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FORMULATION AND EVALUATION OF CLOTRIMAZOLE INSITU GELLING SYSTEM BY USING DIFFERENT POLYMERS

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ABSTRACT

Poor vaginal residence time and rapid leakage of conventional vaginal formulations often lead to reduced therapeutic efficacy in the treatment of vulvovaginal candidiasis. To overcome these limitations, in situ gelling drug delivery systems have been developed to enhance drug retention and provide sustained drug release at the site of action. The present study aimed to formulate and evaluate an in situ vaginal gel of clotrimazole using different polymers. Sodium alginate was employed as the primary gelling polymer due to its ability to form gels in the presence of divalent cations present in vaginal fluid. Hydroxypropyl methylcellulose was incorporated as a viscosity enhancing and mucoadhesive agent to improve retention time. The prepared formulations were evaluated for parameters such as pH, viscosity, drug content, gelation capacity, and in vitro drug release. Among the formulations tested, formulation F4 showed optimal characteristics with appropriate viscosity, good gelation ability, and sustained drug release of approximately 74.63% over 8 hours. Stability studies indicated that the formulation remained stable under different storage conditions. The developed clotrimazole in situ gel demonstrated prolonged drug release and improved therapeutic potential for the treatment of vulvovaginal candidiasis.

KEYWORDS: Clotrimazole, In situ gel, Vaginal drug delivery, Sodium alginate, Hydroxypropyl methylcellulose.

INTRODUCTION

Novel drug delivery systems are designed to improve the therapeutic efficacy and safety of drugs by controlling the rate, time, and place of drug release in the body. Conventional drug delivery methods often result in fluctuations in

plasma drug concentration and reduced therapeutic effectiveness. Therefore, advanced delivery systems such as in situ gels have gained considerable attention in pharmaceutical research.

In situ gel systems are liquid formulations that undergo gelation upon exposure to physiological conditions such as pH, temperature, or ionic strength. This sol-to-gel transition allows easy administration while providing prolonged residence time at the site of action. These systems offer advantages such as sustained drug release, improved bioavailability, reduced dosing frequency, and enhanced patient compliance.

Vaginal drug delivery is an effective route for both local and systemic drug administration. The vagina has a rich blood supply and a large surface area, which facilitates drug absorption while bypassing first-pass metabolism. However, conventional vaginal formulations such as creams, ointments, and suppositories often suffer from leakage and short residence time, resulting in reduced therapeutic efficacy.

Vulvovaginal candidiasis is a common fungal infection caused primarily by Candida albicans. It affects nearly 75% of women at least once in their lifetime and is characterized by symptoms such as itching, irritation, vaginal discharge, and discomfort. Effective management requires antifungal therapy with prolonged contact at the site of infection.

Clotrimazole is a broad-spectrum antifungal agent widely used in the treatment of vulvovaginal candidiasis. However, conventional dosage forms require frequent application and may not maintain adequate drug concentration at the infection site. Therefore, the development of a clotrimazole in situ gelling system could provide improved retention and sustained drug release, enhancing therapeutic effectiveness.

The present study focuses on the formulation and evaluation of clotrimazole in situ vaginal gels using sodium alginate and hydroxypropyl methylcellulose to achieve prolonged drug release and improved therapeutic efficacy.

MATERIALS AND METHODS

Materials

Clotrimazole was used as the active pharmaceutical ingredient. Sodium alginate was used as the primary gelling agent, and hydroxypropyl methylcellulose served as a viscosity enhancing and mucoadhesive polymer. Other excipients included calcium carbonate, preservatives, and distilled water.

Preformulation Studies

Preformulation studies were carried out to evaluate the physicochemical properties of clotrimazole before formulation. The melting point of clotrimazole was determined using the capillary method to confirm its identity and purity. Solubility studies were performed in various solvents such as distilled water, 0.2 M sodium hydroxide, and 0.1 N hydrochloric acid to select a suitable solvent system for formulation. Drug–excipient compatibility studies were conducted using FTIR spectroscopy to ensure that there was no interaction between clotrimazole and the polymers used in the formulation. In addition, a standard calibration curve of clotrimazole was prepared in simulated vaginal fluid and distilled water using a UV–Visible spectrophotometer at 261–263 nm to determine drug concentration during further evaluation studies.

Formulation

SI.No	Ingredients	F1	F2	F3	F4
1	clotrimazole	2mg	2mg	2mg	2mg
2	HPMC	0.5gm	0.5gm	0.5gm	0.5gm
3	sodium alginate	0.5gm	1gm	0.7gm	0.3gm
4	carbopol	0.5gm	0gm	0.3gm	0.7gm
5	poloxamer 127	0.5gm	0.5gm	0.5gm	0.5gm
6	Nacl	0.9gm	0.9gm	0.9gm	0.9gm
7	Benzalkonium chloride	0.02ml	0.02ml	0.02ml	0.02ml
8	Distilled Water	50ml	50ml	50ml	50ml

Formulation design for in situ gelling system of clotrimazole

Preparation of In Situ Gel

The in situ gel formulations were prepared by dissolving sodium alginate in distilled water with continuous stirring. Hydroxypropyl methylcellulose was then added to the solution to enhance viscosity and mucoadhesion. Clotrimazole was incorporated into the polymeric solution with constant stirring until a homogeneous mixture was obtained. Calcium carbonate was added as a source of divalent ions to trigger gel formation in the presence of vaginal fluid.

Evaluation APPEARANCE

The appearance of the developed Clotrimazole in situ gelling systems were subjected to a comprehensive evaluation starting with appearance, where clarity and color were assessed to ensure suitability for vaginal preparation.

pH

The pH of the formulations was measured to ensure stability and compatibility with vaginal tissue. DRUG

CONTENT

Drug content was determined via UV-Vis spectrophotometry at 261 nm. GELATION STUDIES Gelation studies were performed by mixing the system with Simulated Vaginal Fluid (SVF) in a 25:7 ratio to mimic physiological conditions.

RHEOLOGICAL STUDIES

Rheological studies, conducted using a Brookfield DV-111+ Rheometer with spindle LV-3, characterized the viscosity and flow behavior of the formulations.

THE INVITRO STUDIES

The in vitro release studies utilized a modified assembly with a cellophane membrane and SVF (pH 7.4) as the dissolution medium to track drug release over time.

FORMULATION COMARISION STUDIES

Formulations comparison of release profiles with marketed products, a 14-day sterility test using fluid thioglycolate and soya bean-casein digest media.

INVITRO EFFICASY MEDIA

In vitro efficacy testing to confirm biological activity against microorganisms.

STABILITY STUDIES

Stability studies were integrated to ensure the long-term integrity of the prepared gels.

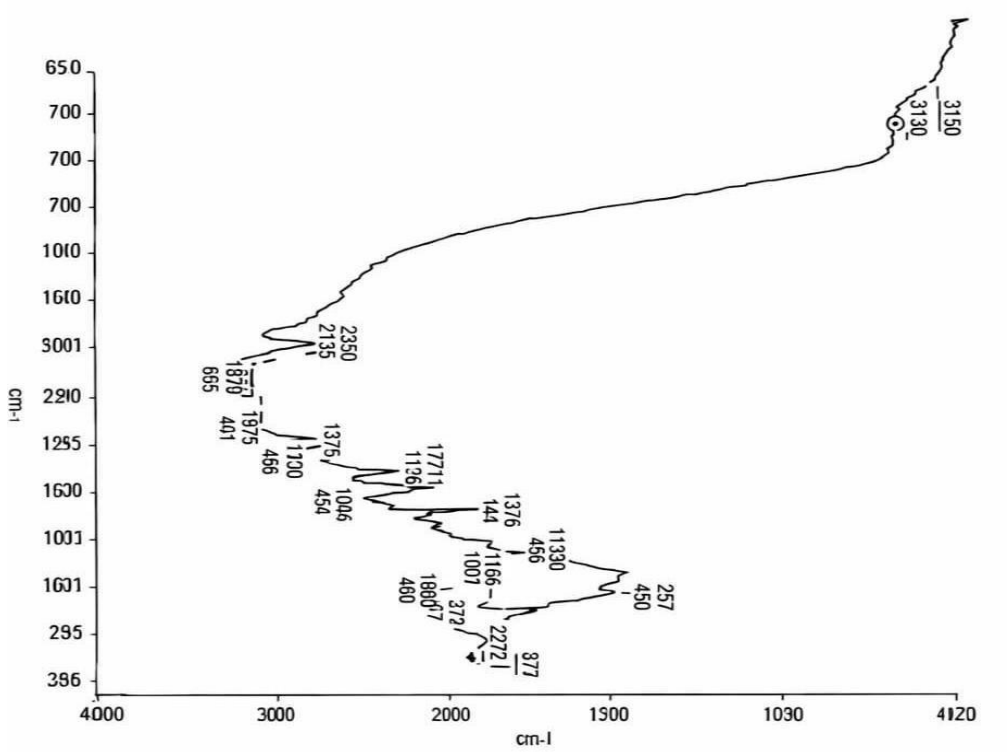


Fig-1: Ftir Spectrum of Api: Clotrimazole.

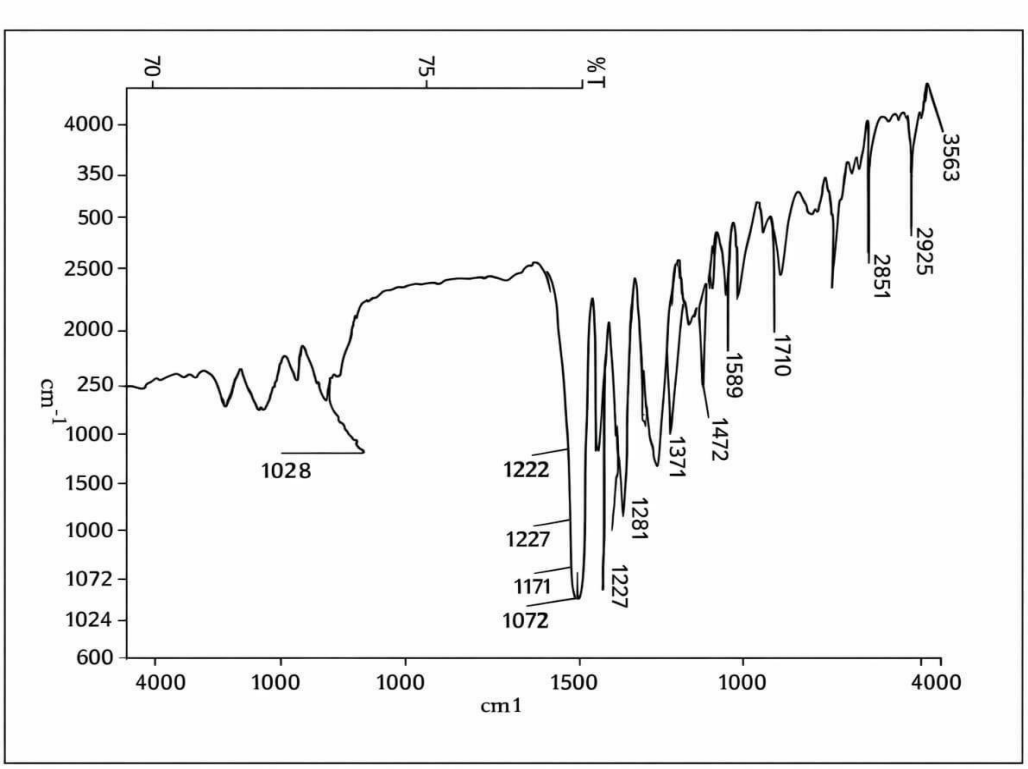
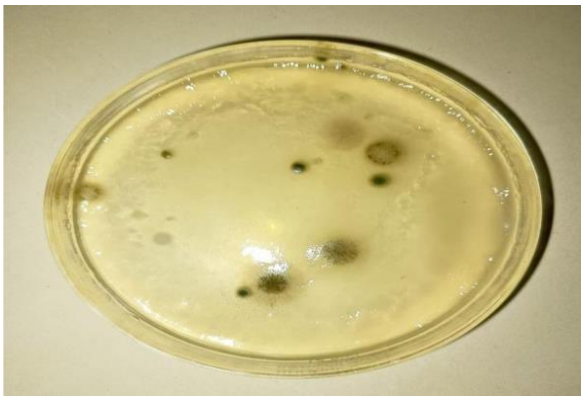


Fig-2: Ftir Spectrum of Clotrimazole & Excipients.

Plate No: 1



In Vitro Efficacy Against Candida Albicans

Plate No. 2

In Vitro Efficacy Against Staphylococcus Aureus

Table 1: Absorbance of Standard Solutions of Clotrimazole at 261 nm in SVF.

Sl. No	Concentration (µg/ml)	Absorbance
1	2	0.112
2	4	0.226
3	6	0.341
4	8	0.455
5	10	0.571
6	12	0.684
7	14	0.795

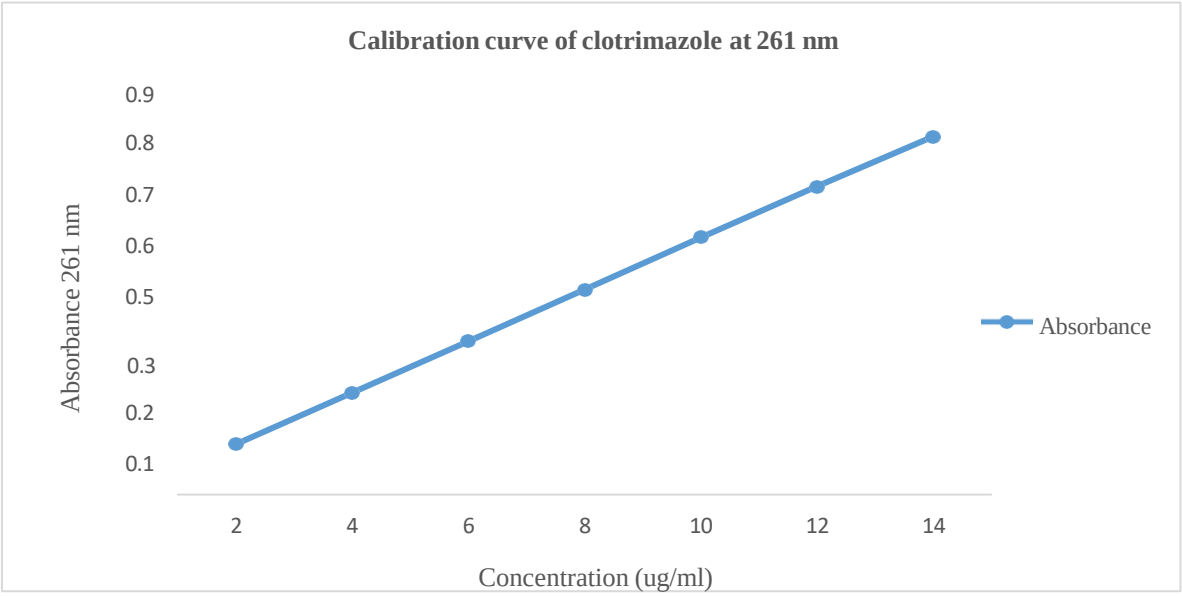


Figure 1: standard curve of clotrimazole 261 nm.

Table 2: Absorbance of Standard Solutions of Clotrimazole at 263 nm in distilled water.

Sl. No	Concentration (µg/ml)	Absorbance
1	2	0.172
2	4	0.331
3	6	0.490
4	8	0.653
5	10	0.824
6	12	0.988

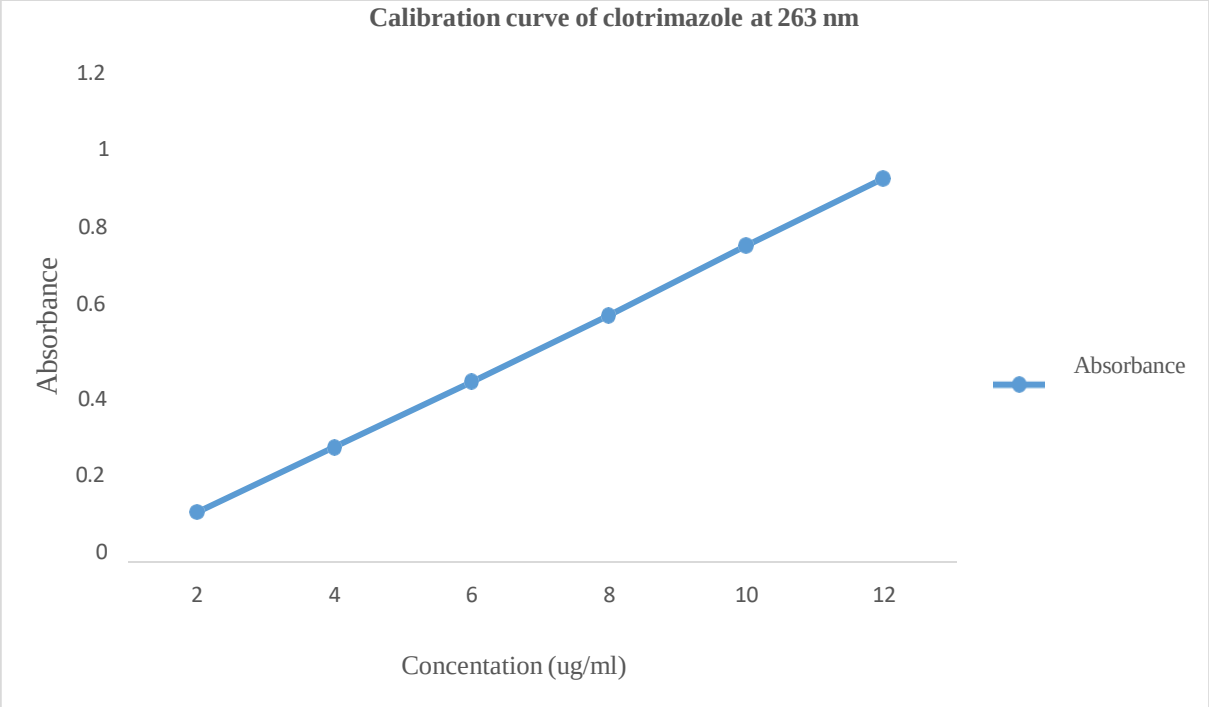


Figure 2: standard curve of clotrimazole at 263 nm.

Table 3: Composition of in situ gelling systems of clotrimazole.

S.No	Ingredients	F1	F2	F3	F4
1	clotrimazole	2mg	2mg	2mg	2mg
2	HPMC	0.5gm	0.5gm	0.5gm	0.5gm
3	sodium alginate	0.5gm	1gm	0.7gm	0.3gm
4	carbopol	0.5gm	0gm	0.3gm	0.7gm
5	poloxamer 127	0.5gm	0.5gm	0.5gm	0.5gm
6	Nacl	0.9gm	0.9gm	0.9gm	0.9gm
7	Benzalkonium chloride	0.02ml	0.02ml	0.02ml	0.02ml
8	Distilled Water	50ml	50ml	50ml	50ml

Table 4: pH and drug content of the prepared in situ gelling systems of clotrimazole.

Formulations	pH	Drug content(%)
F1	3.5	97.8
F2	3.8	98.6
F3	4.2	99.1
F4	4.5	98.3

Table 5: Viscosity of in situ gelling system of clotrimazole

Angular velocity(rpm)	Viscosity in cps			
	F1	F2	F3	F4
10	90	60	70	98
20	35	28	30	45
30	23.3	22.7	23.3	26.7
40	17.5	16.7	17.5	22.5
50	11.7	11.5	12	20
60	10.0	8.75	10	16.7
70	8.75	7.50	7.5	15.7
80	7.78	7.14	7.14	13.8
90	7.00	6.65	6.65	14.4
100	7.00	6.00	6.0	13

Table 6: Release profile of in situ gelling system of clotrimazole formulation F1

Time (T) (hrs.)	Root T	Log T	Cum. % drug release	Cum. % drug retained	Log cum. % drug released	Log cum. % drug retained
1	1.0000	0	32.5	67.5	1.512	1.829
2	1.4142	0.3010	40.8	59.2	1.611	1.772
3	1.7321	0.4771	49.6	50.4	1.696	1.703
4	2	0.6020	58.2	41.8	1.765	1.621
5	2.2360	0.6989	68.9	34.1	1.819	1.533
6	2.4495	0.7781	72.4	27.6	1.860	1.441
7	2.6458	0.8450	77.8	22.2	1.891	1.346
8	2.8284	0.9031	82.6	17.4	1.917	1.241

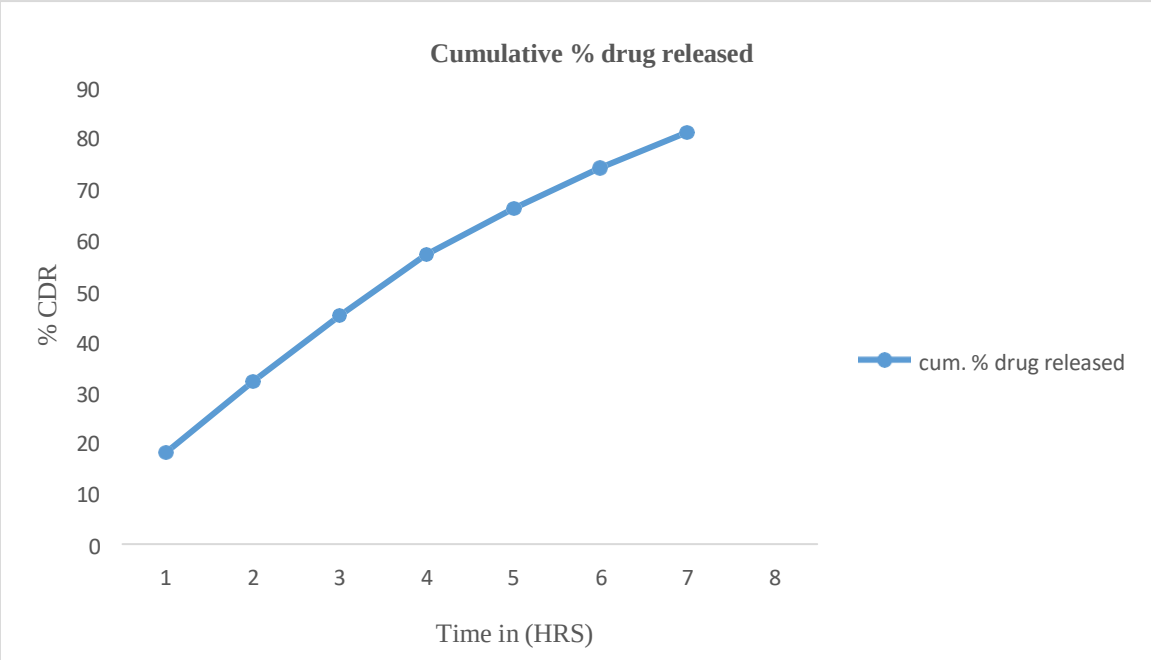


Figure 3: Cumulative % drug released of clotrimazole F1.

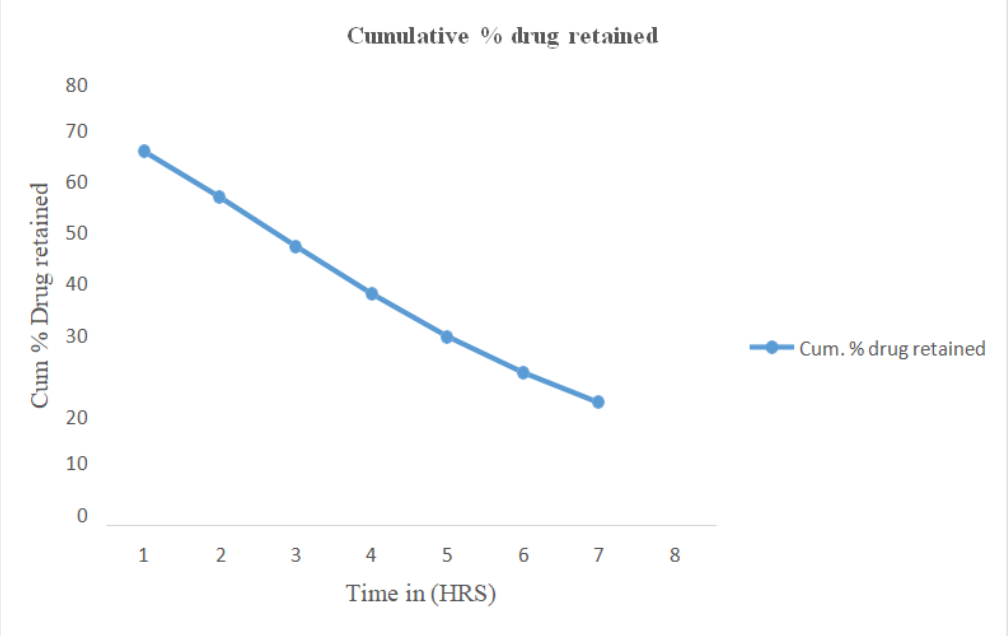


Figure 4: Cumulative % drug retaine of clotrimazole F1.

Table 7: Release profile of in situ gelling system of clotrimazole formulation F2.

Time (T) (hrs.)	Root (T)	Log (T)	Cum.% drug released	Cum.% drug retained	Log cum.% drug released	Log cum.% drug retained
1	1.0000	0	18.00	82.00	1.2553	1.9138
2	1.4142	0.3010	32.00	68.00	1.5051	1.8325
3	1.7321	0.4771	45.00	55.00	1.6532	1.7404
4	2	0.6020	57.00	43.00	1.7559	1.6335
5	2.2360	0.6989	66.00	34.00	1.8195	1.5315
6	2.4495	0.7781	74.00	26.00	1.8692	1.4150
7	2.6458	0.8450	81.00	19.00	1.9085	1.2788
8	2.8284	0.9031	88.00	12.00	1.9445	1.0792

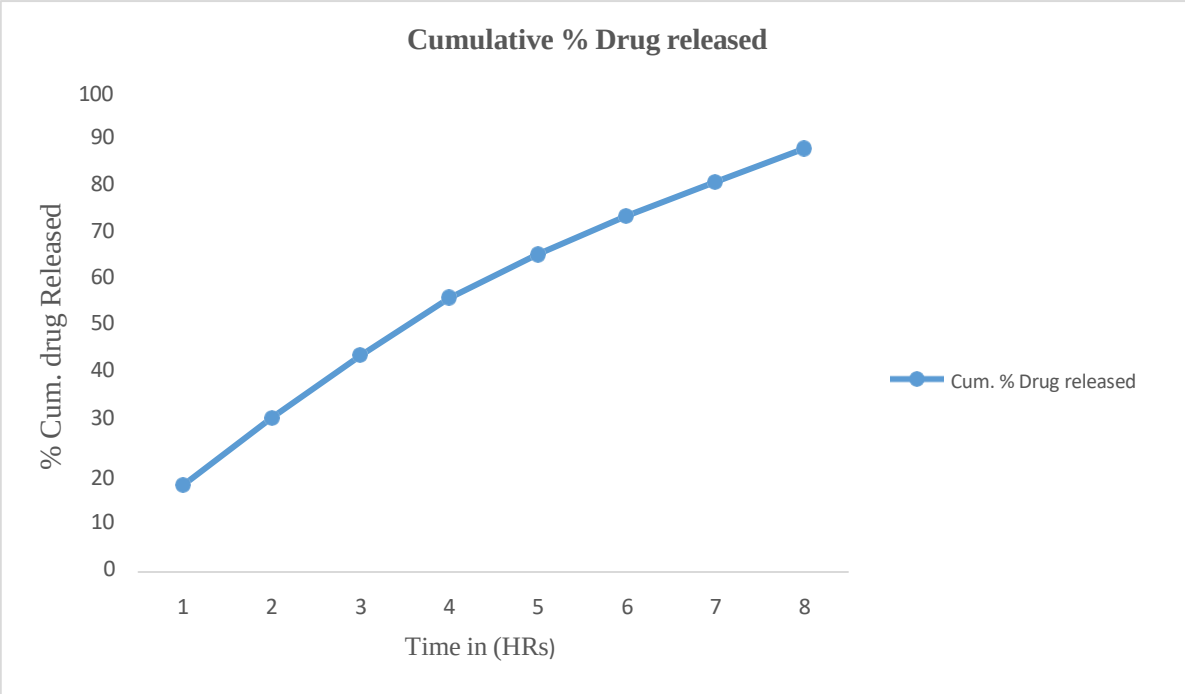


Figure 5: Cumulative % drug released of clotrimazole F2.

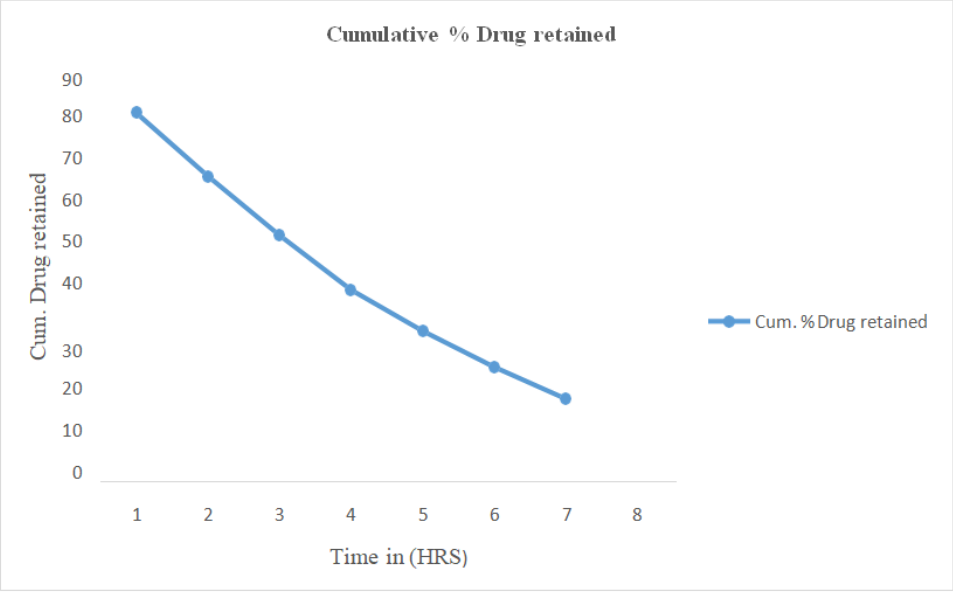


Figure 6: Cumulative % drug retained of clotrimazole F2.

Table 8: Release profile of in situ gelling system of clotrimazole formulation F3.

Time (T) (hrs.)	Root (T)	Log (T)	Cum.% drug released	Cum.% drug retained	Log cum.% drug released	Log cum.% drug retained
1	1.0000	0	38.20	61.80	1.582	1.791
2	1.4142	0.3010	46.50	53.50	1.667	1.728
3	1.7321	0.4771	55.70	44.30	1.746	1.646
4	2	0.6020	64.90	35.10	1.812	1.545
5	2.2360	0.6989	72.80	27.20	1.862	1.435
6	2.4495	0.7781	79.60	20.40	1.901	1.309
7	2.6458	0.8450	85.30	14.70	1.931	1.167
8	2.8284	0.9031	90.80	9.20	1.958	0.964

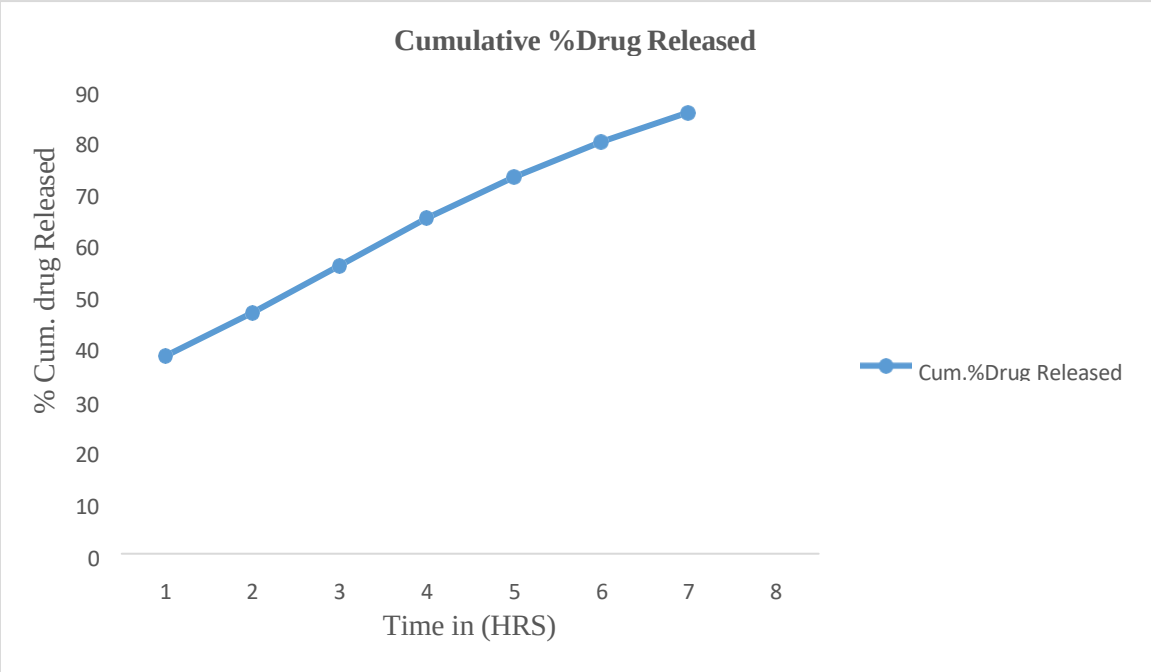


Figure 7: Cumulative % drug released of clotrimazole F3.

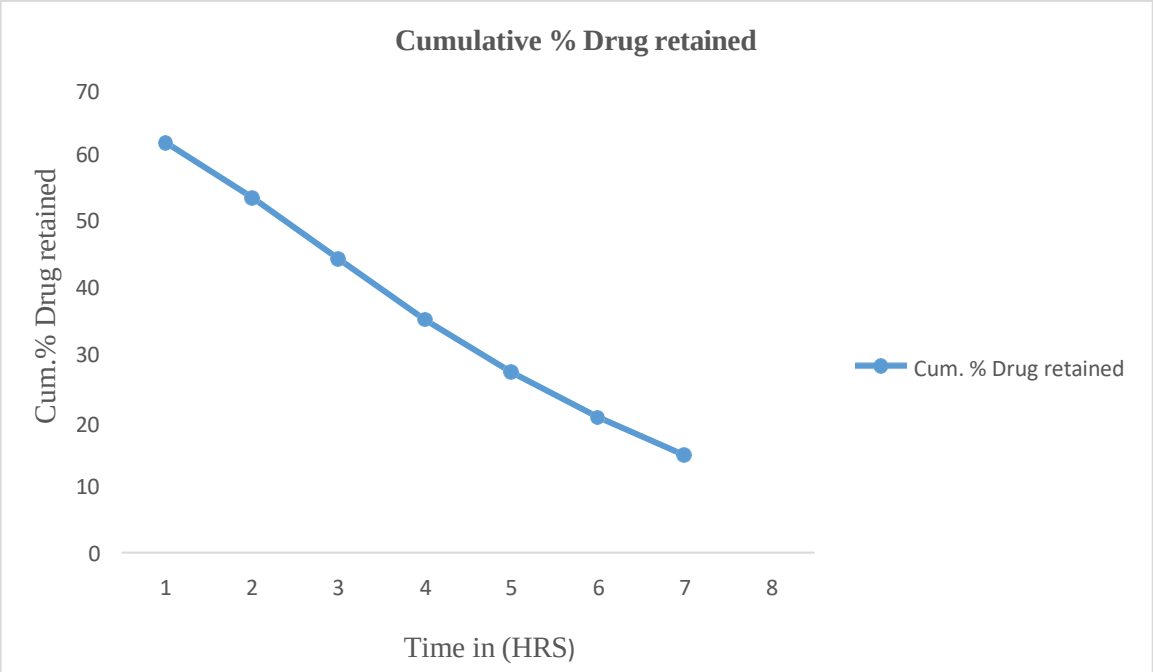


Figure 8: Cumulative % drug retained of clotrimazole F3.

Table 9: Release profile of in situ gelling system of clotrimazole formulation F4.

Time (T) (hrs.)	Root (T)	Log (T)	Cum.% drug released	Cum.% drug retained	Log cum.% drug released	Log cum.% drug retained
1	1.0000	0	28.4	71.6	1.453	1.855
2	1.4142	0.3010	36.7	63.6	1.565	1.801
3	1.7321	0.4771	48.9	54.1	1.662	1.733
4	2	0.6020	54.3	45.7	1.735	1.660
5	2.2360	0.6989	61.8	38.2	1.791	1.582
6	2.4495	0.7781	68.6	31.4	1.836	1.497
7	2.6458	0.8450	73.9	26.4	1.869	1.419
8	2.8284	0.9031	78.5	21.5	1.895	1.332

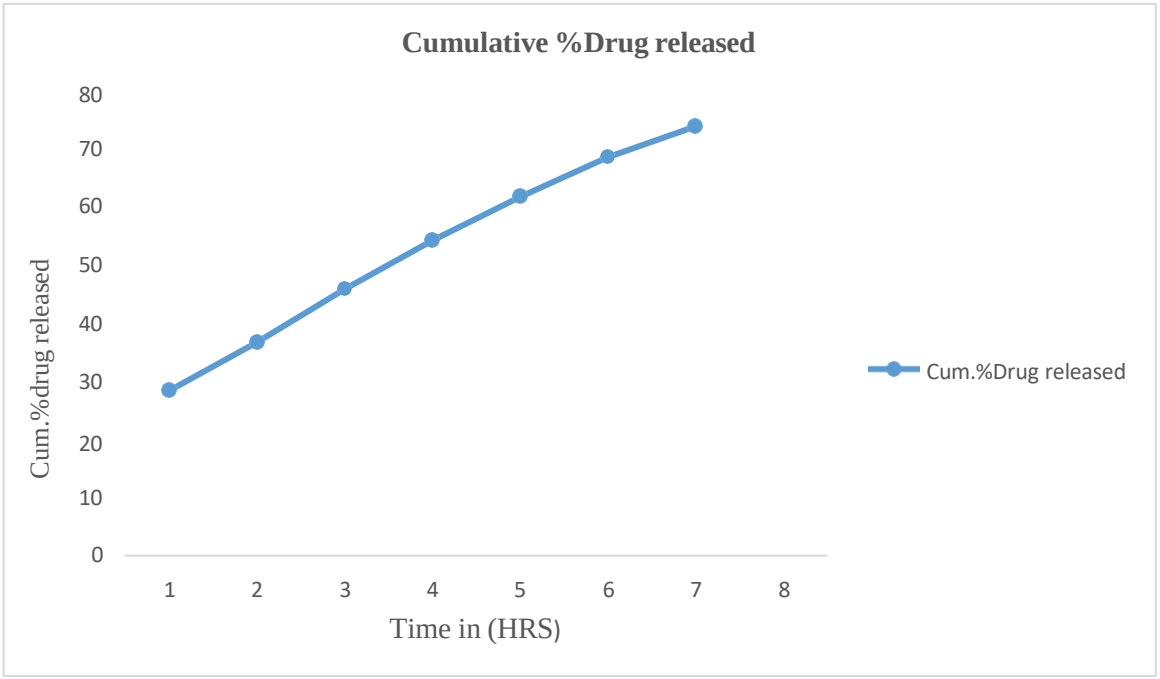


Figure 9: Cumulative % drug released of clotrimazole F4.

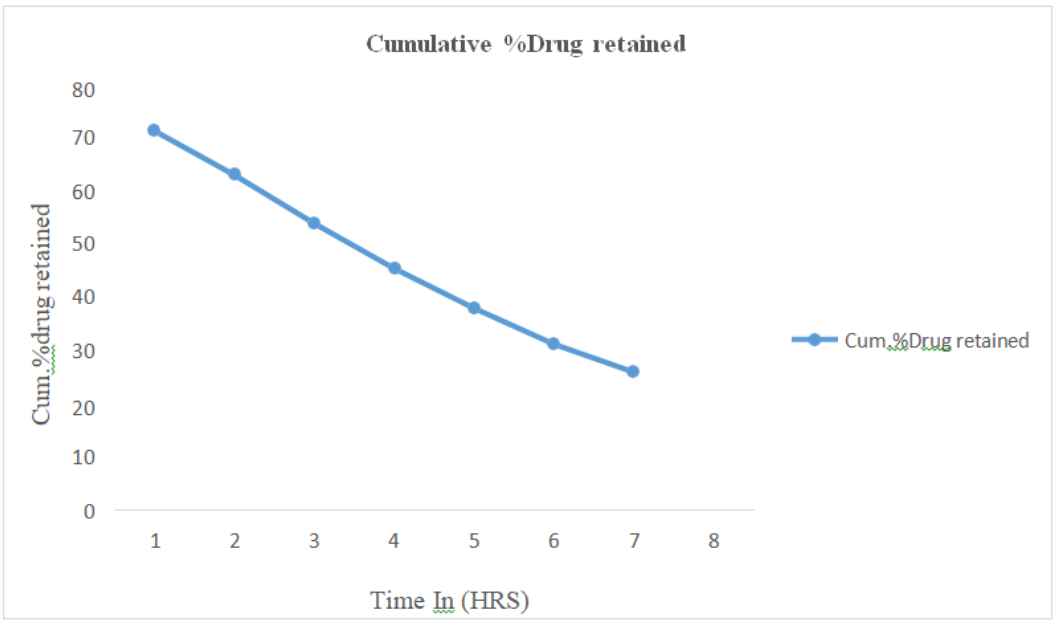


Figure 10: Cumulative % drug retained of clotrimazole F4.

Table 10: Kinetic values obtained from in vitro release data of formulations F1-F4.

formulations	Plot of log cum. % drug retained Vs. Time (T) (first order plot)			Plot of cum.% drug released Vs. Time (T) (Zero order plot)		
	slope	First order rate constant k=slope x 2.303	Regression coefficient	slope	Rate constant k_0= - slope	Regression coefficient
F1	-0.0584	-0.1345	0.9876	5.412	5.412	0.9948
F2	-0.0729	-0.1679	0.9932	5.968	5.968	0.9891
F3	-0.0657	-0.1513	0.9918	5.732	5.732	0.9926
F4	-0.0496	0.1142	0.9894	5.086	5.086	0.9962

Table 11: Kinetic values obtained from in vitro release data of formulations F1-F4.

Formulations	Plot of cum.% Vs. Root time (Higuchi matrix)		Plot of log cum.% drug released Vs. Log T (Pappas equation)	
	slope	Regression coefficient	slope	Regression coefficient
F1	19.84	0.9897	0.3015	0.9824
F2	22.67	0.9962	0.3478	0.9919
F3	21.53	0.9938	0.3294	0.9886
F4	18.92	0.9874	0.2946	0.9808

Table 12: Comparison of release profile of marketed product with formulation F4.

Time(minutes)	Cum% drug release F4
15	28.45
30	45.62
45	61.38
60	74.80
90	88.96
120	97.42

Table 13: In vitro efficacy studies for in situ gelling formulations of clotrimazole.

Micro-organisms selected	Standard ZOI (mm)	Formulations (ZOI) mm				Percentage efficiency
		F1	F2	F3	F4	
Candida albicans	30	26	27	28	29	96.7
Staphylococcus aureus	24	20	21	22	23	95.8

Table 14: Stability studies – formulations F1-F2 stored at 2^0C-8^0.

Formulations	Tested after (time in days)	Parameters evaluated		
		pH	Drug content (%)	Cum. % released (6 h)
F1	7	6.6	97.92	68.84
	15	6.6	97.31	68.12
	30	6.5	96.74	67.95
F2	7	6.8	101.6	75.96
	15	6.8	101.1	75.22
	30	6.7	100.4	74.58
F3	7	6.7	99.84	73.64
	15	6.7	99.26	72.91
	30	6.6	98.63	72.18
F4	7	6.7	100.2	63.78
	15	6.7	99.61	63.02
	30	6.6	98.94	62.41

Table 15: Stability studies – formulations F1-F4 stored at room temperature/ambient humidity.

Formulations	Tested after (time in days)	Parameters evaluated		
		pH	Drug content (%)	Cum. % released (6 h)
F1	7	6.6	96.88	68.45
	15	6.5	96.12	67.62
	30	6.4	95.54	66.73
F2	7	6.7	100.6	74.86
	15	6.6	99.74	73.81
	30	6.5	98.93	72.94
F3	7	6.7	98.92	72.38
	15	6.6	98.21	71.44
	30	6.5	97.36	70.52
F4	7	6.6	99.34	62.84
	15	6.5	98.56	61.93
	30	6.4	97.71	60.88

Table 16: stability studies – formulations F1-F4 stored at 40±1^{0}C room temperature/ambient humidity.

Formulations	Tested after (time in days)	Parameters evaluated		
		pH	Drug content (%)	Cum. % released (6 h)
F1	7	6.6	96.63	68.37
	15	6.5	96.18	67.31
	30	6.4	95.51	66.24
F2	7	6.7	101.5	76.74
	15	6.6	99.81	75.45
	30	6.5	98.32	74.22
F3	7	6.7	99.43	74.92
	15	6.6	98.31	73.57
	30	6.5	97.27	72.16

DISCUSSION

The development of an effective vaginal drug delivery system requires formulations that provide prolonged retention, controlled drug release, and compatibility with vaginal physiology. In the present study, clotrimazole in situ gels were developed using sodium alginate and HPMC to achieve these objectives. The use of sodium alginate as a gelling polymer is particularly advantageous because it undergoes ion-activated gelation in the presence of divalent ions such as calcium. When the formulation comes into contact with vaginal fluid, calcium ions interact with alginate molecules, resulting in cross-linking and the formation of a three-dimensional gel network. This mechanism allows the formulation to remain liquid during administration while forming a gel after application. HPMC was incorporated as a viscosity-enhancing and mucoadhesive polymer. The presence of HPMC increases the viscosity of the formulation and improves adhesion to the vaginal mucosa. This helps prolong the residence time of the formulation, reducing leakage and improving drug absorption. The pH of the prepared formulations was within the physiological vaginal pH range, indicating that the formulations are unlikely to cause irritation or disturb the natural microbial balance. This is an important factor in the development of vaginal drug delivery systems. Drug content analysis confirmed that the formulation process allowed uniform distribution of clotrimazole within the gel matrix. Uniform drug distribution ensures consistent dosing and reliable therapeutic outcomes. The viscosity studies demonstrated that increasing polymer concentration resulted in higher viscosity values. This is expected because higher polymer content increases intermolecular interactions and entanglement of polymer chains, leading to a more viscous system. However, the viscosity remained within acceptable limits that allow easy administration. The in vitro drug release studies revealed sustained release behavior for all formulations. The release rate decreased with increasing polymer concentration

due to the formation of a denser polymeric matrix that slows down drug diffusion. The optimized formulation (F4) showed the best balance between gel strength and controlled drug release. Sustained drug release is particularly beneficial in the treatment of vulvovaginal candidiasis because it maintains effective drug concentrations at the infection site for an extended period. This reduces the need for frequent dosing and improves patient compliance. The stability studies further confirmed that the optimized formulation maintained its physicochemical properties over time, indicating good formulation stability. Overall, the results suggest that the developed clotrimazole in situ gel system is a promising approach for vaginal drug delivery. The combination of sodium alginate and HPMC successfully produced a formulation with appropriate viscosity, rapid gelation, sustained drug release, and good stability.

CONCLUSION

The present study successfully developed and evaluated clotrimazole in situ vaginal gel formulations using sodium alginate and hydroxypropyl methylcellulose. The optimized formulation exhibited suitable physicochemical characteristics, good gelation ability, and sustained drug release for up to 8 hours. The developed system has the potential to improve drug retention and therapeutic effectiveness in the treatment of vulvovaginal candidiasis. Therefore, in situ vaginal gels may serve as a promising alternative to conventional antifungal dosage forms.

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