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Studies on vaginal bioadhesive tablets of acyclovir

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Bioadhesive vaginal tablets were prepared using poly(acrylic acid) (PAA); Methylcellulose (MC), carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC) and hydroxypropylmethyl cellulose (HPMC) as bioadhesive polymers in different concentrations and acyclovir as drug by direct compression technique (DCT) and wet granulation technique (WGT). Physical tests were applied to the tablets. The swelling behavior of vaginal tablets in distilled water, lactic solution and cow vagina, acyclovir release rate in lactic solution and bioadhesion to vaginal mucosa in cow vagina, in situ, were investigated. Swelling of the tablets containing HPC, CMC and MC was very rapid and caused disintegration of the tablets. The swelling behaviour of the tablets containing HPMC lasted 6 h in lactic solution. The force (N) necessary to detach the tablets from the vaginal tissue was found to depend on concentration and type of the bioadhesive polymer. The tablets containing HPMC needed the most detachment force.

1. Introduction

Bioadhesive delivery systems, also known as mucoadhesive systems, may be used for the oral, buccal, sublingual, nasal and vaginal administration of drugs. Mucoadhesive dosage forms may make treatment more effective and safe, not only for topical, but also for systemic diseases. Adhesion to the mucosa, 'bioadhesion', is an interfacial phenomenon which is different from conventional adhesion because of the special properties and characteristics of the natural tissue. Development of a satisfactory adhesive bond between a bioadhesive system and a soft tissue requires contributions of three regions, the surface of the bioadhesive material, the first layer of the natural tissue and the interfacial layer between adhesive polymer and tissue [1–5].

Acyclovir is a synthetic analogue of guanine used in the treatment and prophylaxis of infections due to *Herpes simplex* or *Varicella zoster* viruses. It is administered intravenously, orally or applied topically and is generally well tolerated. When administered intravenously, as acyclovir sodium, it may cause local reactions at the infection site with inflammation and phlebitis. Topical application of acyclovir, especially to genital lesions, may sometimes produce transient stinging, burning or erythema. Eye ointments may occasionally produce transient stinging and superficial punctate keratopathy. Acyclovir taken orally may cause gastro-intestinal side-effects. Its oral bioavailability is in the range of 10% to 30% [6–13].

Bioadhesive acyclovir tablets were prepared using poly(acrylic acid) [14–18], methylcellulose, carboxymethyl cellulose, hydroxyprophyl cellulose [16] and hydroxyprophylmethyl cellulose [3, 15] as bioadhesive polymers in different concentrations by direct compression technique and wet granulation technique. Physical tests and amont of acyclovir were applied to the tablets. Their swelling behavior in distilled water, lactic solution and cow vagina, acyclovir release rate in lactic solution and bioadhesion to vaginal mucosa in cow vagina, in situ, were investigated [19, 20]. The effect on swelling, bioadhesion and release behavior of bioadhesive polymer types and concentrations were also investigated. A formulation without any polymer (F16) was prepared for comparison along with other formulations.

2. Investigations, results and discussion

Sixteen different tablet formulations were investigated. All the tablets were found to satisfy the USP XXII requirements for weight uniformity, thickness and friability test (<0.5, except F4, F8, F9, F10, F12, F13, F16). The hardness of the tablets ranged from 1 to 4 kg.

Sixteen different formulations were used to evaluate the effect of polymer ratio and type on drug release rate. Dissolution results are given in Figs. 1–4. The tablets containing MC, HPC and CMC disintegrated in the first 30 min. The release of acyclovir from the tablets containing HPMC was slower than from the other formulations. These results decisively show that variables associated with type and proportion of the polymer, play an important role in the drug release characteristics. Amount and origin of the polymer are key parameters for the control of drug release. Therefore, the ratio of drug to polymer is an important factor in the release of drug [15, 17].

The formulations containing HPMC continued to swell for 6 h in lactic solution and distilled water. The tablets containing MC, HPC and CMC disintegrated in 60 min in

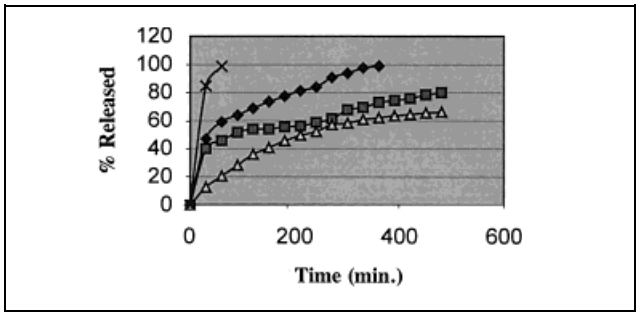

Fig. 1: Dissolution profiles of F1 (◆), F2 (■), F3 (△) and F4 (×)

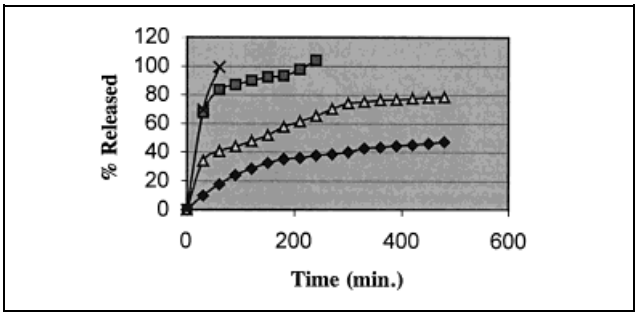

Fig. 2: Dissolution profiles of F5 (◆), F6 (■), F7 (△) and F8 (×)

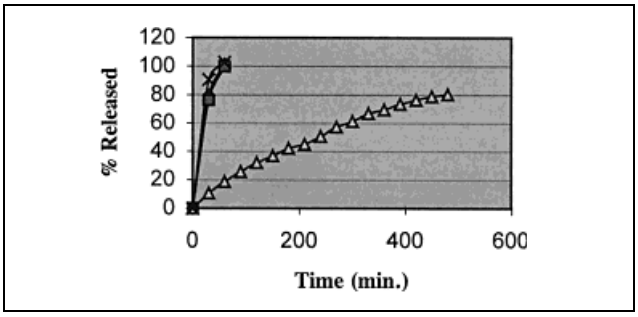

Fig. 3: Dissolution profiles of F9 (◆), F10 (■), F11 (△) and F12 (×)

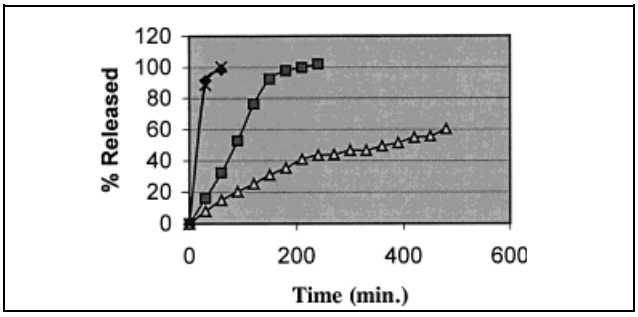

Fig. 4: Dissolution profiles of F13 (◆), F14 (■), F15 (△) and F16 (×)

these media. Swelling of the tablets containing MC, HPC and CMC was very rapid and caused disintegration of tablets. The tablet formulations which were compared with each other, after 1 h by their normalized volume and weight values, in lactic solution, distilled water and cow vagina, gave the results shown in Table 1. As shown swelling of HPMC tablet formulations is higher than that of the others. Maximum normalized swelling volume and weight values were obtained with HPMC tablets. The formulations containing Carbopol 934 (PAA) swelled slower than HPMC formulations. The tablets swelling behavior was analyzed according to the eqs. (2) and (3). The formulations containing HPMC have the best swelling behavior in cow vagina (in situ). HPC and CMC swelled slower than HPMC and MC in cow vagina. When the tablets were examined for their swelling behavior in different media, the amount and origin of the bioadhesive polymer had an important effect on the swelling characteristics [1, 19]. Contact between bioadhesive polymer and tissue results either from a good wetting of the bioadhesion surface, or from the swelling of the bioadhesive [2].

The force necessary to detach tablets from the vaginal tissue depended on concentration and type of the bioadhesive polymer. The detachment force decrease as the bioadhesive polymer contents decreased. The tablets containing HPMC required the highest detachment force. The results are given in Table 2. The bioadhesive force of HPMC, PAA, HPC and CMC was similar. The high viscosity grade such as HPMC, HPC were found suitably adhesive to topical mucous membrans [3]. The amount of accyclovir does not seem to affect the overall bioadhesive strength. Three major categories of polymers have been used with some success as bioadhesive: hydroxyl-containing, carboxyl-containing and other polymers mostly with charged species. Bioadhesive polymers have been applied in the form of viscous liquids or pastes when used to adhere a polymer to a tissue, or as films or microparticles when used in the form of controlled release systems adhering to the mucus [1]. The polymers used to prepare the

Table 1: Normalized swelling for volume (q, cm^3) and weight (ϱ, g) of bioadhesive acyclovir tablets after maintaining for 1b in different media

Formulations	Distilled water		Lactic solution		Cow vagina	
	q	ϱ	q	ϱ	q	ϱ
F1	2.60	1.95	2.04	2.61	1.52	1.38
F2	2.64	1.86	3.40	3.03	1.66	1.54
F3	2.66	2.16	2.20	2.06	1.50	1.42
F4	D	D	D	D	1.70	1.46
F5	2.67	1.82	1.86	1.67	1.39	1.37
F6	2.24	1.54	3.57	2.58	2.24	1.54
F7	2.61	1.64	2.64	2.23	1.85	1.35
F8	1.64	1.65	D	D	1.52	1.37
F9	D	D	D	D	1.21	1.36
F10	D	D	D	D	1.79	1.54
F11	2.23	1.66	2.18	1.60	1.39	1.30
F12	1.56	1.26	1.85	1.44	1.31	1.28
F13	D	D	D	D	1.47	1.27
F14	2.39	1.89	2.71	2.42	1.72	1.43
F15	2.01	1.60	2.03	1.64	1.35	1.26
F16	D	D	D	D	1.09	1.11

D: disintegration, n = 5

Table 2: Detachment force between tablet and cow vaginal mucus

Formulations	Detachment force	
	kg Force	kPa
F1	0.05 ± 0.2	4.42 ± 0.8
F2	0.06 ± 0.7	5.31 ± 0.5
F3	0.05 ± 0.2	4.42 ± 0.2
F4	0.03 ± 0.3	2.65 ± 0.7
F5	0.05 ± 0.8	4.42 ± 0.9
F6	0.02 ± 0.3	1.77 ± 0.3
F7	0.03 ± 0.2	2.65 ± 0.7
F8	0.02 ± 1.2	1.77 ± 0.2
F9	0.02 ± 0.7	1.77 ± 0.3
F10	0.03 ± 0.6	2.65 ± 0.7
F11	0.04 ± 0.9	3.54 ± 0.5
F12	0.05 ± 0.3	4.42 ± 0.8
F13	0.05 ± 1.1	4.42 ± 0.9
F14	0.03 ± 0.2	2.65 ± 1.0
F15	0.02 ± 0.3	1.77 ± 1.2
F16	–	–

mean of $5 \pm$ SD

formulations have a high bioadhesive force. In our study, different results were obtained depending on typ and amount of polymer.

Factors affecting bioadhesion are concentration of the active polymer, swelling, environment-related factors and applied strength. Bioadhesion stage are: intimate contact resulting from a good wetting of the bioadhesion surface and the swelling of the bioadhesive polymer, then penetration of the bioadhesive into the crevice of the tissue surface or interpenetration of bioadhesive chains with those of the mucus, and finally low chemical bonds.

3. Experimental

3.1. Chemicals

Acyclovir (Ilsan-Iltaş, Turkey), HPMC E 15 (Fluca), Carbopol 934 (Goodrich), MC A4M (Aldrich), HPC GF (Aldrich), CMC 7LF (Aldrich), Calcium lactate (Merck), Lactic acid (Merck). All chemicals were of analytical grade.

3.2. Apparatus

Water bath (Grant Y 22, England), UV spectrophotometer (UV-Visible recording spectrophotometer, UV 160 A Shimadzu), Tablet machine (Korsch AR 400, Erweka), Tensile-tester apparatus (Instron 1185, England), pH meter (Jenway), Dissolution test apparatus (Ildam, Turkey), Hamilton syringe (Kebo Gravo, Switzerland), Friabilator (Roche), Hardness apparatus (Monsanto).

3.3. Tablet characteristics

For tablet preparation, acyclovir and excipients were mixed in different ratios (Table 3). Tablets were prepared by DCT and WGT using a single punch tablet machine.

Table 3: Contents of bioadhesive tablets

Formulations	Contents (mg)							
	Acyclovir	HPMC	Carbopol 934	MC	HPC	CMC	Adipic Acid	Amylum Gel
F1	200	100	–	–	–	–	70	–
F2	200	150	–	–	–	–	100	–
F3	200	–	100	–	–	–	70	–
F4	200	–	–	100	–	–	70	–
F5	200	35	35	35	–	–	70	–
F6	200	50	–	50	–	–	70	–
F7	200	200	–	–	–	–	100	–
F8	200	–	–	–	100	–	–	–
F9	200	–	–	–	100	–	70	–
F10	200	–	–	–	–	100	–	–
F11	200	100	–	–	–	–	70	q.s.
F12	200	–	–	–	100	–	70	q.s.
F13	200	–	–	–	–	100	70	q.s.
F14	200	–	50	–	50	–	70	–
F15	200	200	–	–	–	–	70	q.s.
F16	200	–	–	–	–	–	70	–

q.s. = quantity sufficient

The following physical tests were applied to the tablets; weight variation, hardness, diameter-height ratio, friability and amount of acyclovir. A spectrophotometric method was used for acyclovir assay. The tablet weight uniformity was calculated from the weight of the tablets according to USP XXII. Tablet thicknesses were determined using a micrometer. The hardness test was carried out using a Monsanto hardness tester. For friability tests, twenty tablets were weighed (W_1) and rotated for one hundred revolutions in 4 min in a Roche friabilitor. The tablets were then reweighed (W_2) and the percentage friability (%F) was calculated according to eq. (1),

$$\%F = [(W_1 - W_2)/W_1]\,100 \quad (1)$$

3.4. In vitro dissolution studies

Dissolution tests were performed using the dissolution test apparatus [16]. The temperatur was 37 ± 0.5 °C. Dissolution studies were carried out in 50 ml lactic solution. Samples (1 ml) were taken from the dissolution media at appropriate time intervals with the aid of an injector fitted with a Schleicher-Schüll filter paper. An equal volume of the same medium was returned to the system after each withdrawal. Absorbances of samples were measured using UV spectrophotometer at 252.0 nm against blank. Dissolution samples of placebo tablets corresponding to each formulation were used as blank. The amounts of acyclovir released were calculated according to the standard calibration curve equation.

3.5. Swelling studies

Since the pH of cow vagina was found to be between 4.0 and 4.5, tablet swelling was determined in lactic solution (pH ~4.0) and distilled water (pH 5). Lactic solution contained 3.0 g calcium lactate, 1.0 g lactic acid and distilled water q.s. 100 ml. Bioadhesive tablets were placed in 25 ml of the solution tested for at least 6 h at 37 °C. The tablets were periodically removed and their weight and volume changes were measured before and during swelling. The diameter and thickness were measured using a micrometer. Their swelling behavior were calculated according to eqs. (2) and (3) [21].

$$\varrho = W_t/W_0 \quad (g/g) \quad (2)$$

ϱ = normalized swelling values for weight, W_t (wet weight) is the weight of the tablets at time (t) and W_0 is its dry weight at $t = 0$.

$$q = V_t/V_0 \quad (mm^3/mm^3) \quad (3)$$

q = normalized swelling values for volume, V_t is the volume of the swollen tablets (wet volume) and V_0 is the volume of the dry tablet (dry volume).
Swelling studies were also carried out in cow vagina in situ.

3.6. In situ bioadhesive studies

The bioadhesive strength of tablets was determined with a tensile-tester apparatus [14–20]. The vaginas of newly sacrified cows were removed and stored at −30 °C until ready for bioadhesion studies. A tablet was attached to the upper clamp and cow vaginal mucosa of 2 mm thickness was placed in the lower clamp. They were glued to the clamps by a liquid cyanoacrylate adhesive. A sample of 10 µl of water was placed on the tablets surface using a Hamilton syringe and the two surfaces were brought into contact. After 10 min, the necessary force for detachment of the bioadhesive tablet from the mucosa was measured upon application of force at an extension rate of 1 mm/min.

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