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Development of In Situ-Gelling and Mucoadhesive Liquid Suppository of Ondansetron

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Abstract: The main aim of the present investigation was to develop in situ gelling mucoadhesive liquid suppositories of ondansetron by using mucoadhesive polymers such as sodium alginate, methyl cellulose and polyvinylpyrrolidone. Polyethylene glycol was used to modify gelation temperature.

Mucoadhesive liquid suppositories of ondansetron were prepared by adding mucoadhesive polymers (0.8% w/w) to the formulations of thermally gelling liquid suppositories containing poloxamer 407 (18%) and ondansetron (0.8%). The prepared suppositories were evaluated for gelation temperature, mucoadhesive force, gel strength and drug release.Gelation temperature was slightly increased on incorporation of (0.8% w/w) ondansetron in the poloxamer solution, while the addition of the mucoadhesive polymers a reverse effect was observed. These polymers reinforced the gel strength and the mucoadhesive force of the prepared solutions. The addition of PEG 6000 increased the gelation temperature of poloxamer solution. The formulations consisting methyl cellulose required higher concentration of PEG 6000 so as to modulate the gelation temperature of liquid suppository in the range of 30-36^{0}C. Among the various formulations examined, the formulation [poloxamer 407/ondansetron/sodium alginate/PEG 6000 (18/0.8/0.8/1.3% w/w)] exhibited the appropriate gelation temperature, mucoadhesive force, gel strength and acceptable drug release.

Key Words: Liquid suppository, mucoadhesive polymer, thermally gelling, poloxamer, ondansetron, polyethylene glycol, gelation temperature.

Introduction

During the past 20 years, advances in drug formulations and innovative routes of drug administration have been made. The administration of drugs by transdermal or transmucosal routes offers the advantage of being relatively painless[1]. Although, administration via peroral route is the most commonly targeted goal of new drug and dosage form research and development. Oral administration is not always feasible or desirable. Certain patient populations, notably children, the elderly, and those with swallowing problems, are often difficult to treat with oral tablets and capsules[2].

A conventional suppository is a medicated solid dosage form which melts or softens at body temperature. It is a favorable dosage form for infants, children and unconscious patients. One major advantage of suppositories over other oral dosage forms is that the drugs given by suppositories do not undergo the first pass effect in the gastrointestinal tracts and the liver. Moreover, the suppositories are less painful and more acceptable than parenteral forms. However, the conventional solid type suppositories often give the patients a feeling of alien, discomfort and refusal. Furthermore, if the solid suppositories without mucoadhesivity reach the end of colon, the drugs delivered by the suppositories might undergo the first-pass effect[3]. From an industrial viewpoint, solid suppositories are inconvenient to manufacture and handle since a heating process is required for melting the suppositories and filling them in a vessel. The vessel needs to be packaged together to maintain the shape of suppositories until administration. To solve the problems of conventional solid suppositories, it would be desirable to develop a liquid suppository which: (1) forms a gel at body temperature; (2) has a suitable gel strength not to be leaked out from the anus after administration; and (3) has a suitable bioadhesive force so as not to reach the end of the colon[4].

As a base of liquid suppository, poloxamer, a triblock (PEO-PPO-PEO) copolymer with a certain hydrophobic chains of polyoxyethylene (PEO), was used. Poloxamer solutions are known to exhibit the phenomenon of reverse thermal gelation, remaining as

solutions at low temperature and gelling upon increasing the temperature[5, 6].

Ondansetron, a highly selective 5-HT_3 receptor antagonist, is used as an anti-emetic and undergoes extensive first pass metabolism[7]. Under certain condition i.e. (vomiting) it is not possible for patient to administer the drug by oral route and administration by parenteral route is invasive so, rectal drug delivery would be beneficial. Also, the absorption of ondansetron across the colon and rectum is similar to the oral route, suggesting that suppository formulations are feasible[8]. Hence an attempt has been made to develop a liquid suppository of ondansetron.

Materials and method

Ondansetron and Polyvinylpyrrolidone (PVP K-30) were obtained as a gift sample from Piramal Life Sciences Ltd., Mumbai. Poloxamer 407 was obtained as a gift sample from Bharat Serums and Vaccines Pvt. Ltd., Thane. Sodium alginate, methyl cellulose, polyethylene glycol 6000 was obtained from Loba chemie, Mumbai. A UV/Visible spectrophotometer (Shimadzu UV 1700, Japan) was used for drug analysis. FTIR (Jasco- 4100, USA) was used for IR analysis. Brookfield viscometer (RVDV-II + Pro, USA) was used for measurement of viscosity.

Drug excipients interaction study

The pure drug, ondansetron, and its mixture with the polymer sodium alginate, methyl cellulose and PVP K-30 powder were mixed separately with IR grade KBr and pellets were prepared. The pellets were scanned over a wavelength range of 400-4000 cm^{-1} using an FTIR (Jasco- 4100) model instrument. Also the FTIR analysis of prepared liquid suppository was carried out. Prepared gel formulations were dried and its powder was mixed separately with IR grade KBr and pellets were prepared for FTIR analysis.

Preparation of liquid suppository[9]

The liquid suppositories were prepared by cold method. The drug and various amounts of excipients except poloxamer 407 were completely dispersed in distilled water with continuous agitation at room temperature. The mixtures were then cooled to 4^0C. Then poloxamer 407 was added slowly with continuous stirring. The dispersions were then stored in a refrigerator at 4^0C overnight. The composition of various prepared formulations is given in table 1.

Measurement of gelation temperature[4]

A 10 g of the liquid suppository was transferred to 20ml transparent vial containing a magnetic stirring bar (15 x 6 mm). A digital thermosensor connected to thermistor was immersed in the liquid suppository. The vial was heated at an increasing rate of 2^0C/min with constant stirring rate at 100 rpm. The temperature at which the rotation of the bar stopped was taken as the gelation temperature.

Measurement of gel strength[4]

The gel strength of the liquid suppository was determined by using the gel strength measuring device shown in Fig. 1. The liquid suppository (50 g) was put in a 100 ml graduated cylinder and gelled in a thermostat at 36.5^0C. The apparatus for measuring gel strength (weight: 35 g) was then placed onto the liquid suppository. The gel strength, which means the viscosity of the liquid suppository at physiological temperature, was determined by the time in seconds (s) the apparatus took to sink 5 cm down through the liquid suppository.

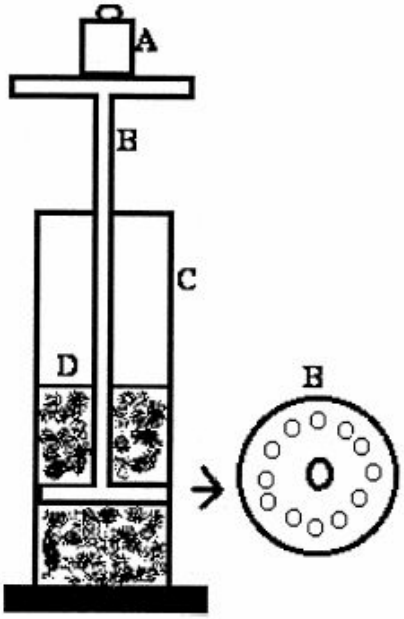


Fig. 1: Gel strength measuring device
(A) weights; (B) device; (C) glass cylinder; (D) poloxamer gel.

Determination of mucoadhesive force[4]

The mucoadhesive force of the liquid suppository was determined by using the mucoadhesive force measuring device shown in Fig. 2.

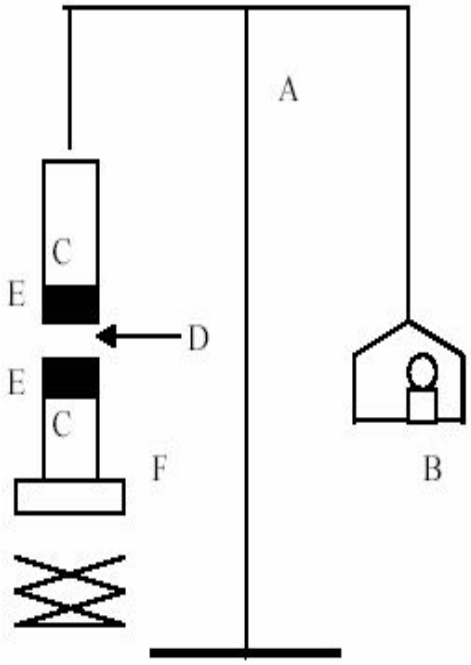


Fig. 2: Mucoadhesive force measuring device
(A) modified balance; (B) weights; (C) glass vial; (D) poloxamer gel; (E) tissue; (F) height adjustable pan.

A section of tissue was cut from the fundus of rabbit rectum and secured with mucosal side out onto each glass vial (C) using a rubber band and an aluminum cap. The vials with the rectal tissues were stored at 36.5^{0}C for 10 min. Next, one vial with a section of tissue (E) was connected to the balance (A) and the other vial was placed on a height-adjustable pan (F). Liquid suppository (D) was added onto the rectal tissue on the other vial. Then, the height of the vial was adjusted so that the liquid suppository could be placed between the mucosal tissues of both vials. The weights (B) were increased until the two vials were detached. Bioadhesive force, the detachment stress (dyne/cm^2), was determined from the minimal weights that detached the two vials. Following formula was used to determine Mucoadhesive force in (dyne/cm^2).

Detachment stress (dyne/cm^2) = (m) x (g /A)

Where,

m = Weight required for detachment of two membrane in grams

g = Acceleration due to gravity [980 cm/s^2]

A = Area of tissue exposed

The mucosa was changed for each measurement. Measurements were repeated three times for each of the gel preparations.

Drug release test

The drug release from the prepared liquid suppository was monitored by the USP paddle method[10-14]. A 2g of the formulation was placed in semipermeable bag and secured with the aid of non absorbing thread. The bag was immersed in a vessel containing dissolution medium, 500 ml phosphate buffer, pH 7.4 at 37^{0}C. The speed of rotation was 100rpm. At predetermined time intervals 4 ml of aliquots were withdrawn and analyzed spectrophotometrically at 310 nm.

Measurement of viscosity

The viscosities of various formulations were determined by using Brookfield viscometer (Brookfield viscometer RVDV- II + Pro). The sample solution was placed in the sample holder. For each formulation the viscosity was recorded with increase in temperature from 20^{0}C-40^{0}C.

Results and discussion

Compatibility study

In the present study, it was found that there is no chemical interaction between ondansetron and the polymers used. The results are as shown in Fig. 3 to Fig. 4. The drug exhibits peaks due to the o-disubstituted benzene, cyano group (C=N), carbonyl group (C=O) in six member ring. Also, the carbon-carbon double bond in aromatic ring and carbon-nitrogen stretching in the five membered ring shows their characteristic peaks in the IR spectra. It was observed that there were no changes in these main peaks in the IR spectra of a mixture of drug and polymers, which shows that there were no physical

interactions involving bond formation between drug and polymers.

Gelation temperature

Gelation temperature range for liquid suppository should be 30-36^{0}C. So that it will be a liquid at room temperature and forms a gel instantly in the rectum. If the gelation temperature of the liquid suppository is lower than 30^{0}C, gelation occurs at room temperature leading to difficulty in manufacturing, handling and administering. If the gelation temperature of the liquid suppository is higher than 36^{0}C, the suppository still stays as a liquid form at physiological temperature, resulting in leakage from the anus.

The gelation temperature of (18% w/w) poloxamer 407 solution was found to be 24.9^{0}C. The incorporation of (0.8% w/w) ondansetron slightly increased the gelation temperature. The increase in gelation temperature was not great because of low concentration of the drug in formulations and also because of the low water solubility of the drug.

The addition of sodium alginate, methyl cellulose to the poloxamer 407 solutions at 0.8% w/w concentration lowered the gelation temperature by 2^{0}C, while PVP K-30 had no effect on the gelation temperature of poloxamer 407 solutions. The gelation temperature-lowering effect of mucoadhesive polymers could be explained by their ability to bind to the polyoxyethylene chains present in the poloxamer molecules[12]. This will promote dehydration, causing an increase in entanglement of adjacent molecules and extensively increasing intermolecular hydrogen bonding which will lead to gelation at lower temperature. Effect of drug and mucoadhesive polymers on gelation temperature of plain poloxamer 407 is shown in table 2.

In order to achieve the gelation temperature of liquid suppository formulations in the range of 30-36^{0}C, PEG 6000 in concentration range of (0.5-2.0% w/w) was studied for its effect on gelation temperature of formulations. It was found that the gelation temperature was increased by addition of PEG 6000. This finding is in agreement with that obtained by Gilbert[15] et al., Pisal[16] et al., who stated that water soluble substance cause modification of the process of miscellar association of poloxamer solutions leading to an increase in gelation temperature. Also the fact that weaker hydrogen bonding of PEG 6000 consisting hydroxyl groups compared to liquid suppository base, resulting in decrease in gel strength and increase in gelation temperature. Effect of PEG 6000 on gelation temperature of mixtures is shown in fig. 5.

Higher concentration of PEG 6000 was required to modulate gelation temperature of liquid suppository containing methyl cellulose and intermediate concentration of PEG 6000 was required to modulate gelation temperature of liquid suppository containing sodium alginate. While, only (0.5% w/w) concentration of PEG 6000 was required to modulate gelation temperature of liquid suppository consisting PVP K-30. When concentration of PEG 6000 in PVP formulations was increased further it lead to no gelation. Gelation temperature, mucoadhesive force and gel strength of all the formulations is described in table 3. From the evaluation of all formulations it was found that increase in PEG 6000 concentration increased the gelation temperature of all the formulations.

Mucoadhesive force

Mucoadhesive force means the force with which liquid suppository binds to mucosal membrane at 36.5^{0}C. Poloxamer gels without mucoadhesive polymer had low bioadhesive force which was (20.94 x 10^2 dyne/cm^2). It was increased with the addition of mucoadhesive polymer into the formulations. Formulations containing of sodium alginate had the highest mucoadhesive force followed by methyl cellulose while the mucoadhesive force for the PVP K-30 formulations was low as compared to the other formulations. Also, PEG 6000 had an effect on the mucoadhesive force of all formulations. As the concentration of PEG 6000 increased the mucoadhesive force of all formulations was decreased. The mucoadhesive force of formulation F3 was highest. It has been previously reported by Ryu[10] et al., that increase in mucoadhesive force increased the rectal bioavailability of propranolol HCl from liquid suppository.

Gel strength

It has been previously reported that the optimal in situ gelling liquid suppository must have suitable gel strength, in the range of 10 to 50 seconds. This would allow ease of administration for the liquid suppository and no leakage from the anus. All the formulations were subjected to measurement of gel strength. Increase in gel strength of formulation F2, F6 and F10 clearly indicates that incorporation of mucoadhesive polymers increases the gel strength because of increase in viscosity of formulation. It was observed that the presence of PEG 6000 decreases the gel strength of formulation and as the concentration of PEG 6000 increased in formulations gel strength was decreased. Gel strength of formulations containing PVP along with PEG 6000 was very low which are found to be unsuitable formulations in terms of gel strength.

In vitro drug release study

Drug release was retarded by the addition of mucoadhesive polymers. Sodium alginate and methylcellulose exhibited the highest retardation, followed by PVP K-30. On the other hand formulations containing PEG 6000 enhanced the drug release.

We observed that formulations containing PVP K-30 showed more than 85% drug release in 100 min while formulations containing sodium alginate and methyl cellulose without PEG 6000 showed 52.40% and 46.36% drug release in 100 min respectively (Fig. 6-8). The retarding effect of the sodium alginate and methyl cellulose could be attributed to high viscosity. Further, it

was observed that as the concentration of PEG 6000 increased the drug release increased. This could be due to low viscosity of the formulations containing PEG 6000 and release enhancing effect of PEG. It was observed that the formulations containing PVP showed comparatively fast release. It may be attributed partly due to its water solubility and low viscosity which allowed more rapid penetration of dissolution fluid into the gel leading to dissolution or erosion. The same results were obtained for release of propranolol HCl from its thermally gelling liquid suppository[10, 12].

To understand the release mechanisms of ondansetron from liquid suppositories, following equations were used:

$M_t/M = kt^n$

$\log (M_t/M) = \log k + n \log(t)$

Where M_t/M is the fraction of released drug at time t, k is a characteristic constant of the liquid suppository and n is an indication of release mechanism. As the k value becomes higher, the drug is released faster. The n value of 1 corresponds to zero-order release kinetics, $0.5 < n < 1$ means a non-fickian release model and $n = 0.5$ indicates fickian diffusion.

As shown in table 4 the n values of formulations are close to 0.5, suggesting that the ondansetron released from liquid suppository by fickian diffusion through extramicellar aqueous channel of the gel matrix. Among the formulations the k value of formulation F2 and F6 is very low which indicates that the drug was most slowly released from those gels. From the k value it can be concluded that higher concentration of PEG 6000 leads to fast drug release from the gels.

Viscosity study

The plots of viscosity versus temperature studies of all formulations are shown in Fig. 6-8. There was no considerable change in viscosity up to the point of gelation temperature. Near the point of gelation temperature, increase in viscosity was observed, followed by sudden increase in viscosity at the transition temperature. From viscosity studies, it was found that formulations containing PEG 6000 were in liquid state below 30^0C and will be getting converted into gel at physiological temperature.

Conclusion

Based on gelation temperature, gel strength, mucoadhesive force and drug release the formulation F3 is optimized formulation. Higher mucoadhesive force of formulation will lead to retention of liquid suppository to rectum. Thus, the first pass metabolism of drug will be avoided and ultimately the bioavailability of ondansetron will be improved.

Table 1. Composition insitu liquid suppositories of ondansetron

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Ondansetron	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
PF-127	18	18	18	18	18	18	18	18	18	18	18	18	18
Na alginate	-	0.8	0.8	0.8	0.8	-	-	-	-	-	-	-	-
PVP K-30	-	-	-	-	-	0.8	0.8	0.8	0.8	-	-	-	-
Methyl cellulose	-	-	-	-	-	-	-	-	-	0.8	0.8	0.8	0.8
PEG 6000	-	-	1.3	1.4	1.5	-	2.0	2.1	2.2	-	0.2	0.3	0.4
Distilled water	q.s.	q.s.	q.s	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

***All concentrations in percentage Batch size 75 ml**

Table 2. Effect of ondansetron and mucoadhesive Polymers on gelation temperature of poloxamer 407 (18% w/w)

Composition	Gelation Temperature (^{0}C)	
	Mean (n=3)	S.D.
18%Poloxamer 407	24.90	0.10
18%Poloxamer 407+0.8%Ondansetron	26.16	0.25
18%Poloxamer 407+0.8%Na Alginate	22.80	0.10
18%Poloxamer 407+0.8%Methyl Cellulose	22.86	0.15
18%Poloxamer 407+0.8%PVP K-30	24.83	0.25

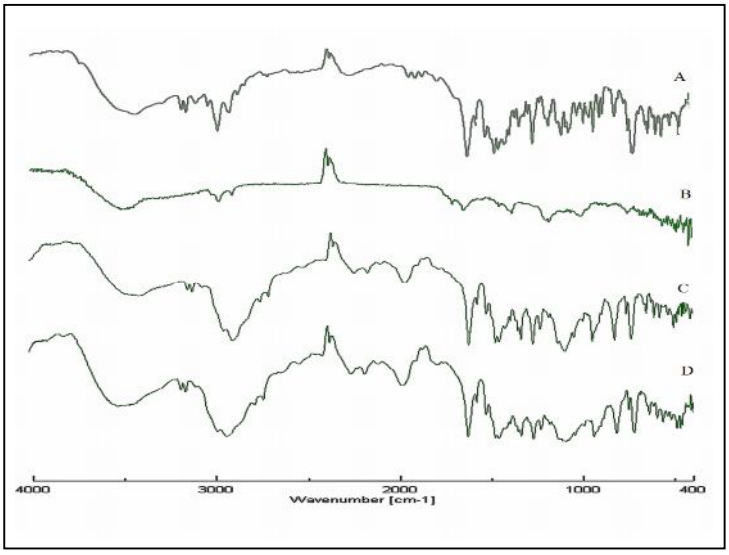
Na Alginate- Sodium Alginate; PVP- Polyvinylpyrrolidone

Table 3. Gelation temperature, mucoadhesive force and gel strength of formulations containing various mucoadhesive polymers

Sr. No.	Formulation Code	Gelation Temperature (^{0}C) Mean ± S.D. n=3	Mucoadhesive Force (dyne/cm^2 x 10^2) Mean ± S.D. n=3	Gel Strength Mean ± S.D. n=3
1	F1	26.36±0.05	20.9±0.059	15.0±2.0
2	F2	25.83±0.05	210.5±0.545	58.0±4.0
3	F3	31.46±0.25	162.7±0.059	43.6±2.9
4	F4	32.40±0.10	150.9±0.059	37.3±1.5
5	F5	35.46±0.05	128.9±0.272	30.6±0.6
6	F6	24.73±0.05	93.5±0.059	70.0±2.0
7	F7	30.73±0.05	67.1±0.103	36.0±1.0
8	F8	33.10±0.10	62.2±0.059	31.6±0.6
9	F9	36.03±0.05	52.9±0.103	28.6±0.6
10	F10	27.53±0.10	46.4±0.059	18.3±1.1
11	F11	33.03±0.05	39.8±0.059	7.6±0.6
12	F12	34.16±0.05	38.5±0.059	5.3±0.6
13	F13	35.46±0.11	31.9±0.103	4.3±0.6

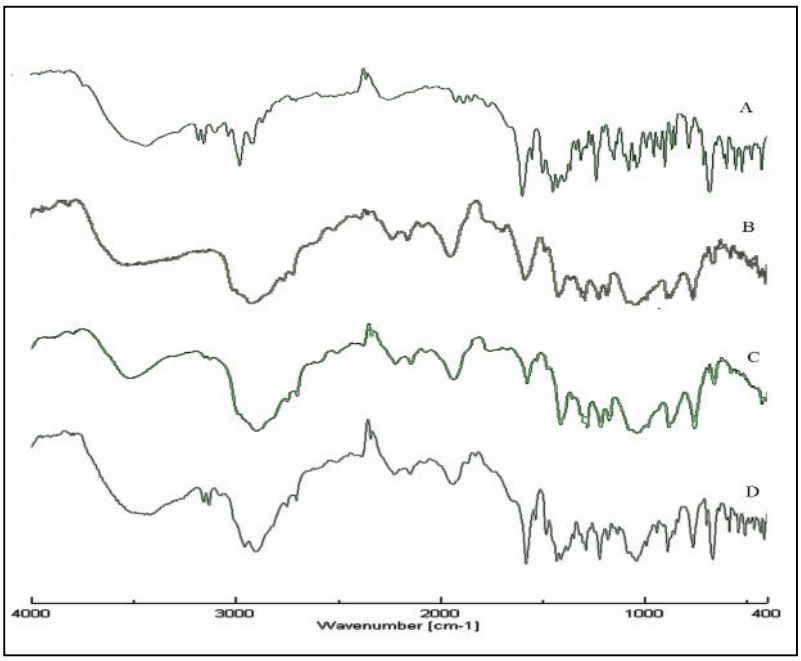
Table 4. Characteristics of the in vitro release of ondansetron from liquid suppository

Formulation Code	(%) Drug Release in 100 min.	n Value	k Value	Mechanism of Drug Release
F1	85.54	0.4860	8.4058	Fickian
F2	52.40	0.5296	4.3344	Fickian
F3	71.15	0.5479	5.5740	Fickian
F4	74.07	0.5430	5.9433	Fickian
F5	78.90	0.4946	7.7227	Fickian
F6	46.36	0.5179	4.0494	Fickian
F7	81.08	0.4965	7.6727	Fickian
F8	82.16	0.4623	9.1773	Fickian
F9	84.02	0.4535	9.7177	Fickian
F10	85.64	0.5541	6.1968	Fickian
F11	87.88	0.5200	7.4379	Fickian
F12	91.14	0.5119	7.9386	Fickian
F13	92.54	0.4902	8.9793	Fickian



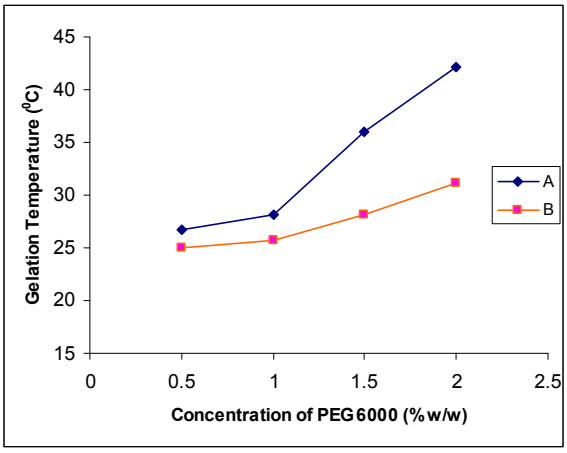
Drug; B- Drug+Sodium Alginate; C- Drug+Methyl Cellulose; D- Drug+PVP K-30

Fig. 3: IR spectrum of drug and mixtures of various polymers with drug



A- Drug; B- F3; C- F7; D- F11

Fig. 4: IR spectrum of drug and formulation F3, F7, F11.



A- (18%Poloxamer 407+0.8% Drug+0.8% Na Alginate+ PEG 6000)

B- (18%Poloxamer 407+0.8% Drug+0.8% Methyl Cellulose+ PEG 6000)

Fig. 5: Effect of different concentrations of PEG 6000 on gelation temperature

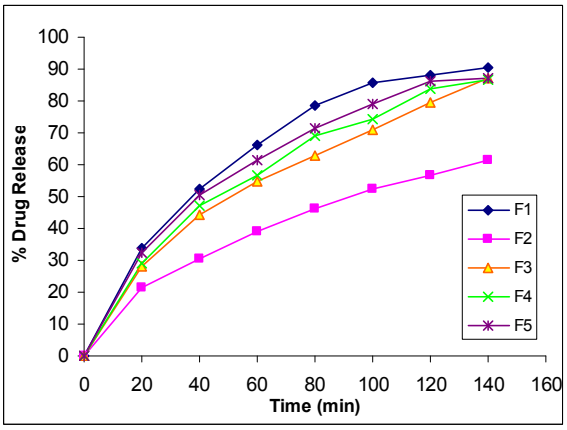


Fig. 6: Drug release profile of plain poloxamer 407 formulation and formulation containing sodium alginate with and without PEG 6000.

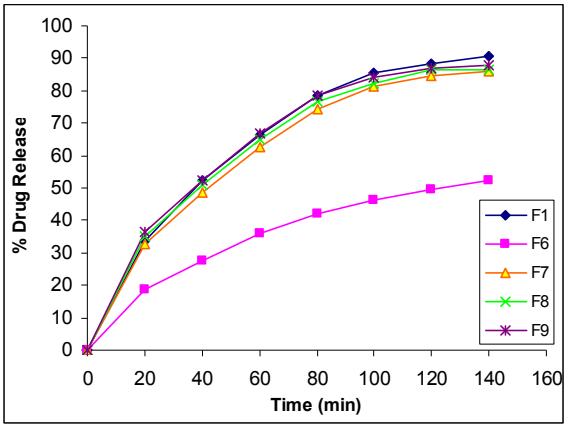


Fig. 7: Drug release profile of plain poloxamer 407 formulation and formulation containing methylcellulose with and without PEG 6000.

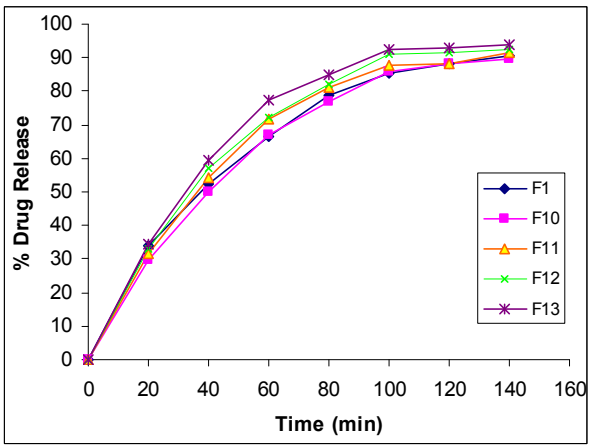


Fig. 8: Drug release profile of plain poloxamer 407 formulation and formulation containing PVP K-30 with and without PEG 6000.

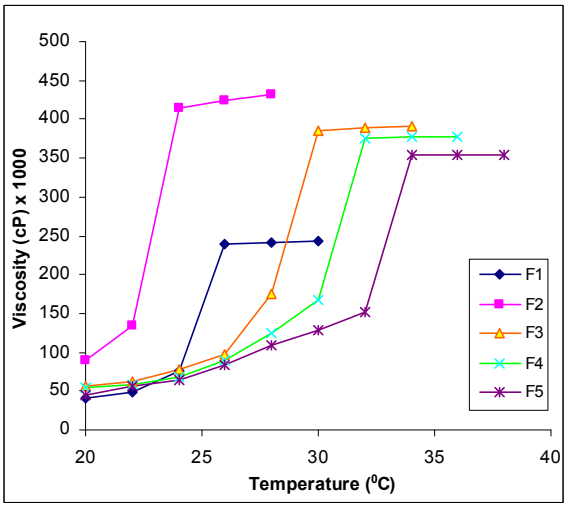


Fig. 9: Effect of temperature on viscosity of plain poloxamer 407 formulation and formulation containing sodium alginate with and without PEG 6000.

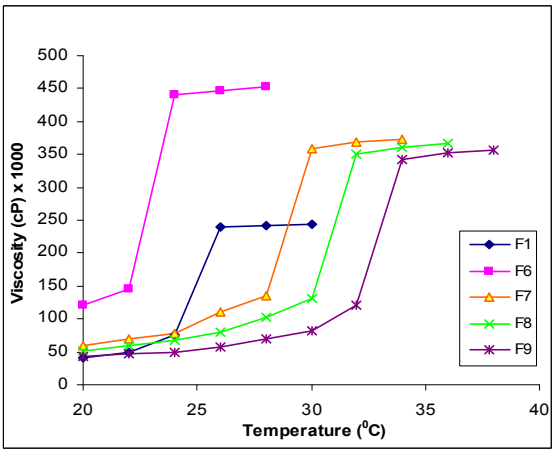


Fig. 10: Effect of temperature on viscosity of plain poloxamer 407 formulation and formulation containing methylcellulose with and without PEG 6000.

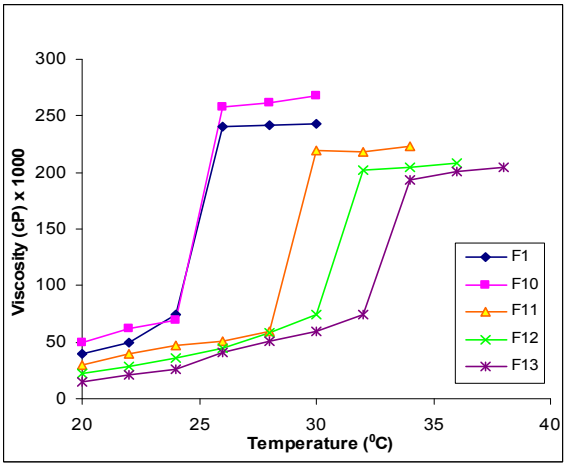


Fig. 11: Effect of temperature on viscosity of plain poloxamer 407 formulation and formulation containing PVP K-30 with and without PEG 6000.

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