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ORIGINAL ARTICLE **OPEN ACCESS**

Formulation of Metronidazole Containing Thermosensitive Bioadhesive Gel for Vaginal Drug Delivery System

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ABSTRACT

The aim of the present study was to formulate and evaluate metronidazole containing thermosensitive bio adhesive gel for vaginal drug delivery to achieve a better therapeutic efficacy and patient compliance in the treatment for vaginosis. Here metronidazole (1%) was formulated as a vaginal gel using thermosensitive polymer, pluronic F127 (20%) along with bioadhesive polymers such as carbopol 934, HPMC, SCMC and polycarbophil. The drug polymer compatibility was studied using FTIR. The prepared formulations were evaluated for parameters such as gelation temperature, gelation time, viscosity, bioadhesive strength and drug release. Gelation temperatures for various formulations were found in the range of 30-38 ºC with gelation time varying from 1-5 min. The developed formulations had optimum viscosity, good bio adhesive strength and hence will have high retention property which is required for convenience at the site ofapplication. Among the prepared formulations, one with the combination of pluronic F127, polycarbophil and carbopol 934 showed optimum gelation temperature, gelation time, viscosity, bioadhesive strength with sustained drug release for 12 hrs. The optimized formulation (F8) showed insignificant change in physical property and drug content when stability testing was carried out at 25ºC/60%RH for 3 months.

Keywords: *Metronidazole, Thermosensitive, Bioadhesion, Gel, Bacterial Vaginosis.*

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INTRODUCTION

The vagina has been studied as a favorable site for the local and systemic delivery of drugs, specifically for female-relatedconditions. Traditionally, the vaginal cavity has been used for the delivery of locally acting drugs such as antibacterial, antifungal, antiprotozoal, antiviral, labor-inducing, spermicidal agents, prostaglandins and steroids [1]. Compared with other mucosal tissues, which are of interest for noninvasive drug administration, the vagina offers various advantages from a delivery point of view. The delivery system can be localized on the vaginal mucosa for many hours without causing a pronounced irritation unlike most other mucosal absorption membranes, such as the buccal or ocular mucosa. Intravaginal enzymatic activity is comparatively lower in the vagina than in the gastrointestinal tract [2]. Recently, increased interest in the development of localized drug delivery systems within the vaginal cavity has been shown due to the advantage of localized drug levels, which reduces dosing frequency, drug administration, and side effects [3]. Topically administered agents are generally very well tolerated and systemic side effects can be overcome. Topical therapy is also safe for pregnant and nursing women under medical supervision, and there is no risk of damage to the unborn child. Moreover, a large number of interactions occur with many other drugs, and for this reason oral therapy may not be given to many patients, or it may only be given when absolutely vital, under close medical supervision.The commercial

preparations, such as creams, foams, gels, irrigations and tablets, are known to reside in the vaginal cavity for a relatively short period of time owing to the self- cleaning action of the vaginal tract, and often require multiple dailydoses to ensure the desired therapeutic effect. Therefore, vaginal route appears to be highly appropriate for bioadhesive drug delivery systems [4]· By the use of bioadhesive polymers, the intravaginal retention time of drug delivery systems can be significantly prolonged. Consequently, the therapeutic efficacy of locally acting drugs can be improved by their increased availability at the target membrane[2]. Phase change polymers which exhibit sol–gel transition in response to body temperature and prolong the residence time of the dosage form in the vagina can be used along with bioadhesive polymers to improve the therapeutic efficacy and patient compliance [1].The use of syringe applicators is probably the most efficient way for intravaginal administration of semisolid formulations; therefore, the formulation has to display a sufficiently low viscosity to be used in a syringe. Once administered, the viscosity of the gel or cream should be as high aspossible in order to avoid a premature and inconvenient outflow of the formulation. As a result, *in situ* gelling polymers are in high demand for vaginal delivery systems. Overall, parameters needed for an *in situ* gelation are change in temperature, change in pH, increase in ionic strength, or access of oxygen. Poloxamers are polymers, which exhibit increase in viscosity at body temperature and have already been tested in vaginal delivery systems *in vivo* [2]. These *in situ*gelling liquid formulations can provide: (1) the necessary vaginal and cervical coverage as a result of their fluidity before gelation, and (2) retention owing to the formation of a mucoadhesive gel [1].

VAGINAL ROUTE OF ADMINISTRATION [3]

The human vagina, a fibromuscular tube 6-7 cm long, extends upwards and backwards from the vulva to the lower uterine cervix. Blood is supplied to the vagina via the uterine and pudendal arteries, and is drained from the vagina by a rich plexus, which flows into the internal iliac veins. The surface of the vaginal epithelium is kept moist by cervical secretions.The pH of vaginal fluid is 4-5. Vaginal drug delivery is used mostly for local effects, but vaginal absorption can give rise to rapid and efficient systemic delivery. Good systemic absorption, and also the ability of the vagina to retain delivery devices, has given rise to many vaginal dosage forms, in particular for steroid contraceptives. A large number of vaginal controlled release dosage forms are available, including vaginal rings and biodegradable microspheres. Products available include vaginal contraceptives, antifungals, antimicrobials, cleansers, deodorants, and lubricants. These products are formulated as tablets, capsules, creams, suppositories, foams, films, solutions, ointments, and gels.

MATERIAL AND METHODS

ANALYTICAL METHODS

λ_{max} of metronidazole in pH 4 citrate phosphate Buffer

Stock solution: Metronidazole in pH 4 citrate phosphate buffer (100mg in 100ml) Scanning: From the stock solution, 6µg/mL solution of metronidazole was prepared and scanned between the wavelengths of 200-400 nm. The spectrum isreproduced in Fig 3. The absorption maximum was found to be 319.9 nm and this wavelength was selected for further studies.

λ_{max} of metronidazole in pH 5.5 citrate phosphate buffer

Stock solution: Metronidazole in pH 5.5 citrate phosphate buffer (100mg in 100ml) Scanning: From the stock solution, 6µg/mL solution of metronidazole was prepared and scanned between the wavelengths of 200-400 nm. The spectrum is reproduced in Fig 4. The absorption maximum was found to be 319.5 nm and this wavelength was selected for further studies.

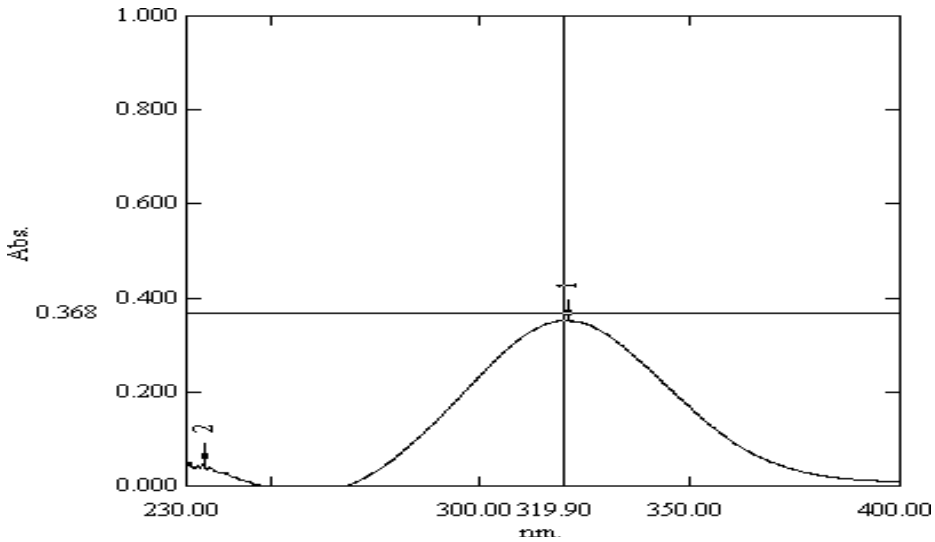


Fig 1. λmax of metronidazole in pH 5.5 citrate phosphate buffer

Calibration curve of metronidazole in pH 4 and 5.5 citrate phosphate buffer

Stock solution: 100 mg of metronidazole was accurately weighed and transferred in to a 100ml volumetric flask. The drug was dissolved and diluted upto the mark with pH 4 citrate phosphate buffer. This was further diluted to 100µg/ml.From the above stock solution, aliquots of 0.3, 0.6, 0.9, 1.2, and 1.5ml were transferred to 10 ml volumetric flasks and made upto the mark with pH 4 citrate phosphate buffer. The absorbance of these solutions was measured at 319.9 nm and a graph of concentration versus absorbance was plotted. The calibration curveof metronidazole in pH 4 citrate phosphate buffer is reported in Table 4 and the graph in Fig 5. In the similar pattern, thecalibration curve for metronidazole was plotted in pH 5.5 citrate phosphate buffer and the calibration curve obtained isreported in Table 5 and the graph in Fig 6.

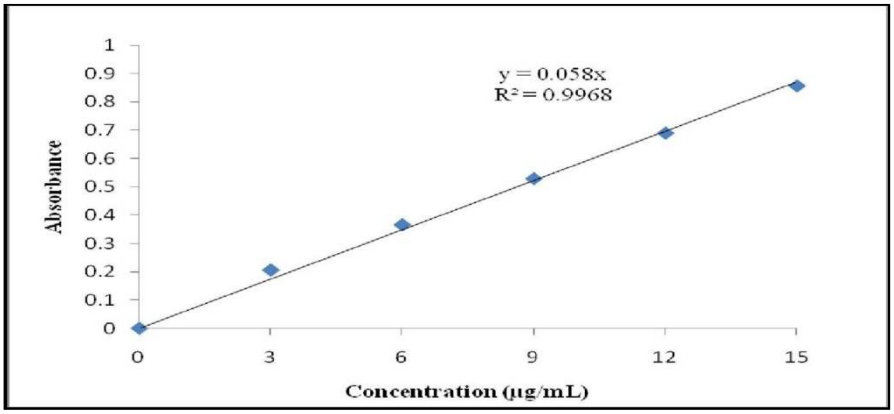


Fig. 2 Calibration curve of metronidazole in pH 4 citrate phosphate buffer

Table 1: Calibration curve data of metronidazole in pH 4 citrate phosphate buffer

Sl No.	Concentration (µg/mL)	Absorbance ± std dev*
1	0	0
2	3	0.206±0.0049
3	6	0.366±0.0021
4	9	0.529±0.0050
5	12	0.690±0.0015
6	15	0.857±0.0021

***mean ± SD, n = 3**

Table 2: Calibration curve data of metronidazole in pH 5.5 citrate phosphate buffer

Sl No.	Concentration (µg/mL)	Absorbance ± std dev*
1	0	0
2	3	0.202 ± 0.0051
3	6	0.368 ± 0.0056
4	9	0.481 ± 0.0114
5	12	0.652 ± 0.0140
6	15	0.800 ± 0.0205

***mean ± SD, n = 3**

PREPARATION OF THERMOSENSITIVE BIOADHESIVE GEL [14]

Thermosensitive bio-adhesive gel was prepared by cold method.

- Metronidazole and bio adhesive polymers except pluronic F127 were completely dispersed in pH 4 citrate phosphate buffer with continuous agitation at room temperature and cooled down to 4ºC.
- Pluronic F127 was then slowly added to the solution with continuous agitation.
- The resulting solution was then left at 4ºC until a clear solution was obtained.

Table 3. Formulation chart of Thermosensitive Bio-adhesive Gel

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pluronic-F127 (%w/v)	20	20	20	20	20	20	20	20	20
HPMC (%w/v)	0.2	-	0.2	-	-	-	-	-	-
SCMC (%w/v)	-	0.2	0.2	-	-	-	-	-	-
Carbopol (%w/v)			-	0.2	0.4			0.2	0.4
Polycarbophil (%w/v)	-	-	-	-	-	0.2	0.4	0.2	0.4
Metronidazole (%w/v)	1	1	1	1	1	1	1	1	1
pH 4 citrate phosphate buffer	q.s to20 mL	q.s to 20 mL	q.s to 20 mL	q.s to 20 mL	q.s to 20 mL	q.s to 20 mL	q.s to 20 mL	q.s to 20 mL	q.s to 20 mL

RESULTS AND DISCUSSION

Thermosensitive bioadhesive gels were prepared by cold method. This *in situ* gelling behaviour with bioadhesion properties offers the advantage of sustained drug release leading to improved therapeutic efficacy for vaginal infection. Thermosensitive bioadhesive gel formulations containing metronidazole were prepared by using pluronic F127 and bioadhesive polymers in a mixture which gels at the body temperature at a specific concentration. Carbopol, SCMC, HPMC, polycarbophil in the concentrations 0.2 and 0.4 % w/v were used as mucoadhesive polymers required to modulate the gel strength and increase the residence time of the gel by adhering to vaginal mucosa. Pluronic F127 is of particular interest since concentrated solutions (≥20% w/w) of the copolymer are transformed from low viscosity transparent solutions to solid gels on heating to body temperature. At low temperatures in aqueous solutions, a hydration layer surrounds pluronic F127 molecules. However, when the temperature is raised, the hydrophilic chains of the copolymer become desolvated as a result of the breakage of the hydrogen bonds that had been established between the solvent andthese chains. This phenomenon favors hydrophobic interactions among the polyoxypropylene domains, and leads to gelformation. Because of the dehydration process, the hydroxyl groups become more accessible [4].

PREFORMULATION STUDIES

The following preformulation studies were performed for metronidazole:

SOLUBILITY

The drug was found to be sparingly soluble in water, slightly soluble in ethanol and chloroform; soluble in dilute acids, slightly soluble in ether.

DETERMINATION OF pH

The pH of 1%w/v solution of metronidazole in water was found to be 5.60

DRUG-EXCIPIENTS COMPATIBILITY STUDIES BY FTIR

Metronidazole pure drug and the optimized formulation were subjected for FTIR spectroscopic analysis for compatibility studies and to ascertain whether there was any interaction between the drug and the

polymers used. The IR spectra of metronidazole and optimized formulation F8 were found to be identical and presented Fig 8. The characteristic IR absorption peaks of metronidazole at 1265 cm^{-1} (C-O stretch), 2879 cm^{-1} (Aliphatic C-H stretch), 1624 cm^{-1} (C=C stretch) and 1357 cm^{-1} (C-N vibration) were present in the formulation. The data is tabulated in Table 7. FTIR spectra of the optimized formulation F8 showed all the metronidazole characteristics absorption bands suggesting the absence of interactions between the drug and the other components of the formulations.

Table 4: FTIR spectral data of pure drug and optimized formulation F8

Groups	Peak positions in pure drug (cm^{-1})	Peak positions in F8 (cm^{-1})	Intensity range (cm^{-1})
C-O stretch	1265.3	1269.2	1250-1350
C-H stretch	2879.82	2873.1	2962-2853
C-H bending	740.6	737.5	975-780
C=C stretch	1624.1	1622.5	1680-1620
C-N vibration	1357.9	1352.3	1400-1000
OH bending	1076.3	1069.6	1050-1150

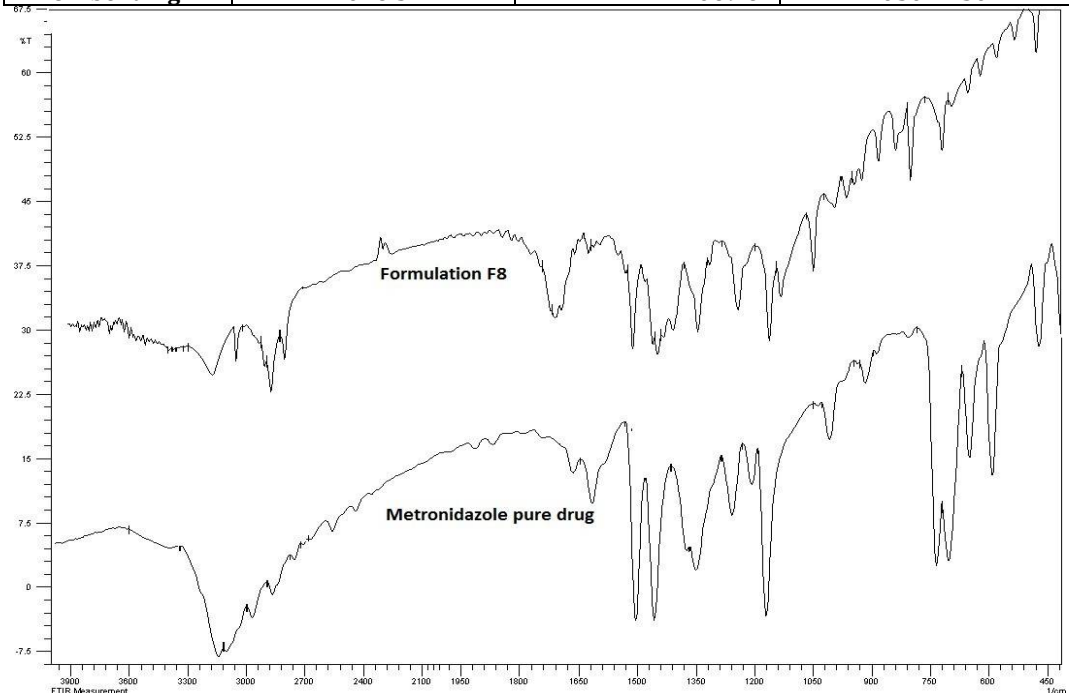


Fig 3. FTIR spectra of metronidazole pure drug and optimized formulation F8

EVALUATION OF THERMOSENSITIVE BIOADHESIVE GEL

GELATION TEMPERATURE AND GELATION TIME

Gelation temperature is the temperature at which the liquid phase makes a transition to gel. Gelation temperature rangesuitable for formulations would be 30–36°C. If the gelation temperature is lower than 30°C, gelation occurs at room temperature leading to difficulty in manufacturing, handling and administering. If the gelation temperature is higher than 36°C, the formulation still stays as a liquid at body temperature, resulting in leakage. Therefore, formulations must havethe suitable gelation temperature between 30-36°C.During preliminary work it was observed that the formulation containing less than 20 % w/w PF-127 did not gel over the temperature range tested (up to 50ºC) and that increasing PF-127 concentration, by increments of 2-3%, the gelation temperature of solution was decreased. A modulation of the gelation temperature to reach the desired range (30-37ºC) could be achieved through the use of a combination of the pluronic F127 with mucoadhesive polymers. The addition of mucoadhesive polymers lowered the gelation temperature of all formulations. The impact of mucoadhesive polymers on the gelation temperature was found to depend on their nature and concentrations. Increase in the concentration of mucoadhesive polymers from 0.2% to 0.4% decreased the gelation temperature. Gelation temperatures of the prepared formulations are tabulated in Table 8.The gelation temperature lowering effect of mucoadhesive polymer could be explained by two possibilities:

- The gelation temperature lowering effect might be caused by increased viscosity after dissolution of mucoadhesive polymer [13] or

- Due to their ability to bind to the polyoxyethylene chains present in the pluronic molecules. 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 [11, 12].

Table 5. Gelation temperature of formulations F1-F9

Sl No.	Formulation code	Gelation temperature (ºC)Mean ± SD*
1	F1	35.8 ± 0.289
2	F2	35.0 ± 0.289
3	F3	37.0 ± 0.577
4	F4	36.0 ± 0.577
5	F5	35.3 ± 0.577
6	F6	36.5 ± 0.500
7	F7	35.0 ± 0.577
8	F8	34.2 ± 0.289
9	F9	33.0 ± 0.578

*Standard deviation, mean n=3

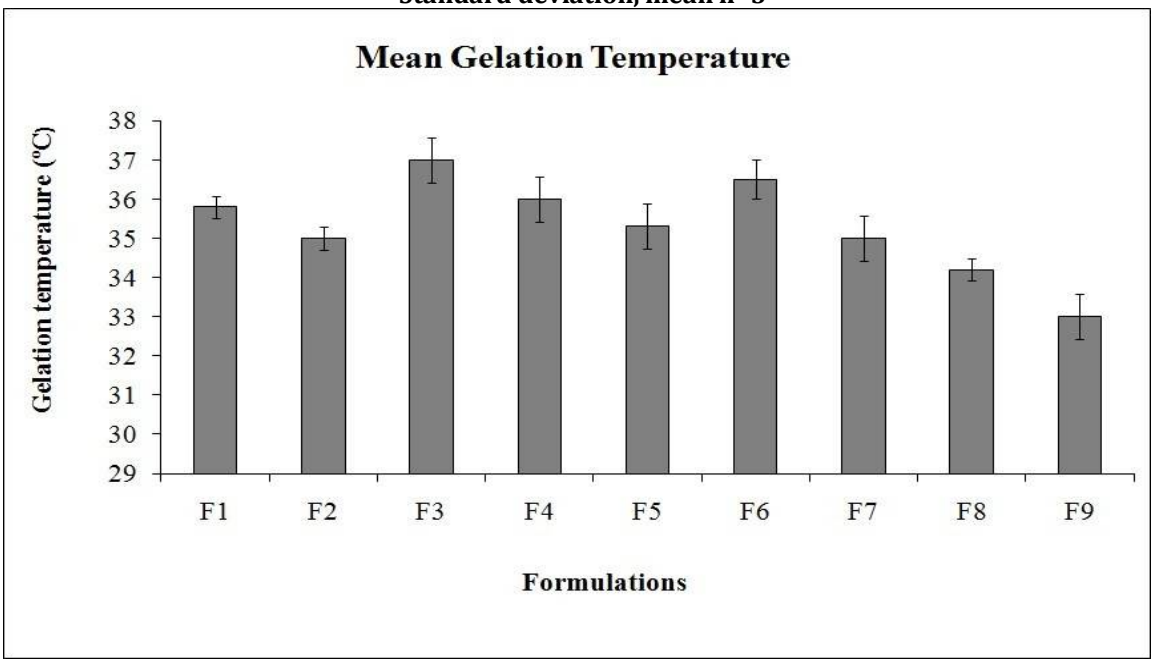


Fig. 4 Gelation temperature for formulations F1- F9GELATION TIME

Table 6. Gelation time of formulations F1-F9

Sl No.	Formulation code	Gelation time (mins)Mean ± SD*
1	F1	6.0 ± 0.500
2	F2	4.2 ± 0.289
3	F3	4.0 ± 0.500
4	F4	3.5 ± 0.289
5	F5	3.0 ± 0.500
6	F6	4.5 ± 0.500
7	F7	4.0 ± 0.289
8	F8	3.7 ± 0.577
9	F9	3.0 ± 0.289

*Standard deviation, mean n=3

When the solutions were heated at 37ºC, they transformed into non flowing gels within less than 10 minutes. It can beseen that increase in concentration of mucoadhesive polymers decreased gelation time.

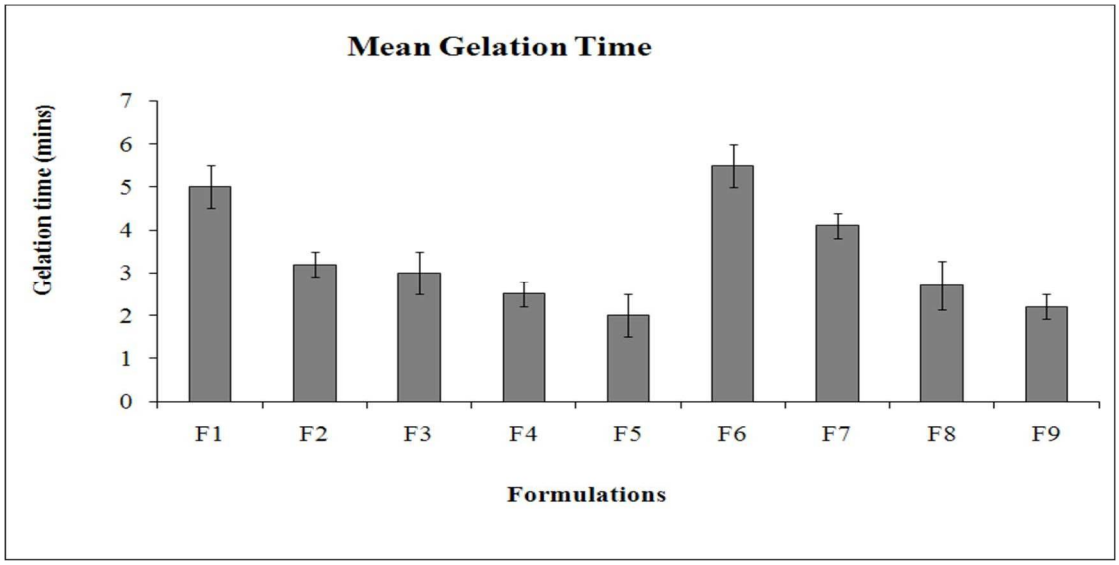


Fig. 5. Gelation time for formulations F1- F9DETERMINATION OF DRUG CONTENT

The prepared formulations were analyzed for drug content and the data is reported in Table 10. It was observed that the drug content was satisfactory and the drug was uniformly distributed in all the formulations.

Table 7. Drug content of formulations F1-F9

Sl No.	Formulation code	% Drug contentMean ± SD*
1	F1	98.79±0.63
2	F2	96.90±0.70
3	F3	96.95±0.43
4	F4	96.95±1.36
5	F5	98.33±0.52
6	F6	97.47±1.03
7	F7	98.16±0.94
8	F8	97.87±0.87
9	F9	98.56±1.34

***Standard deviation, mean n=3**

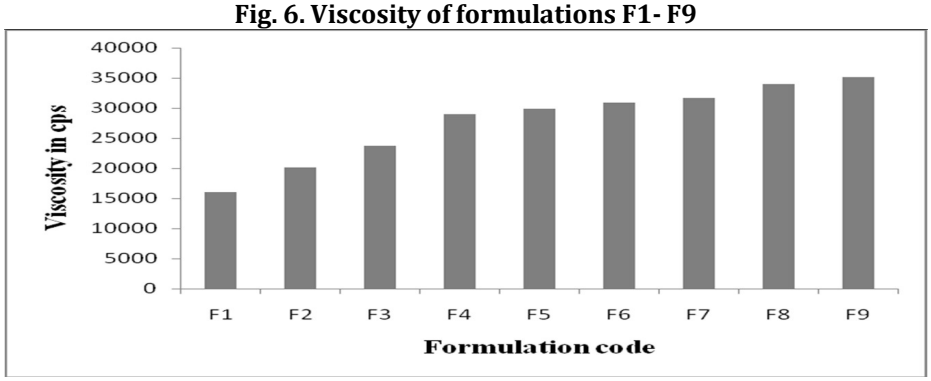
EFFECT ON VISCOSITY

Viscosity studies showed a marked increase in viscosity of the gels at 37ºC due to sol-gel conversion (Table 11). Concentration of bioadhesive polymers also had significant effect on the viscosity of the gels. Increase in the concentrations of the bioadhesive polymers increased the viscosity of the gels. The order for increase in viscosity observed can be given as follows: Polycarbophil > Carbopol > SCMC > HPMC.

Table 8. Viscosity of formulations F1-F9

Sl No.	Formulation code	Viscosity (cps) at 37ºC
1	F1	16050
2	F2	20130
3	F3	23685
4	F4	29040
5	F5	29880
6	F6	30975
7	F7	31628
8	F8	33930
9	F9	35104

Fig. 6. Viscosity of formulations F1- F9



***IN VITRO* BIOADHESION STUDIES**

Bioadhesive strength was determined in terms of detachment stress i.e. force required to detach the formulation from the mucosal surface. Data in Table 12 indicated that the increase in the concentration of bioadhesive polymers increasedthe bioadhesive strength. The mucoadhesive polymers could be arranged according to their mucoadhesive force enhancing effect at 0.2% concentration of vaginal gel as, CP> Polycarbophil>SCMC> HPMC. Increasing the polymer amount may provide more adhesive sites and polymer chains for interpenetration with mucin, resulting consequently in aggrandization of mucoadhesive strength. The mechanism of the mucoadhesion enhancing effect of different polymers might be related to hydrogen bonding between the polymers and the mucosal
membrane (glycoprotein) via carboxyl groups in the mucoadhesive polymers [6].The mucoadhesive effect of HPMC couldbe due to the cellulose derivatives having many hydroxyl groups promote dehydration of poloxamers and consequentlythe hydrophobic interactions between the poly(oxypropylene)blocks [7, 8].

Table 9. Bioadhesive strength of Formulations F1-F9

Sl No.	Formulation code	Bioadhesive strength (dynes/cm^2)Mean ± SD	
		2mins	5mins
1	F1	1068.1 ± 3.78	1470.8 ± 2.36
2	F2	1905.3 ± 4.01	2177.1 ± 3.78
3	F3	2364.2 ± 2.65	2940.1 ± 4.9
4	F4	3277.0 ± 2.89	3920.2 ± 3.97
5	F5	3800.0 ± 4.12	4028.3 ± 2.54
6	F6	3214.2 ± 3.96	3484.5 ± 4.35
7	F7	3270.5 ± 2.87	3593.2 ± 2.86
8	F8	4120.7 ± 3.61	4464.5 ± 4.20
9	F9	4693.1 ± 4.25	4900.5 ± 3.91

***Standard deviation, mean n=3**

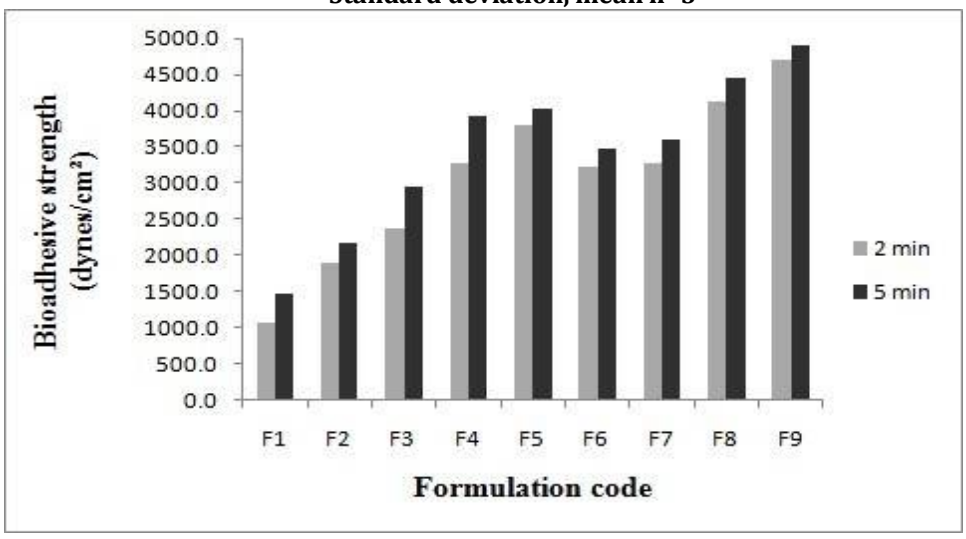


Fig. 7. Bioadhesive strength of formulations F1-F9

IN VITRO DRUG RELEASE STUDY

The *in vitro* drug release of metronidazole forms the formulations are reported in Table 13 and their profile in Fig 13.

Table 10. Cumulative % drug release from formulations F1-F9

Time in hrs	Cumulative % drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	28.1 ± 4.62	22.6 ± 4.13	22.6 ± 3.87	25.2 ± 5.71	23.5 ± 3.67	24.8 ± 3.72	22.7 ± 5.1	18.8 ± 4.69	18.0 ± 3.9
1	54.6 ± 5.01	35.3 ± 4.01	35.3 ± 4.26	38.6 ± 5.64	35.3 ± 3.04	37.3 ± 4.11	35.0 ± 5.23	27.3 ± 3.67	22.7 ± 4.81
2	78.5 ± 4.1	46.7 ± 4.68	45.6 ± 3.98	52.9 ± 4.1	49.8 ± 4.25	56.1 ± 4.26	45.0 ± 4.36	36.5 ± 4.16	34.9 ± 4.56
3	89.0 ± 3.83	56.9 ± 3.71	58.8 ± 4.11	64.6 ± 5.02	58.8 ± 2.69	67.5 ± 2.89	57.4 ± 4.05	46.8 ± 5.03	44.6 ± 5.13
4	91.2 ± 3.04	69.8 ± 2.14	68.1 ± 3.58	73.8 ± 4.23	71.4 ± 5.06	78.6 ± 3.67	65.2 ± 3.89	55.4 ± 2.79	55.3 ± 4.03
5	90.4 ± 2.15	79.4 ± 2.01	79.4 ± 2.79	78.7 ± 3.97	76.4 ± 4.15	80.7 ± 5.04	74.2 ± 4.72	67.5 ± 3.58	63.8 ± 2.67
6	90.1 ± 2.36	85.1 ± 2.67	87.0 ± 2.87	81.7 ± 2.79	79.6 ± 3.76	83.2 ± 2.97	81.0 ± 2.96	79.2 ± 4.24	75.1 ± 3.09
8	--	84.2 ± 2.39	89.0 ± 3.45	87.1 ± 3.41	81.9 ± 4.03	89.1 ± 3.5	84.1 ± 5.02	84.0 ± 3.25	81.2 ± 3.96
10	--	--	--	87.0 ± 2.59	83.5 ± 2.97	89.6 ± 4.24	83.7 ± 4.33	88.8 ± 2.16	84.8 ± 2.74
12	--	--	--	--	--	--	--	93.6 ± 3.26	87.1 ± 2.69

From the *in vitro* drug release studies it was observed that the concentration of mucoadhesive polymers affected the drug release from the formulations. The addition of mucoadhesive polymers like SCMC, carbopol and polycarbophil retardedthe drug release from the formulations, whereas HPMC exhibited burst release. The retardation of drug release increased with increase in the concentration of mucoadhesive polymers. Increase in the overall product viscosity might contributeto the retarding effect of these mucoadhesive polymers [9] as well as their ability to distort or squeeze the extra- micellar aqueous channels of poloxamer micelles through which the drug diffuses thereby delaying the release process [10]. The increase in gel strength and/ or molecular interaction between the drug and polymers could also retard release of the drug.

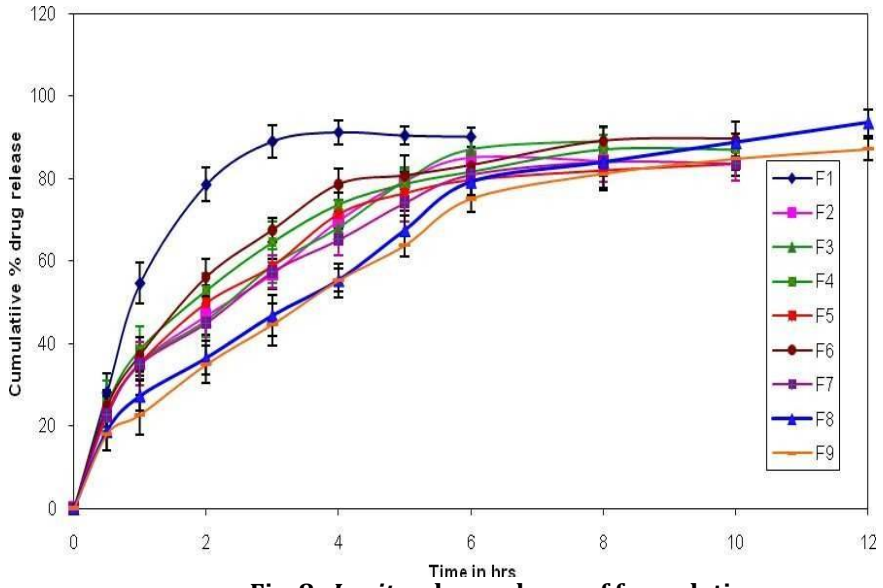


Fig. 8. *In vitro* drug release of formulations

CONCLUSION

The prepared formulations were stable and in solution state at or below room temperature. While it transformed intogel at body temperature (37ºC) and released drug for prolonged time.

The following conclusions were obtained drawn from the results obtained

- From the FTIR spectra, it was observed that similar characteristic peaks appear with minor differences for the drug and their formulations. Hence, it appeared that there was no interaction between drug andthe polymer used.
- From the results of drug content determination, it can be inferred that drug content was satisfactory andthe drug was uniformly distributed in all the formulations.
- All the formulations had gelation temperature between 31ºC-37ºC thus the solutions readily gelled at body temperature, making them ideally suited to function as drug depot.
- From the gelation time determination it was observed that when the solutions were heated at 37ºC theytransformed into non flowing gel with increased viscosity within less than 10 mins.
- Viscosity studies of the gel showed a marked increase in viscosity at 37ºC due to sol- gel conversion property of polymer with increase in temperature. The viscosity of the formulations increased with increase in the concentration of the bioadhesive polymers. Amongst the various bioadhesive polymers used polycarbophil showed maximum increase in viscosity. The formulation with combination of polycarbophil and carbopol showed highest viscosity.
- Bioadhesive strength of the formulations increased with increase in polymer concentration. Carbopol showed maximum bioadhesive strength followed by polycarbophil and SCMC, whereas HPMC had leastbioadhesive property.
- From the *in vitro* drug release data, it was observed that the concentration of bioadhesive polymers affected the drug release from the formulations. The release rate of drug was found to decrease with increase in the concentration of the bioadhesive polymers. Formulation F1 containing HPMC showed burst release of about 91% in 4^{th} hour, whereas F2 and F3 showed maximum release of about 84% and 89% respectively at 6^{th} hour. Formulations F4, F5, F6 and F7 showed maximum release of about 87%, 83%, 89% and 83% respectively at 10^{th} hour. Formulations containing combination of polycarbophil and carbopol F8 and F9 showed maximum release of 93% and 87% respectively at 12^{th} hour.
- The result of stability studies carried out on the optimized formulation, F8 indicated that after 90 days there was no significant change in the drug content when stored at recommended accelerated storage conditions i.e., 25ºC/60%RH. From the study, it can be concluded that the temperature sensitive bioadhesive gel can be used to achieve sustained drug release. All the gels formulated had gelation temperature well below body temperature thus they readily became gels, making them ideally suited tofunction as drug depot. Thus the developed dosage form was found easy to administer, simple, comfortable, with increased patient compliance.

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