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Preparation and *in- vitro* Evaluation of Bioadhesive Vaginal Film of Tinidazole

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Abstract

Bioadhesive vaginal films, as compared to vaginal suppositories and gels, are emerging as a more efficient and practical dosage form. This study aimed to prepare and characterize bioadhesive films of tinidazole to be used for vaginal delivery over a prolonged period to treat local infections. Fourteen formulas of tinidazole films were prepared by solvent evaporation method. Each film was composed of 10 mg tinidazole with different ratios and concentrations of a polymeric combination of polyvinyl alcohol/ polyvinyl pyrrolidone (PVA/PVP) or polyvinyl alcohol/ hydroxypropyl methylcellulose (PVA/HPMC) for films A1-A7 and B1-B7, respectively. The prepared films were evaluated for their physicochemical characteristics, content uniformity, swelling, mucoadhesive strength, mucoadhesive time, and drug release. All the prepared films were transparent, had a uniform thickness (0.1-0.15 mm), and exhibited sufficient flexibility with drug content uniformity. The mucoadhesive strength of films was in the range of 28 ± 0.2 to 75 ± 0.01 g. Films containing PVA/HPMC showed higher swelling and lower mucoadhesive strength than those containing PVA/PVP polymeric combination. The *in vitro* drug release study showed no significant differences ($p > 0.05$) among films containing PVA/PVP or PVA/HPMC polymeric combinations. Films A3 and B4 were considered as the optimal bioadhesive films containing 3% of PVA: PVP (4:1) and 4% of PVA: HPMC (2:1), respectively as they showed complete flexibility, acceptable mucoadhesive strength and time (43 ± 0.1, 45 ± 0.23 g and 30 ± 0.02, 34 ± 0.01 min, respectively) and prolonged drug release rate. In conclusion, films of formulas A3 and B4 possess the potential as a delivery system for tinidazole for the treatment of vaginal infections at the site of application.

Keywords: Tinidazole, Bioadhesive vaginal films, Hydroxypropyl methylcellulose (HPMC), Polyvinyl pyrrolidone (PVP), Polyvinyl alcohol (PVA).

تحضير وتقييم خارج الجسم لشرائح مهبلية ملتصقة للتينيدازول

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الخلاصة

أصبحت الشريحة المهبلية الحيوية من اشكال الجرع الدوائية الاكثر فعالية وملاءمة مقارنة بالتحاميل والهلام المهبلي كطريقة لعلاج الالتهابات المهبلية. هدفت هذه الدراسة إلى تحضير وتوصيف شرائح لاصقة حيوية للتينيدازول لاستخدامها لعلاج الالتهابات المهبلية الموضعية على مدى فترة طويلة. تم تحضير أربعة عشر صيغة من شرائح تينيدازول بطريقة تبخر المذيبات. تتكون كل شريحة من ١٠ ملغ تينيدازول مع نسب وتراكيز مختلفة من مزيج البوليمرات من بولي فينيل الكحول/ بولي فينيل بيروليدون (PVA /PVP) او بولي فينيل الكحول / هايدروكسي بروبيل مثيل سيليلوز (PVA/HPMC) للشرائح A1-A7 ، B1-B7 على التوالي. بعد ذلك ، تم تقييم الشرائح المعدة لخصائصها الفيزيائية والكيميائية ، المحتوى الدوائي ، الانتفاخ ، قوة الالتصاق المخاطي ، وقت الالتصاق المخاطي وتحرر الدواء. كانت جميع الشرائح المعدة شفافة ، لها سمك موحد (٠,١-٠,١٥ ملم) وأظهرت مرونة كافية مع توحيد محتوى الدواء. كانت قوة الالتصاق المخاطي للشرائح في نطاق ٢٨ ± ٠,٢ إلى ٧٥± ٠,٠١ غ. وأظهرت الشرائح التي تحتوي على PVA/HPMC أعلى أنتفاخ وأقل قوة التصاق مخاطي من تلك التي تحتوي على مزيج البوليمر المتكون من PVA /PVP. أظهرت دراسة تحرر الدواء في المختبر عن عدم وجود فروق ذات دلالة إحصائية ($p > 0.05$) بين الشرائح المحتوية على مزيج البوليمرات PVA /PVP او PVA/HPMC . تم اعتبار الشرائح A3 و B4 كشرائح لاصقة حيوية مثالية تحتوي على 3% من PVA /PVP (٤:١) و 4% من PVA/HPMC (١: ٢) ، على التوالي لأنها أظهرت مرونة كاملة ، قوة لاصقة مخاطية مقبولة مع الوقت (٤٣± ٠,١ ، ٤٥ ± ٠,٢٣ غ مع ٣٠±٠,٠٢ ، ٣٤ ± ٠,٠١ دقيقة ، على التوالي) ومعدل تحرر دوائي لفترات طويلة. في الختام ، تتمتع شرائح الصيغتين A3 و B4 بأمكانية كنظام توصيل للتينيدازول لعلاج الالتهابات المهبلية الموضعية

الكلمات المفتاحية: تينيدازول ، شرائح مهبلية لاصقة ، هايدروكسي بروبيل مثيل سيليلوز ، بولي فينيل بيروليدون ، بولي فنيل الكحول.

Introduction

Vaginal infections are one of the main health issues commonly seen in women. The main causes of vaginal infections are bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and trichomoniasis [1, 2]. Mixed vaginal infections have also been identified [3]. A variety of antimicrobials have been used for the treatment of gynecological infections using various systemic and topical drug delivery approaches. The recommended antimicrobial agents include metronidazole, clindamycin, and tinidazole in addition to azole therapies (such as miconazole, fluconazole, clotrimazole, butoconazole, tioconazole, and terconazole) [4-6].

Among topical approaches, different intravaginal dosage forms are available, including vaginal tablets, capsules, pessaries, solutions, creams, ointments, and gels. Compared to systemic drug delivery, topical dosage forms have the advantage of being able to achieve lesser side effects with higher local drug concentration. However, they have some limitations associated with leakage, inadequate spreading, poor adhesive property, and short residence time requiring multiple applications. Such limitations may cause low acceptance of treatment by the patient [7]. To overcome such limitations, a variety of novel approaches had been studied by researchers to improve vaginal drug-delivery [8, 9].

Polymeric films represent one of the developed approaches used to deliver pharmaceuticals in the treatment of vaginal infections [1011]. There have been many studies on vaginal films as effective delivery of drugs for the treatment of vaginal infections utilizing different types of polymers with the ability to achieve different release profiles [12, 13]. Vaginal films are flexible, soft, and easy to use and are preferred over conventional semisolid formulations. Drugs dissolve or disperse upon contact with vaginal fluids while films adhere to the vaginal wall providing a localized prolonged action [14].

Mucoadhesive polymeric vaginal films are effective drug delivery methods, suitable in achieving prolonged drug release by utilizing several biocompatible polymers [15]. Calvo *et al.* [16] developed tioconazole vaginal mucoadhesive film using a blend of chitosan/ hydroxypropyl methyl cellulose. Dolci *et al.* [17] used gelatin as a mucoadhesive polymer for preparation of econazole vaginal films with good adhesiveness and anti-Candida activity.

Tinidazole, a nitroimidazole derivative, is effective against protozoa including *T. vaginalis*, as well as several anaerobic bacteria. It is similar to metronidazole but has a more favorable side effect profile and a longer plasma half-life, thus allowing less frequent administrations. It is classified as a Class II drug in the Biopharmaceutical Classification System due to its high permeability and limited solubility in aqueous media [18, 19].

The efficacy of tinidazole for the treatment of bacterial vaginosis has been reported [20, 21]. Fernando *et al.* [22] prepared polymeric matrices using poly (Ɛ-caprolactone) suitable as in intravaginal device for controlled delivery of tinidazole in treatment of trichomoniasis. Compared to oral dosing, vaginal delivery of tinidazole has been studied and offers opportunities for reduced systemic effects as well as improving treatment by targeting drugs to the site of infection [23,24].

The aim of this research was to create a tinidazole vaginal bioadhesive film made of PVA/PVP or PVA/HPMC mixed polymers as a promising vaginal delivery platform, as an alternative to the oral route, with suitable properties and a prolonged drug release behavior, thus offering a better drug delivery approach for the treatment of vaginal infections.

Materials and Methods

Materials

Tinidazole (Sigma Chemical Co.), Hydroxypropyl methylcellulose (Himedia, India), polyvinyl alcohol and polyvinyl pyrrolidone K30 (Sinopharm chemical reagent. Co., Ltd., China), and propylene glycol (SD Fine Chemical Ltd., India). All other reagents and solvents used were of analytical grade.

Preparation of bioadhesive vaginal film of tinidazole

Fourteen formulas of polymeric films of tinidazole (2 x 2 cm^2) based on PVA with PVP or HPMC polymers were prepared by solvent evaporation method [25]. Different polymeric mixtures were used: PVA/PVP and PVA/HPMC, represented by formulations (A1-A7) and (B1-B7), respectively (Table 1).

Aqueous stock solution of polymer was prepared by dispersing the required polymer in distilled water at room temperature using a magnetic stirrer (Remi, Mumbai) until completely dissolved. Boiled water was used to dissolve PVA. A separate solution of tinidazole was prepared as a (1 % w/v) stock solution using (1.5 % v/v) solution of HCl to solubilize the drug.

For the preparation of a 40 mL batch for each formula, a calculated volume of tinidazole solution (19.6 mL from the stock solution) was used so that tinidazole content per film (2 x 2 cm^2) was 10 mg; this volume was added to a calculated volume of polymeric solution. A plasticizer (0.8 mL of propylene glycol, corresponding to 2% v/v) was added to the drug-polymer solution. The resultant solution was thoroughly mixed using a magnetic stirrer to get a homogenous solution, then the volume was completed to 40 mL by distilled water.

The resulting solution was placed undisturbed for about 1 hr for complete removal of entrapped air bubbles. The resulting air-bubbles-free solution was poured into a 10 cm diameter glass Petri dish and allowed to dry at room temperature for 48 h. Films with air bubbles, cuts, or imperfections were excluded from the study. Dried films were removed from the Petri dishes with the help of a sharp blade and were cut into pieces of 4 cm^2. The resultant films were protected between two aluminium foils and stored in plastic bags at room temperature until subjected to different evaluation studies [26].

Table 1. Composition of different formulations of tinidazole vaginal bioadhesive films.

Polymer combination	Formula Code	Polymer Ratio	Total polymer concentration (%w/v)
PVA: PVP	A1	2:1	3 %
	A2	3:1	
	A3	4:1	
	A4	2:1	4 %
	A5	3:1	
	A6	4:1	
	A7	4:1	5 %
PVA: HPMC	B1	2:1	3 %
	B2	3:1	
	B3	4:1	
	B4	2:1	4 %
	B5	3:1	
	B6	4:1	
	B7	4:1	5 %

Film Characterization

Film appearance, thickness, and weight

The prepared films were visually evaluated for their aesthetic parameters such as colour, transparency, and flexibility. The thickness of each film was measured at five different locations (at the centre and four corners) using a digital vernier caliper and the mean value was calculated.

For the evaluation of film weight, each film was weighed individually and the average weight was calculated. All measurements were performed in triplicate [27].

Film pliability test

The films' mechanical properties were evaluated by determining their pliability. The pliability of the film was tested manually by folding the film in half and releasing it to allow its return to its initial form. The films were graded on a qualitative scale from "Completely Flexible" to "Very Fragile" defined by the film's ability to be rolled and folded.

"Completely Flexible" pliability was defined as the film's ability to be folded in any way without breaking, even back on itself, and recover its original shape. "Very Fragile" pliability was defined as when the film breaks easily, even during unmoulding [28].

Content uniformity test

To ensure the uniformity of distribution of tinidazole in films, a drug content test was individually performed for each film. One film (2 x 2 cm^2) containing 10 mg tinidazole was weighed and placed in 100 mL of 0.1 N HCl solution and stirred for 2 h, sonicated for 15 minutes, filtered and then analysed by using a UV/visible spectrophotometer (Biotech Eng. UV 9200, UK). The absorbance was measured at λ max 276 nm [29]. The drug content was calculated using the equation obtained from a previously constructed calibration curve of tinidazole in 0.1 N HCl solution ($y = 0.0186x$, $R^2 = 0.9982$). The drug content of each film was determined in triplicate.

Swelling index determination

A film sample of each formula with an area of (2 x 2 cm^2) was individually weighed (W_1) and placed in a pre-weighed stainless-steel basket with 200 mesh apertures. Then, the basket containing the film sample was submerged into 5 mL citrate buffer (pH 4.2) and maintained at 37 ± 0.2 °C in a glass petri-dish. The basket was removed from the medium at certain time intervals and excess water was removed by filter paper. The basket containing the film was reweighed (W_2), and the percentage of swelling was calculated for each film using the following equation [30]:

$$\textit{Swelling Index}\ (\%) = (W2 - W1/W1)\ x\ 100$$

The increase in the weight of the films ($n = 3$) was determined for a period of 6 h.

Ex vivo mucoadhesion strength measurement

A modified physical balance was utilized for measuring the mucoadhesive strength of all prepared films (A1-A7, B1-B7). Fresh sheep vaginal mucosa was obtained from a local slaughterhouse. The mucosal membrane was cut into pieces of appropriate size and washed with citrate buffer (pH 4.2) before being attached to the bottom of a petri-

dish using cyanoacrylate glue. A glass stopper was hung by threads at the left hand of the pan. Using a double-sided adhesive tape, the film was stuck to the lower part of the glass stopper and was lowered such that the other side of the film adhered to the mucosal membrane. The right side of the balance had a pan containing an empty beaker. The two sides of the balance were made equal before the study by keeping a weight on the right hand pan. A weight of 5 g was removed from the right hand pan, thereby causing a lowering of the glass stopper along with the film over the mucosal membrane. The balance was kept in this position for 3 min. Then, distilled water was added slowly to the beaker on the right pan until the film separated from the mucosal membrane. The weight on the right pan (total weight of water minus 5 g) required to separate the film from the mucosal membrane was taken as a measure for the mucoadhesive strength in grams [31].

Ex vivo mucoadhsion time measurement

A sheep vaginal mucosa was glued to a glass slide and positioned at an angle of 60°in a 50 mL beaker containing 30 mL citrate buffer (pH 4.2). The mucosal membrane was wetted with the buffer and the film was brought in contact with the wetted mucosal membrane. The buffer was gently stirred and the time required for complete detachment of the film[32].

Dissolution study

Dissolution studies of tinidazole from the films were performed using 900 ml of citrate buffer (pH 4.2) at 37°C, using a USP II apparatus with a paddle rotating at 50 rpm. At different time intervals for 6 h, a volume of 5 mL samples was withdrawn through a syringe filter. The amount of tinidazole released was determined by a UV spectrophotometer at λ max 276 nm. The results were presented as mean values of three determinations [33].

Statistical analysis

Results of the experimental work were demonstrated as a mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was employed. Statistical significance was defined as ($p < 0.05$).

Results and Discussions

Film appearance, thickness, and weight

All studied formulas produced films that could be removed easily from the petri-dish. The resultant films were colorless and transparent in appearance, having a thickness of 0.10 ± 0.02 to 0.15 ± 0.01 mm and weight in the range of 0.035 ± 0.01 to 0.075 ± 0.01g (Table 2). The variation in thickness and weight between films is related to variation in polymeric combination concentration and ratio, for both PVA/PVP and PVA/HMPC films; however, these variations were not statistically significant ($p > 0.05$), indicating that there was reproducibility in the film preparation process.

Film pliability

The flexibility of a polymeric film is important for easy handling of intravaginal film which should not result in a breakage during use. A well formulated vaginal film can be applied by fingers of patients without requiring an applicator [34].

Polyvinyl alcohol has a good film-forming ability as compared to other synthetic biodegradable polymers but has limited flexibility [3435]. To improve its physical properties and performance, it is blended with a variety of polymers by many workers [36, 37]. The obtained results with PVA/PVP and PVA/HPMC blends indicated that film pliability ranged from “Flexible” to “Completely Flexible” (Table 2) and therefore have better flexibility than films containing PVA alone.

Content uniformity

The drug content of film among all formulas was found to be within a range of 94.1 ± 0.13 to 98.2 ± 0.1 % which indicated that the drug was uniformly dispersed throughout the film.

Swelling index

The swelling index of films (A1-A7) and (B1-B7) in citrate buffer solution (pH 4.2) are shown in Figures 1 a and 1 b, respectively. The highest values were exhibited by film A4 (6.42%) containing 4% (PVA/ PVP, 2:1) and film B4 (5.44%) containing 4% (PVA/ HPMC, 2:1).

Results demonstrated the effect of polymer type on the swelling behavior. Films containing PVP had a significantly higher swelling index ($p < 0.05$) than those containing HPMC. This may be attributed to the hydrophilic nature of PVP and its high-water uptake capacity. These observations are concordant with the results of Perioli *et al.* [38] who prepared buccal patches using several film-forming and mucoadhesive polymers and observed that swelling using HPMC was higher than NaCMC.

Considering the polymer ratio, increasing the ratio of PVP in polymeric combinations of PVA/PVP (films A1-A3, A4-A6, and A6 against A7 at 3, 4 and 5 % PVA/HPMC polymeric blends, respectively) showed significant increase ($p < 0.05$) in the extent of swelling. The same observation was found with increasing ratio of HPMC in polymeric combinations of PVA/HPMC (films B1-B3, B4-B6, and B6 against B7 at 3, 4 and 5 % PVA/HPMC, respectively). This may be due to the increased water penetration ability within the film with the inclusion of higher amounts of water-soluble polymers in the PVA matrix which increase surface wettability and water penetration ability within the matrix [39].

Films containing higher concentrations of polymeric blends for both PVA/PVP and PVA/HPMC combination films showed higher values of swelling index. Similar observations were

reported by Thomas *et al*. [40] who investigated PVA/PVP blends as a potential material for a nucleus pulposus substitute. However, there was a reduction in the swelling index in formulations containing polymeric concentrations higher than 4 % (films A7 and B 7). Such an effect may be due to the formation of a gel layer which may hinder water penetration and therefore decrease the swelling index. Similar observations were reported by Pudžiuvelytė *et al.* [41] who prepared nitrocellulose based film-forming gels with cinnamon essential oil for covering surface wounds.

After 24 hours of incubation in the studied buffer solution, all films were still well recognizable and demonstrated good flexibility and structural integrity.

Table 2. Physicochemical characteristics (mass, thickness, pliability), % swelling index, mucoadhesive strength, and mucoadhesion time of formulations

Formula Code	Weight (g)	Thickness (mm)	Pliability	Drug Content (%)	Swelling index(%)	Muco-adhesive strength (g)	Muco-adhesive time (min)
A1	0.042± 0.01	0.10± 0.02	Flexible	95 .5 ± 0.03	5.47 ± 0.01	38 ± 0.3	43 ± 0.23
A2	0.057± 0.02	0.14± 0.01	Completely flexible	97± 0.01	5.32 ± 0.01	40 ± 0.03	38 ± 0.01
A3	0.065± 0.01	0.12± 0.02	Completely flexible	96.3± 0.14	5.30 ± 0.01	43 ± 0.1	30 ± 0.02
A4	0.070± 0.02	0.15± 0.01	Completely flexible	98.2 ± 0.1	6.42 ± 0.02	28 ± 0.2	41 ± 0.13
A5	0.054± 0.01	0.12± 0.01	Flexible	96.4 ± 0.1	6.32 ± 0.03	30 ± 0.3	35 ± 0.14
A6	0.075± 0.01	0.10 ±0.03	Completely flexible	94.1 ± 0.13	5.37 ± 0.01	35 ± 0.3	34 ± 0.13
A7	0.062± 0.02	0.11 ±0.13	Flexible	94.5± 0.01	2.84 ± 0.3	33 ± 0.02	46 ± 0.10
B1	0.035± 0.01	0.10± 0.20	Flexible	97.3 ± 0.12	5.34 ± 0.1	40 ± 0.1	34 ± 0.01
B2	0.049± 0.03	0.12 ±0.03	Completely flexible	97.2 ± 0.14	4.65 ± 0.1	50 ± 0.01	19 ± 0.11
B3	0.050± 0.01	0.10± 0.02	Completely flexible	96.2 ± 0.13	4.60 ± 0.3	47 ± 0.14	18 ± 0.10
B4	0.051± 0.03	0.11 ±0.03	Completely flexible	95.0 ± 0.01	5.44 ± 0.03	45 ± 0.23	34 ± 0.01
B5	0.051± 0.02	0.10± 0.03	Flexible	94.3 ± 0.01	4.94 ± 0.01	75 ± 0.01	33 ± 0.20
B6	0.062± 0.03	0.12± 0.01	Completely flexible	94.6 ± 0.13	4.90 ± 0.14	60 ± 0.13	27 ± 0.15
B7	0.048± 0.01	0.11± 0.03	Flexible	97.02 ± 0.03	2.1 ± 0.13	46 ± 0.11	40 ± 0.11

Values expressed as mean ± SD, $n = 3$

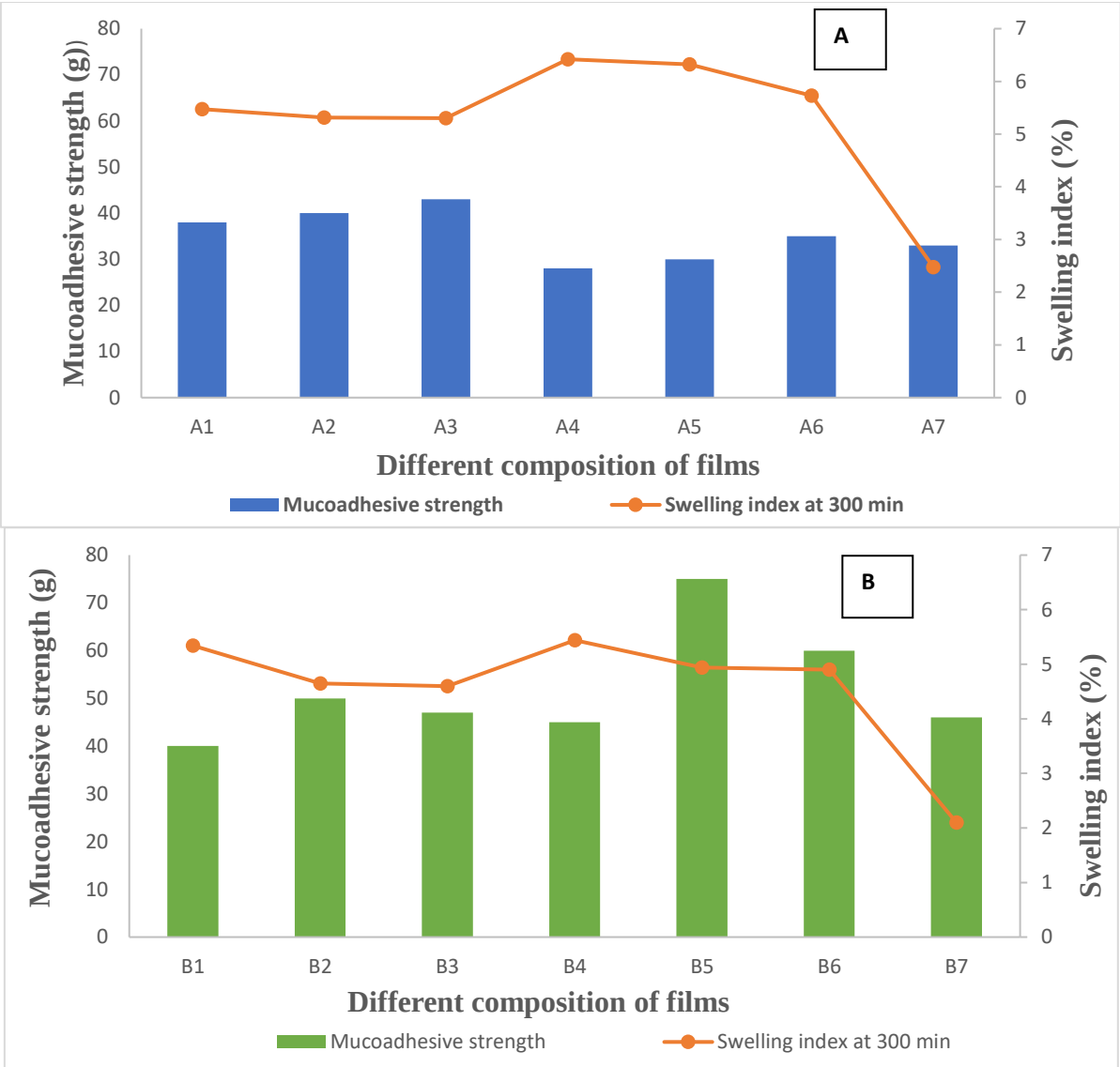

Figure 1. Comparison of the swelling index and mucoadhesive strength of various film formulations (A): Films containing PVA/PVP, (B): Films containing PVA/HPMC

Ex vivo mucoadhesion strength

The results of the mucoadhesive strength measurement are shown in Figure 1. The mucoadhesive strength was in the range of 28 ± 0.2 to 75 ± 0.01 g. The highest mucoadhesive strength was found in film B5.

Films based on PVA/PVP (A1-A7) demonstrated lower mucoadhesive strength than those based on PVA/HPMC (B1-B7). Such observations indicate that HPMC exhibited better adhesion properties than PVP. Similar observation was shown by Karavas *et al.* [42] who reported that polymer films based on PVP has a negligible mucoadhesive strength compared to those based on HPMC.

For films based on PVA/PVP combinations, increasing the total polymer concentration in the film (films A1-A3, A4-A6, and A7) or increasing the amount of PVP in the polymeric blend (A1 <A2 < A3 or A4 < A5 < A6) at constant polymeric concentration reduced the mucoadhesive strength. These results are concordant with the swelling index results and agreed with the findings of Bassi *et al.* [43]. The reduction in mucoadhesive strength may be due to over-hydration and swelling of polymer that led to disentanglement at the polymer/tissue interface resulting in a reduction in adhesive strength [44].

For films based on PVA/HPMC combinations, the mucoadhesive strength increased with increasing the concentration of polymers up to 4% (films B1-B6) or with increasing the amount of HPMC in the polymeric blend (films B1 against B4 and B 2 against B5), up to a ratio of (3:1) after which it will decrease (as apparent in films B3, B6 and B7). This finding was similar to the findings of Dobaria *et al.* [45] and suggested that the improvement in adhesion was due to the increased availability of interacting groups at higher concentrations of

polymer while the reduction of adhesive force observed at higher polymer concentrations may be due to polymeric over hydration that reduced the flexibility of polymer chains and shielding of the active binding sites of the polymer inside the polymeric coils, therefore an impediment of the interpenetration of the polymer with tissue mucin-glycoproteins resulting in a reduction in participation in the adhesion process [46].

Ex vivo mucoadhesion time

The mucoadhesion time of all formulas ranged from 18 ± 0.10 to 46 ± 0.10 minutes (Table 2).

An increase in total polymeric concentration increased mucoadhesion time. The highest value is observed for formula A7 composed of 5% PVA/ PVP at a ratio of 4:1, and formula B7 composed of 5% PVA/ HPMC at a ratio of 4:1. It was observed that mucoadhesion time was higher for formulas composed of PVA/ PVP (A1-A7) as compared to corresponding formulas composed of PVA/ HPMC (B1- B7). Such an effect may be due to increased availability of hydrophilic functional groups, such as hydroxyl and carboxyl groups, which can increase H-bonding and electrostatic attractions with mucin, and thereby increase mucoadhesion contact time [47].

Regarding the polymeric ratio for the same polymeric concentration for formulas A and B, as the ratio increased, the mucoadhesion time decreased. A similar observation was reported by Koland *et al.* [48]. The explanation for such an effect may be due to the enhanced swelling behavior of PVA films on the inclusion of second water-soluble polymers (PVP or HPMC). The higher degree of swelling can reduce the interaction between mucoadhesive polymers and mucin [44].

No correlation was found between the mucoadhesion strength and the mucoadhesion time. It seems that highly bioadhesive polymers do not necessarily reside longer on the mucosal surface. Similar observations were reported with Jain *et al.* [49] in their work for development of a mucoadhesive buccal film bearing progesterone.

Dissolution study

The release profile of the tinidazole from the films for 6 h was demonstrated in Figures 2 a and 2 b. Burst release was observed within the first 15 minutes. Comparing the release of tinidazole, films with PVA/ PVP (A1-A7) showed slower release than corresponding films with PVA/ HPMC (B1-B7). This variation was not significant ($p > 0.05$).

Considering the polymer ratio, significant differences were observed upon using the same polymeric combinations at different ratios (2:1, 3:1, 4:1) for films A1-A3, A4-A6, and A6 against A7, at 3, 4, and 5 % polymer mixture concentrations, respectively. The same results were observed for films B1-B3, B4-B6, and B6 against B7. These results indicated that the polymer ratio influenced the release of tinidazole from the formulated films.

At different polymer concentrations (3, 4, and 5 %), for the same polymer type and ratios, a significant difference ($p < 0.05$) in the release of tinidazole was observed as shown in films A1-A3 against corresponding films A4-A6. Similar results were obtained for films B1-B3 against corresponding films B4-B6. These results indicated that the concentration of the polymer mixture also influences the release properties of tinidazole from the prepared vaginal films. This effect can be explained by the fact that increasing polymer concentration will increase the viscosity of the gel layer with corresponding increase in diffusional path, and therefore a reduction in the drug release rate [50].

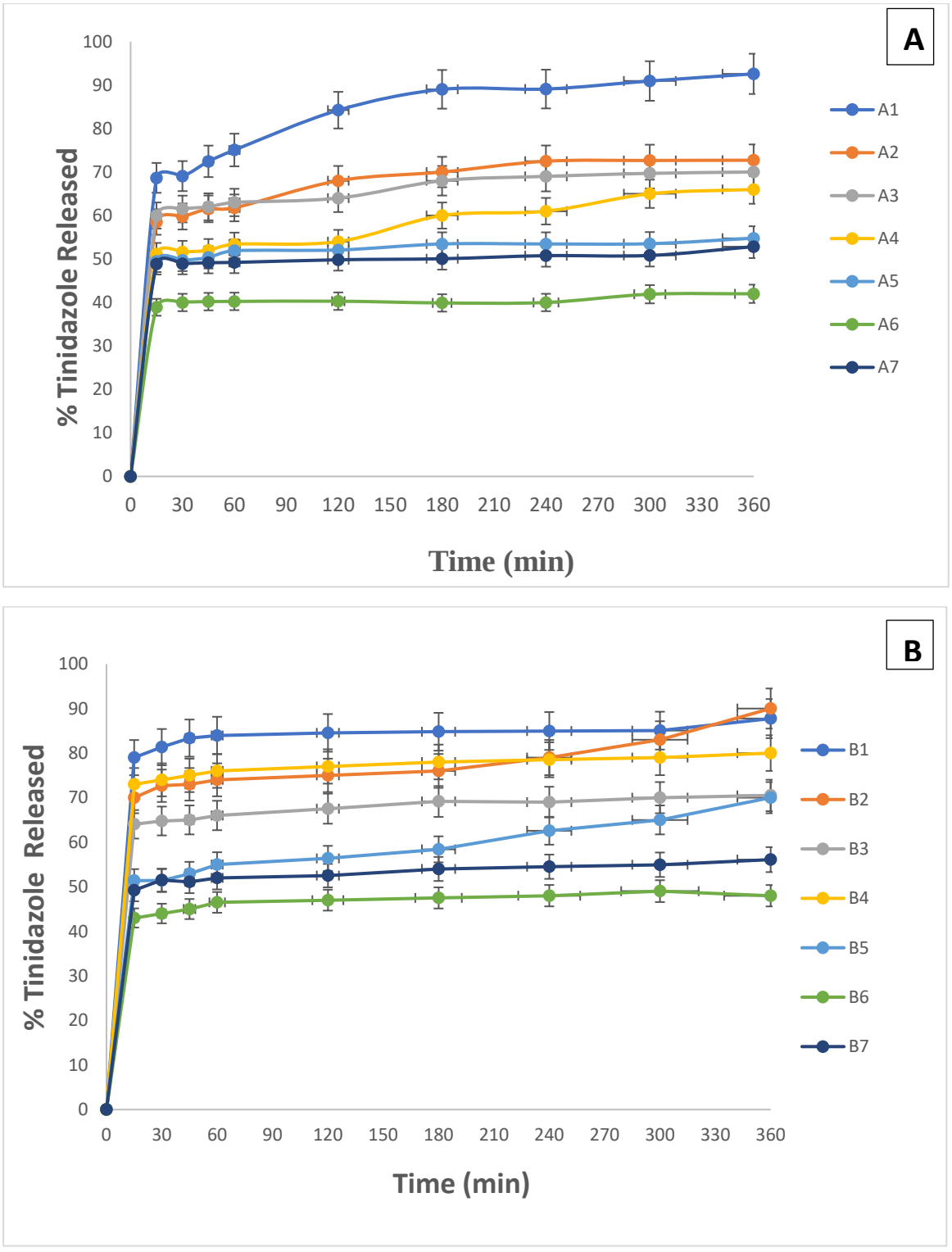

Figure 2. Release profile of tinidazole from prepared bioadhesive vaginal films: effect of polymer type and ratio (A): PVA/PVP films, (B): PVA/HPMC films

Conclusion

Tinidazole bioadhesive vaginal films using different polymers were successfully prepared and can be considered a promising drug delivery system. Films A3 and B4 can be regarded as the optimal bioadhesive films of tinidazole (10 mg) containing 3% of PVA: PVP (4:1) and 4% of PVA: HPMC (2:1), respectively as they exhibited complete flexibility, acceptable mucoadhesive strength and time with prolonged release behaviour.

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Conflicts of Interest

None.

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Ethics Statements

No ethical statement is required (no *in vivo* study was conducted).

Author Contributions

L.M and E. J conceived and designed the experiments; L.M, E. J and N.M. researched and performed the experiments; L.M wrote, edited and analyzed the data of the paper. E. J critiqued and reviewed the paper.

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