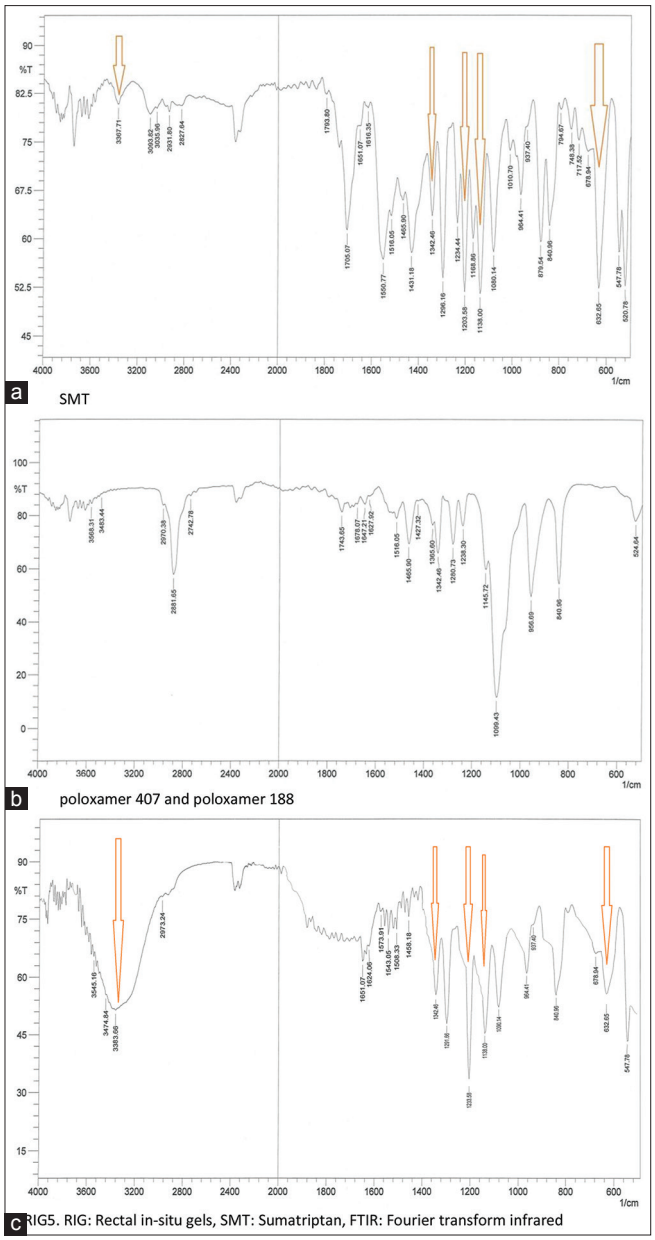

Figure 5: FTIR of (a) SMT, (b) poloxamer 407 and poloxamer 188, (c) RIG5. RIG: Rectal *in-situ* gels, SMT: Sumatriptan, FTIR: Fourier transform infrared

CONCLUSION

A factorial 3^2 design was used to successfully formulate SMT as a rectal *in situ* gel.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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