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Original Article

DEVELOPMENT OF BIGELS CONTAINING ANTIFUNGAL AGENT FOR VAGINAL INFECTION

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ABSTRACT

Objective: Bigels are unique semi-solid preparations that have piqued the focus of numerous scientists owing to their significant advantages over ordinary gels. The purpose of this study was to develop and characterize innovative Bigels for applications in drug delivery by combining Hydroxypropyl methylcellulose hydrogel and sorbitan monostearate, oils like coconut and olive-based organogel. The existence of both aqueous and oil phases as bigel was revealed by microscopy.

Methods: Hydrogels and organogels were prepared separately, and bigels were formed by combining hydrogel and organogel in a predetermined ratio. They were then analyzed employing various physicochemical tests i. e *in vitro* drug release, microscopy, and other techniques. Microscopy, viscosity measurement, mechanical analysis, and differential scanning calorimetry were used to examine the bigel's microstructures and physicochemical properties.

Results: Tube inversion tests reveal that the bigel doesn't flow under its own weight till 167 min. The microscopy suggested that the gels exhibited fiber-like structures due to the trapping of the organogel inside hydrogel molecules; this entrapment was demonstrated to be uniformly accomplished, resulting in formulation stability, and the DSC study reveals that the terbinafine is not decomposed also after formulating in bigel, and the terbinafine bigel was also found to be stable. The drug-loaded gels demonstrated effective antibacterial activity against *Candida* species. The formulated bigel shows initial release in 2 h and slowly release later in 4 h. The formed bigel is found to be stable after 3 mo with a pH range of 7.07±0.04, showing good spreadability and drug content was 99.99±0.75.

Conclusion: Terbinafine, the drug of preference for the treatment of bacterial vaginosis, demonstrated diffusion-mediated drug release when placed into bigels. In general, the produced bigels might be employed as delivery vehicles for drugs delivered vaginally.

Keywords: Hydrogel, HPMC, Organogel, Vagina, Vaginal infections, Surfactant

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INTRODUCTION

The vagina is an exquisite route for drug administration for both regional and systemic action due to its dense network of blood arteries [1]. The distribution of drugs into the vaginal opening to produce local or, less commonly, systemic pharmacological effects is referred to as vaginal drug delivery. The desirable vaginal formulations must have the following properties: It should not interact with coitus, be inert and odourless, and be used at least a couple of hours before intercourse. It ought to not cause leaks, messiness, or a sense of vaginal fullness [2].

Microbes aggravate fungal/bacterial infection. Infections develop because of an excessive number of bacteria and yeast in the vagina. Conventionally, vaginal compositions have included suppositories, solutions, foams, gels, and tablets. Oral and topical treatments are currently the most available for the treatment of vaginal infections.

Antifungal medications that can be taken orally include itraconazole, fluconazole, ketoconazole and terbinafine. Fluconazole causes nausea, vomiting, and headaches. It may increase the risk of spontaneous abortion during or before childbirth, and high doses may result in birth defects. Oral therapy should be avoided during pregnancy. As a side effect, the drug is less effective than topical therapy [3].

Topical treatment involves suppositories and pessaries, which are simple to make and administrate; however, the vaginal domicile era of such formulations is limited and inadequate, necessitating recurrent treatment in many cases. Creams are difficult to apply, unpleasant, and sometimes embarrassing to wear because they drip and leak into the undergarments. Furthermore, because of non-uniform patterns and leakage, creams may not provide an accurate dosage [4]. Vaginal gel compositions, on the contrary hand, are useful when action must be taken quickly. Acceptability, practicality, and non-toxic, non-irritating behavior for vaginal mucosa are all important characteristics of vaginal gels. Gels provide regionalized action with minimal side effects, seem to be non-greasy, and allow drugs to easily penetrate [5].

These conventional vaginal distribution techniques are partially effective; however, they have some limitations that need to be resolved to effectively deliver antifungal medicine. To conquer the limitations of gels hydrogel, organogel, and emulgel), Bigels were developed. Bigels are formed by combining hydrogel and organogel in specific proportions. By transforming organogels into bigels, the efficiency during which drugs are released from them can be multiplied several times [6].

They are emulsions with immobilized components on the inside and outside. The possibility of continuous phase coagulation is nullified because the immobility of the external phase destabilises any mobility of the continuous phase. If the outer component of a bigel is externally cross-linked, a permanent bigel is formed. Physical bigels are formed when physical cross-linking predominates in the outer phase. The current study's goal is to develop bigel as a treatment for female genital infection [6].

MATERIALS AND METHODS

Materials

Terbinafine was gifted by KLM Laboratories Pvt Ltd, Vadodara, Gujarat, India. Food grade oils were obtained from the Local Market in standard packs. Span 80, Span 20, Hydroxy Propyl Methyl Cellulose (HPMC), and various materials required for preparing reagents were purchased from SD Fine Chem Ltd., Mumbai, India. *Candida albicans* were obtained as an isolated culture from Food and Drug Laboratory, Vadodara, Gujarat, India.

Methods

Development of bigels

Individually, the nonpolar phase (organogels) and polar phase (hydrogel) were produced.

Development of hydrogel phase

A 2 percent w/w gel was formed by dispersing 2 g of HPMC K-100 in water and diluted it to 100 ml at 60-70 °C, 500 RPM. Similarly, a 4 percent HPMC K-100 hydrogel was made as stated in table 1 [7],

Development of organogel phase

To make surfactant-based organogels, the surfactants (Span 80 and Span 20) were dispersed in various oils (Olive oil and Coconut oil) at 60 °C, 500 RPM, and then cooled to 25 °C, as given in table 2 [7]. The surfactant combination of span 20(9%) and span 80(1%) was added in based on the RHLB values of coconut and olive oil (i.e. 8 and 7, respectively).

Development of bigel phase

To prepare bigel, the nonpolar phase (organogel) was gently mixed with the polar phase (hydrogel) using an overhead stirrer (60-700C, 500 RPM.). The stirring was repeated until the mixture was uniform and homogenous [7]. During the mixing process, the drug was introduced into both phases, 0.2% in hydrogel and 0.8% in organogel.

Characterization of bigel

Physio-chemical properties

The pH, Spreadability, colour, odour, and appearance of the gels were evaluated at various time intervals.

Viscosity: The Brookfield viscometer was used to evaluate the rheological properties of bigel as a time variable (Version DVELV).

Spreadability: Spreadability was evaluated by placing 0.5 g of the prepared gel inside a circle of 1 cm diameter premarked on a glass plate. A comparable glass plate was placed on top of this glass plate. For 5 min, the 500 g weight was held on the top glass plate. The expanded diameter (cm) produced by the gel spreading was measured [8].

$$S = \frac{Mx\,D}{T}$$

S=Spreadability

M=Weight put on the upper slide

D= diameter of spreading

T=Time for spreading

Microscopy

A scanning electron microscope was used for the microscopy.

Stability study

The stability study was conducted for three months in compliance with ICH norms. The stability studies are designed to provide information on how the API varies over time as a result of environmental conditions such as humidity, temperature, and light. The experiment was carried out at 25 °C±2 °C (60% RH) and 45 °C±2 °C (75%RH). All the prepared bigels were crimped into a collapsible metal tube. The packaged bigels were then kept at the aforementioned temperature and environmental parameters. After the experiment, the bigels were tested for % drug concentration, spreadability, and pH.

Thermal properties of bigels

The drop-ball method with the EI melting point apparatus-931 was used to determine the thermal characteristics (Tm) of the generated bigels. The temperature profiles of the bigels were examined using a differential scanning calorimeter (DSC 200F3 Maia). Bigels were accurately weighed and packed in pierced metal pans. The experiment was conducted in a nitrogen environment at a flow rate of 40 ml/min. The heating and cooling DSC profiles were obtained by scan at a frequency of 5.0 °C/min within the temperature region of 0 to 300 °C [10].

***In vitro* drug release**

A two-compartment modified Franz's diffusion cell was used to study the *in vitro* release patterns of drugs from bigels. For the release experiments, simulated vaginal fluid (SVF) was employed. Each sample was properly weighed and placed on the donor co (goat vaginal membrane). The donor section was submerged in a receptor compartment containing SVF while being agitated at 100 rpm (37 °C). Specimens were collected at regular intervals and spectroscopically evaluated with a UV-visible spectrophotometer. The cumulative percentage of drug release (CPDR) was calculated. [9]

Antimicrobial testing

The agar well diffusion methodology is frequently employed to evaluate drug antibacterial activity. By dispersing a quantity of microbial inoculum across the whole agar surface, the agar plate surface is colonization in the same manner as the disk-diffusion technique is. A hole with the such diameter of 6 mm is aseptically punched with a sterile cork borer or tip, and a volume (20-100 µl) of terbinafine is placed in the well. The test microorganisms, *Candida albicans,* were then incubated under proper circumstances. The antimicrobial drug spreads throughout the agar media, preventing the growth of the tested microbiological strain [10].

Inversion test

The most frequent gelation diagnostic test is to tilt a beaker with the sample upside down and see if the sample flows under pressure.

RESULTS AND DISCUSSION

The organogel and hydrogel were made separately, as indicated below (table 1).

Table 1: Formulation of hydrogel and organogel

Ingredients	H1	H2	O1	O2
HPMC	2 g	4 g	-	-
Olive oil	-	-	90 ml	-
Coconut oil	-	-	-	90 ml
Surfactant mixture	-	-	10 ml	10 ml
Water	up to 100 ml	up to 100 ml	-	-

*Surfactant mixture: Span20 and Span80 in a ratio of 90:10, the bigel batches were formed by combining hydrogel and organogel at the following 60:40 ratio (table 2). The bigels were then tested.

Table 2: Formulation of bigel

Formulation batches	B1	B2	B3	B4
Hydrogel (2%)	12g	8g	-	-
Hydrogel (4%)	-	-	12g	12g
Organogel (Olive oil)	8g	-	8g	-
Organogel (Coconut oil)	-	8g	-	8g
Total	20g			

Inversion test

All four batches of bigel were subjected to an inversion test.

Table 3: Inversion test for bigels

Formulation code	Time (min)
B1	36±1.2
B2	79±3.5
B3	54±2.6
B4	167±4.5

n=3, all the data are in mean±SD; the outcomes are outlined in the table below. Based on the data, it can be concluded that B2 and B4 pass in inversion tests, showing that they do not flow against gravity by their own weight.

Microscopy

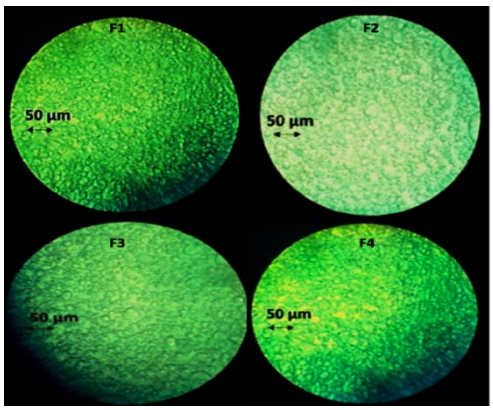

Fig. 1 Microscopy of Bigel batches B1, B2, B3, B4, Bigel's homogeneous structural properties are due to increased gel homogeneity as shown by SEM

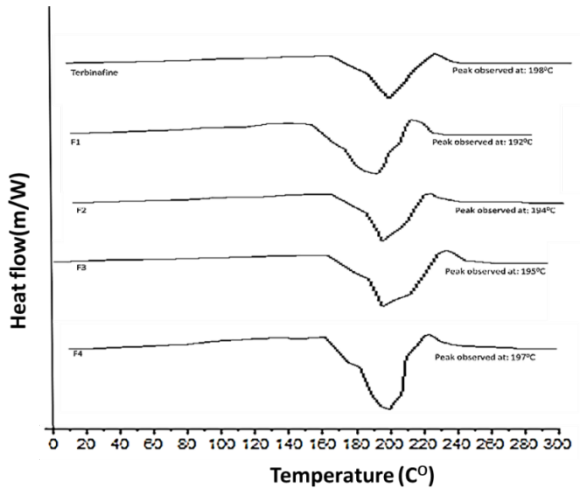

Fig. 2: DSC of terbinafine and Bigels

Thermal properties

The peak observed for the drug was at 1980C, and the peaks obtained for B1, B2, B3, and B4 were at 192 °C, 194 °C, 195 °C, and 197 °C, respectively.

Microbial testing

The agar diffusion technique was used to perform a microbial experiment on all four batches of bigels, with Candida albicans as the test microorganism. Table 4 shows the findings.

Table 4: Zone of inhibition of bigel batches

Formulation code	Zone of inhibition in mm
Clotrimazole(standard)	15.0±0.05
F1	15.7±0.04
F2	14.0±0.06
F3	15.8±0.04
F4	14.3±0.03

n=3, all the data are in mean±SD, Based on the results, it can be stated that Terbinafine is effective against Candida species.

***In vitro* drug release**

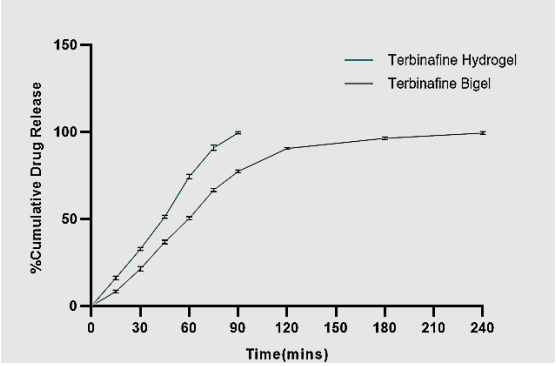

Fig. 3 Percentage cumulative drug release of hydrogel and bigel (F4), n=3, all the data are in mean±SD

According to the data plot, the drug is was first released from the hydrogel phase and afterward slowly released from the organogel phase. The Higuchi equation illustrates diffusion-mediated drug release based on statistical analysis (r2-0.99).

Stability of the hydrogel, organogel, and bigel with physiochemical properties

The physicochemical properties of organogel, hydrogel, and bigel were evaluated.

After 90 d, the bigels were determined to remain stable, with no notable changes in colour, appearance, pH, or viscosity. The gels demonstrated fibres frameworks due to the entrapment of the organogel within hydrogel molecules; this entrapment was evidenced to be uniformly accomplished, resulting in formulation stability, and the DSC study indicates that the drug (terbinafine) is not decomposed even after formulation in bigel, and the terbinafine bigel was also found to be stable. According to the microbiological data, the drug has high antimicrobial/antifungal efficacy. The *in vitro* release demonstrates that bigel can be effective for up to 6 h, whereas hydrogel alone exhibits release in 2 h. Based on the data, it can be inferred that terbinafine is released from the hydrogel phase in 2 h and slowly released from the organogel phase in the remaining 4 h. The Higuchi model suggests that the release is diffusion mediated. The optimized bigel had good viscosity and it also passes the inversion test. The bigel produced using coconut oil-based organogel and HPMC hydrogel (B4) was found to be stable for more than 90 d.

Vinay K. Singh, Arfat Ani, *et al.* in 2014 developed a drug containing antibacterial bigels that outperformed the commercially available formulation against E. coli. According to a preliminary study, the produced bigels might be employed as matrix for the controlled administration of antimicrobial medicines to treat bacterial vaginosis [11]. Margaret O. Ilomuanya *et al.* in 2020 developed a maraviroc and tenofovir dual compartment bigel. Bigel was shown to be stable and nontoxic to the vaginal and rectal epithelium, as well as actively preventing HIV transmission. The bigel formulations were non-toxic to the human vagina since there was a 1 log10 change in Lactobacilli crispatus viability [12].

The current study shows that the bigel developed is stable and may be useful to treat infections vaginally.

Table 5: Physiochemical studies

Batches	Physiochemical properties	Storage conditions		
HG1		Initial	25 °±2 °C/65±5%RH	40 °±2 °C/75±5%RH
		0 Mo	3 mo	3 mo
	Colour	Translucent	Translucent	Translucent
	Appearance	Homogenous	Homogenous	Homogenous
	pH	7.06±0.03	6.97±0.06	6.89±0.05
	Viscosity	4093±40	4001±35	3978±34
	Spreadability	10.00±0.09	10.21±0.10	10.38±0.15
	Drug content	99.99±0.68	99.99±0.69	99.94±0.58
	Colour	Translucent	Translucent	Translucent
HG2	Appearance	Homogenous	Homogenous	Homogenous
	pH	7.13±0.07	7.09±0.05	7.11±0.06
	Viscosity	4572±40	4545±39	4510±39
	Spreadability	7.59±0.08	7.49±0.10	7.43±0.07
	Drug content	99.97±0.67	99.97±0.68	99.95±0.65
	Colour	Yellow	Yellow	Yellow
OG1	Appearance	Homogenous	Homogenous	Homogenous
	pH	6.9±0.08	6.81±0.09	6.79±0.0
	Viscosity	1569±16	1555±15	1521±20
	Spreadability	10.58±0.19	10.00±0.15	10.58±0.17
	Drug content	99.99±0.98	99.99±0.75	99.97±0.84
	Colour	Yellow	Yellow	Yellow
OG2	Appearance	Homogenous	Homogenous	Homogenous
	pH	7.1±0.04	6.98±0.07	6.87±0.07
	Viscosity	1613±16	1613±15	1613±14
	Spreadability	15.87±0.27	15.0±0.39	11.03±0.29
	Drug content	99.97±0.69	99.97±0.75	99.95±0.82
	Colour	Non-transparent	Non-transparent	Non-transparent
F1	Appearance	Homogenous	Homogenous	Homogenous
	pH	6.98±0.05	6.75±0.04	6.59±0.10
	Viscosity	5328±53	5298±51	5295±50
	Spreadability	12.38±0.29	12.07±0.16	12.25±0.19
	Drug content	99.99±0.89	99.99±0.92	99.99±0.69
	Colour	Clouded white	Clouded white	Clouded white
F2	Appearance	Homogenous	Homogenous	Homogenous
	pH	6.83±0.04	6.75±0.04	6.56±0.07
	Viscosity	5537±53	5439±49	5408±54
	Spreadability	12.89±0.19	12.58±0.28	12.39±0.36
	Drug content	99.99±0.47	99.99±0.37	99.99±0.51
	Colour	Opaque	Opaque	Opaque
F3	Appearance	Homogenous	Homogenous	Homogenous
	pH	7.31±0.02	7.25±0.03	7.18±0.05
	Viscosity	5898±59	5865±58	5795±57
	Spreadability	14.29±0.36	14.08±0.48	13.95±0.50
	Drug content	99.99±0.74	99.98±0.58	99.98±0.25
	Colour	Milky white	Milky white	Milky white
	Appearance	Homogenous	Homogenous	Homogenous
	pH	7.21±0.05	7.14±0.07	7.07±0.04
F4	Viscosity	6053±59	5975±54	5928±59
	Spreadability	16.28±0.35	16.05±0.29	15.98±0.28
	Drug content	99.99±0.59	99.99±0.60	99.99±0.75

n=3, all the data are in mean±SD

CONCLUSION

When the recommended medication for bacterial vaginosis, terbinafine, was put into bigels, it demonstrated diffusion-mediated drug release. In general, the produced bigels might be employed as delivery vehicles for medications given vaginally.

ABBREVIATIONS

HPMC-Hydroxypropyl methylcellulose, SEM-Scanning Electron Microscope, DSC-Differential Scanning Calorimetry.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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