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RESEARCH PAPER

Oral Sustained-Release Bioadhesive Tablet Formulation of Didanosine

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ABSTRACT

The objective of this study was to formulate a hydrogel-forming bioadhesive drug delivery system for oral administration of didanosine (ddI). The aim of this tablet dosage form is to improve the oral absorption of ddI by delivering it in small doses over an extended period and localizing it in the intestine by bioadhesion. Compressed tablets of ddI using Polyox® WSRN-303, Carbopol® 974P-NF, and Methocel® K4M as the bioadhesive release rate-controlling polymers were prepared. The effect of polymer concentration on the release profile and in vitro bioadhesion of the matrix tablets was studied. Tablet formulations with Polyox WSRN-303 (10%) and Methocel K4M (30%) showed 93 and 90% drug release, respectively, after 12 h. The drug release was found to be linear when fitted in the Higuchi equation (square-root time equation), suggesting zero-order release. Carbopol 974-P-NF was found to inhibit the complete release of ddI because of drug-polymer interaction; hence, is not suitable for formulation of ddI. Drug diffusion and swelling of the polymer (anomalous Fickian release) was found dominant in ddI release. In general, in vitro bioadhesion increased with an increase in polymer concentration. Tablets containing a single polymer can be designed to form hydrogels serving the dual purpose of bioadhesion and sustained release.

KEY WORDS: Bioadhesion; Didanosine (ddI); Hydrogel; Polymer; Sustained-release; Tablets.

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INTRODUCTION

Didanosine, [2′,3′-dideoxyinosine; ddI; (Videx)] is the second antiretroviral agent approved by the FDA for treatment of human immunodeficiency virus (HIV) after zidovudine (AZT). ddI is relatively free from bone marrow toxicity in progenitor cells, a common toxicity with AZT, but causes dose-related peripheral neuropathy and pancreatitis (1). In addition, ddI has exhibited several delivery-related disadvantages, including low and variable bioavailability primarily because of extensive gastric degradation and erratic absorption (2). ddI has an active intracellular metabolite 2′,3′-dideoxyadenosine-5′-triphosphate having a half life ($t_{1/2}$) of more than 12 h (3), suggesting that the drug would be clinically effective when administered less frequently. A significant reduction in oral bioavailability has been reported in patients receiving high doses (4), which suggests that the drug would be better absorbed when administered in smaller doses. Low absorption inspite of a large $t_{1/2}$ and dose-related toxicity make ddI an ideal candidate for the design of an oral controlled-release delivery system.

Oral controlled-release drug delivery systems provide a continuous delivery of drugs at predictable and reproducible kinetics for a predetermined period during the course of gastrointestinal (GI) transit. The potential advantages of these systems are repatenting of successful drugs, reduced dosage frequency and total dose, decreased occurrence and intensity of toxicity, and a constant therapeutic effect (5). These systems can be modified to modulate the GI transit time so that the system reaches the site of absorption and resides there for an extended period so as to maximize drug absorption. With due consideration to this fact, bioadhesive dosage forms do hold potential advantages with respect to delivery of certain drugs by means of delay in the intestinal transit, localization of drug delivery, and reduction in dosage frequency of drug administration compared with a conventional dosage form (6,7). For the purposes of drug delivery, a bioadhesive has been defined as a synthetic or biological material that is capable of adhering to a biological substrate or tissue (8,9).

The use of hydrophilic polymers as drug-release modulating agents in a pharmaceutical dosage form is well established. Hydrogels are a special class of hydrophilic water-insoluble or slowly dissolving materials available in a variety of molecular weights and compositions that absorb water and swell to form a gel-like structure (10). This swollen gel acts as a reservoir slowly releasing the drug dispersed in the hydrogel matrix. Bioadhesion is also a property observed with some of these hydrogels and, therefore, they can serve the dual purpose of release control and bioadhesion. Release from a polymeric matrix is controlled primarily by the molecular weight and the solubility, whereas bioadhesion is a function of molecular weight, hydrophilicity, chain length, chain flexibility, and functional groups (7,11); hence, hydrogels offer a great versatility in the design of oral controlled-release dosage forms.

The rate-controlling properties, bioadhesive performance, and safety profile of the polymer are the primary criteria for selection of a rate-controlling bioadhesive agent. Polyethylene oxide (12), cross-linked polyacrylic acids, and hydroxypropylmethyl cellulose (13) are some of the agents that have been commonly used for release rate control in the past. These polymers have shown bioadhesive properties (14), and hence their dual purpose use in design of oral drug-delivery system holds promise. This study looks into the feasibility of the use of Polyox WSRN-303, a high-molecular-weight polyethylene oxide, Methocel K4M, a rapidly hydrating high-molecular-weight hydroxypropylmethyl cellulose, and Carbopol 974P NF, a high-molecular-weight cross-linked polyacrylic acid polymer, in design of oral sustained-release bioadhesive tablets.

MATERIALS AND METHODS

Materials

Polyox® WSRN-303 was a gift from Union Carbide Corporation (Danbury, CT), Carbopol® 974P-NF was a complimentary sample from B. F. Goodrich Co. (Cleveland, OH), and Methocel® K4M was a gift from Dow Chemical Company (Midland, MI). ddI (Videx)® was obtained from Bristol-Myers and Squibb (Princeton, NJ). Talc and magnesium stearate were obtained from Fisher Scientific Co. (Fairlawn, NJ). Microcrystalline cellulose (Avicel PH-112) was a gift from FMC Corporation (Newark, DE). HPLC-grade anhydrous dibasic sodium phosphate, anhydrous monobasic sodium phosphate, anhydrous monobasic potassium phosphate, and sodium chloride were obtained from Sigma Chemical Co. (St. Louis, MO). Fresh intestinal tissue was obtained from white New Zealand male rabbits purchased from Myrtle's Rabbitry (Thompson Station, TN).

Preparation of Tablets

The ingredients (ddI, polymers, Avicel PH-112, magnesium stearate, and talc) were weighed using an analytical balance model A-200DS (Denver Instrument Co.,

Arvada, CO), mixed using a mortar and a pestle, and tableted (direct compression) using a 16-station rotary tablet machine (B3B, Manesty Machines Ltd., Liverpool, England). Tablets with a hardness of 12–15 kg/cm^2 (Tablet Hardness Tester, Pt 102, J. H. DeLamar & Sons Inc., Chicago, IL), negligible friability (TA3 Friability Tester, Erweka Apparatebau, G.M.B.H., Heusenstamm kr. Offenbach/ Main, Germany) and weight between 295 and 305 mg were prepared. Nine different formulations were prepared (Table 1). Tablets without any polymer were prepared as controls for the release studies. A set of 8/32″ concave punches purchased from Natoli Engineering Co. (Chesterfield, MO) was used.

Dissolution Study

In vitro release of ddI from the nine different formulations (sample size = 6) and control tablets was studied using the conventional USP Type I dissolution apparatus (SR-2, Hanson Research, Northridge, CA). Phosphate–buffered saline (PBS) (pH 7.4 ± 0.1; 900 mL) at 37 ± 1°C was used as the dissolution medium. Samples of 5 mL were withdrawn at predetermined intervals in triplicate and replaced by 5 mL of PBS maintained at 37 ± 1°C. ddI was analyzed with a Beckman Spectrophotometer (DU-65) at λ_{max} of 240 nm (Beckman Instruments Inc., Fullerton, CA). A cumulative correction factor was applied to account for previously removed samples according to Equation (1):

$$c_n = c_{n,\text{obs}} + (5/900)(c_{n-1}) \tag{1}$$

where $c_{n,\text{obs}}$ is the observed concentration of the nth sample, c_{n-1} is the concentration of $(n-1)$th sample, and C_n is the corrected concentration of the nth sample.

Table 1

Composition of Tablet Formulations of Didanosine (ddI)

	Quantity per Tablet (mg)		
Ingredients	I	II	III
Didanosine	50.0	50.0	50.0
Avicel PH-112	232.0	217.0	157.0
Polymer (A/B/C)[a]	15.0	30.0	90.0
Talc	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	1.5
Total	300.0	300.0	300.0

[a] A, B, C: Polyox WSRN-303, Methocel K4M, and Carbopol 974P NF.

Table 2

Transport Mechanisms from a Polymer Slab Under Sink Conditions

n[a]	Transport Mechanism
0.5	Fickian diffusion
$0.5 < n < 1.0$	Non-Fickian (anomalous)
1.0	Time-independent linear transport

[a] n is determined from the equation $M_t/M_\infty = kt^n$.

The dissolution data obtained *as* mean ± SE (standard error of the mean) were plotted as cumulative drug release versus square-root time as per the Higuchi equation [Eq. (2); (19)].

$$Q = kt^{1/2} \tag{2}$$

Linear regression analysis was performed on those data. A linear relationship indicates a constant or near-zero order release for cylindrical homogenous matrix systems.

The release data was further treated by the equation by Ritger and Peppas, [(15); Eq. (3)]. This equation was treated logarthimically to determine the value of n. The value of n (Table 2) determines the type of drug release.

$$M_t/M_\infty = kt^n \tag{3}$$

Bioadhesion Study

In vitro tablet bioadhesion studies used excised rabbit intestinal tissue. The tissue was used immediately after the animal was sacrificed. The breaking force (force required to separate the tablet and the tissue surfaces) was determined. The force required to separate the tablet from the rabbit intestinal tissue was measured using a universal tensile apparatus (Instron, model 1122, Liverpool, UK). The test method was based on the methods described by Chang and co-workers (16) and Lejoyeux and co-workers (17). The intestinal tissue and the tablet were stuck onto screw-type supports with a stainless steel cylindrical base (12 mm in diameter) using glue. The mucus support was attached to the upper jaws of a pneumatic load cell, and the tablet support was clamped to the lower jaws of a vertically mobile cross-piece. Care was taken to ensure that both surfaces were parallel. The movable crosspiece was raised to maintain contact between the two surfaces. PBS (pH 7.4 ± 0.1) was used as the test medium, and 20 μL was spread on the surface of contact. The surfaces were allowed to remain in contact for 10 min. No external force was applied to enhance adhesion. The apparatus was calibrated

at this point, and the crosspiece was lowered at a rate of 5 mm/min. The force required to separate the tablet from the tissue was measured. All three polymers were tested at three different concentrations in triplicate. Tablets without any polymer were used as controls. The polymer was replaced by Avicel PH-112.

HPLC Analysis

A stability-indicating HPLC analysis was conducted on the samples obtained from the dissolution studies to detect degradation attributable to drug-excipient interactions or experimental conditions. The method described by Nassar and co-workers (18) was used with minor modifications. The HPLC system consisted of a Star 9010 solvent delivery system, Star 9095 autosampler with a 100 μL loop, and Varian Star 9050 variable wavelength UV-IS detector connected to a Dynamax® MacIntegrator. The column used was ALLTIMA C18, 5 μm, 4.6 mm $\times$ 250 mm (Alltech Associates, Deerfield, IL).

The mobile phase consisted of acetonitrile and phosphate buffer (10 m*M*, pH 7; 10:90). The buffer was filtered through 0.22-μm membrane filter (Millipore Corp., Milford, MA) before use. The flow rate was 1.0 mL/min; the sensitivity was 0.1 AUFS. The chromatogram was monitored at a wavelength of 254 nm, suitable for detection of all the degradation products of didanosine.

RESULTS

The cumulative release profile of ddI from tablets prepared using various amounts of Polyox is shown in Figure 1. Polyox at concentrations of 10 and 30% is capable of satisfactorily extending the release of ddI. The drug release in tablets containing 5% Polyox (Fig. 1) indicates that the polymer is not capable of extending drug release. The data with 10% Polyox, when plotted as release of ddI versus square root of time (see Fig. 4), presented a linear relationship ($R^2 = 0.995$), indicating a linear release profile, a behavior typical of a cylindrical homogenous matrix system (19). When treated with Equation (3), anomalous release profile was observed ($n = 0.65$), which is in agreement with the previous work by Apicella and coworkers (20).

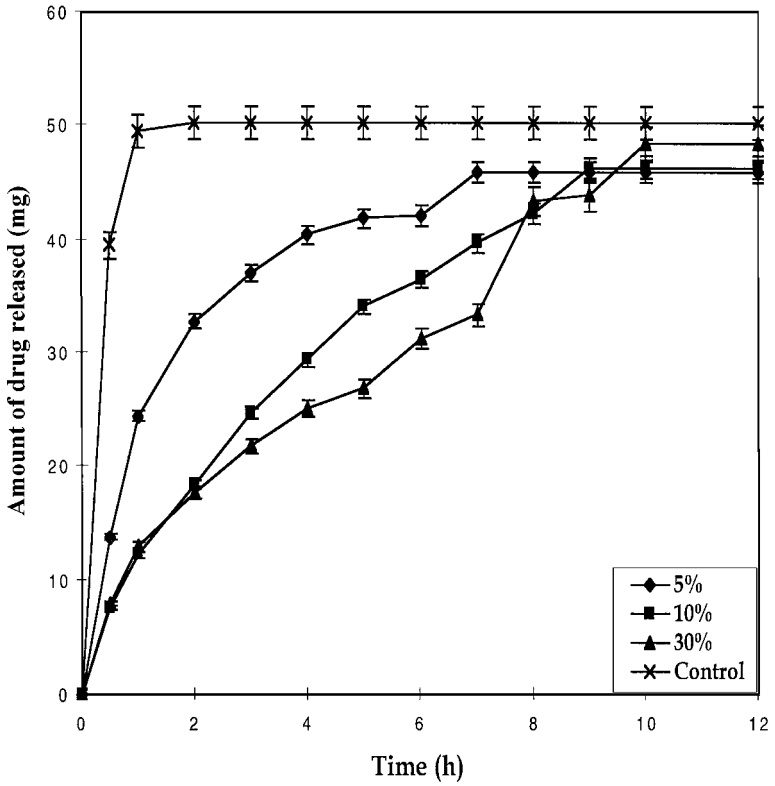

Figure 1. Release of ddI from tablets containing varying concentrations of Polyox WSRN-303.

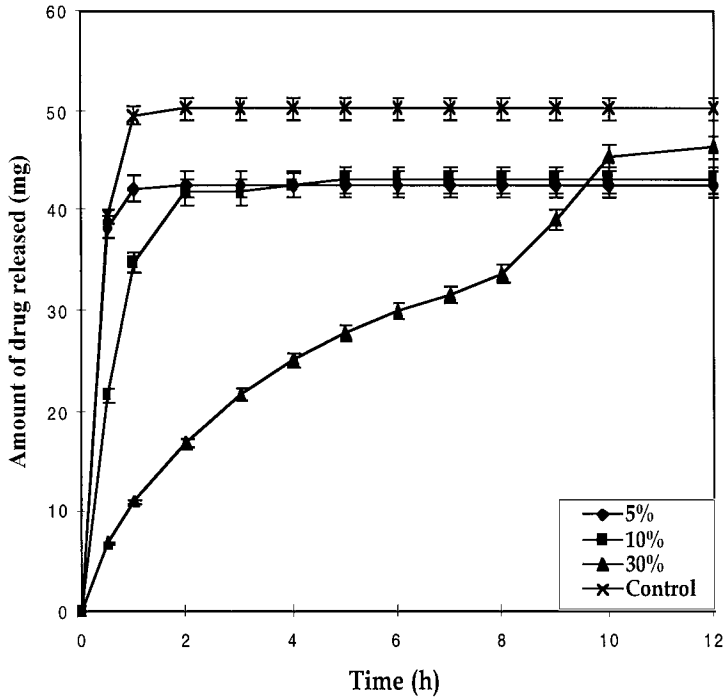

Figure 2. Release of ddI from tablets containing varying concentrations of Methocel K4M.

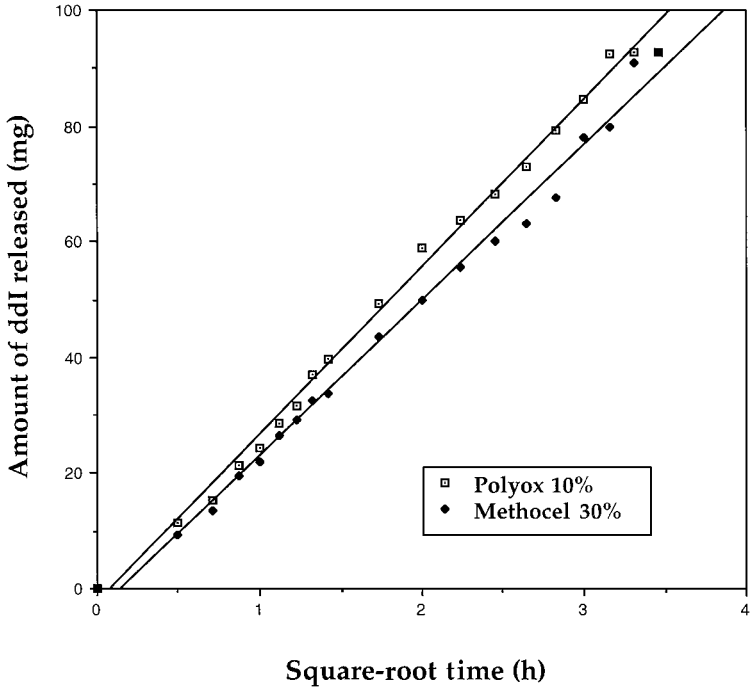

Figure 3. Cumulative ddI release vs. square-root time for tablets containing Polyox WSRN-303 (10%) and Methocel K4M (30%).

The cumulative release profile of ddI from tablets prepared using various amounts of Methocel is shown in Figure 2. Methocel K4M, present at lower concentrations (5 or 10%), was not able to significantly extend the release. At a 30% concentration, Methocel resulted in >90% ddI release over a period of 12 h. When the data were plotted as release of ddI versus square root of time (Higuchi plot), a linear relationship ($R^2 = 0.992$) was obtained (see Fig. 3), indicating constant release. The n value of 0.59 indicates anomalous Fickian release, which agrees with the observations made by Colombo (21).

Figure 4 shows the cumulative release profile of ddI from tablets prepared with Carbopol polymer. The overall release profile of ddI was found to differ remarkably from that observed with Polyox and Methocel. A significan change in the total amount of drug released with an increase in concentration was observed with Carbopol. These observations indicate a interaction between Carbopolr and ddI resulting in inhibition of ddI release.

The results of the bioadhesion studies (Fig. 5) for all nine formulations compared with the control formulation indicate that all formulations are capable of producing bioadhesion in vitro. Formulations devoid of any polymer, used as controls, did not show any bioadhesion. Good bioadhesion with high-molecular-weight polymers is in agreement with earlier work (22–24).

DISCUSSION

In the case of all three polymers, the rate of release decreased with an increase in the polymer concentration, which can be explained by insufficient gel viscosity at lower concentrations during the early stages of drug release. ddI release from the tablets containing Polyox WSRN-303 (10%) and Methocel K4M (30%) is characterized by a swelling/drug diffusion phenomenon at all three concentrations, which is explained by $0.5 < n < 1$ values. It has been postulated that for soluble hydrogels, a synchronization between the rates of swelling and erosion results in a true zero-order release (21). Although Polyox and Methocel are soluble hydrogels, there seems to be no synchronization between their rates of swelling and erosion, resulting in a pseudo-zero-order release. This can be attributed to the high molecular weights of the polymer leading to lowered solubilities.

Binding of certain cations with anionic Carbopol has been reported in the marketing literature available for Carbopol. The ddI molecule is characterized by the presence of cationic sites, which are capable of interaction with anionic Carbopol. HPLC analysis was carried out to investigate this phenomenon. Because the results did not indicate any loss of drug due to stet degradation, the incomplete release can be attributed to the formation of complex, in

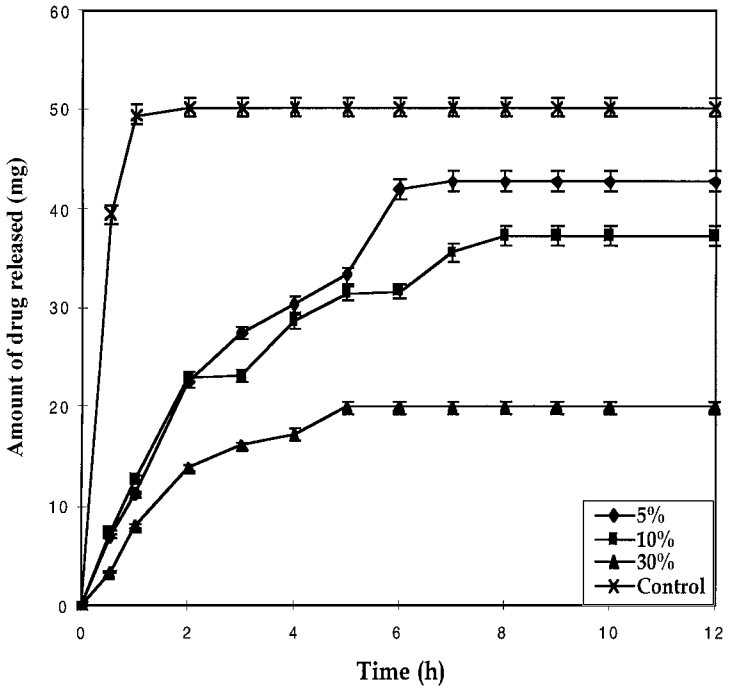

Figure 4. Release of ddI from tablets containing varying concentrations of Carbopol 974P NF.

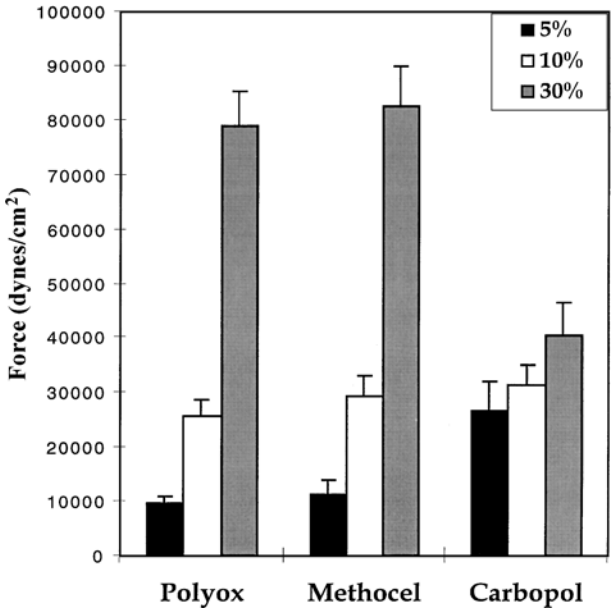

Figure 5. Comparative profile of in vitro bioadhesive strength of Polyox WSRN-303, Methocel K4M, and Carbopol 974P NF.

an indirect way. Carbopol prevents complete release of ddI and, hence, is not a suitable polymer for formulation of ddI.

Polyox is a nonionic polymer with a flexible, linear structure that has the ability to form entangled physical bonds by interpenetrating deeply in to the mucous substrates (20). Thus, an increased bioadhesion observed with increased concentration is naturally attributable to the higher number of physical bonds formed between the tablet and the mucous substrate. It has already been shown that release from matrix systems composed of Polyox is dominated by swelling and not by erosion, irrespective of the soluble nature of the hydrogel. This implies that there is no significant loss of bioadhesion, attributable to hydrogel dissolution.

With HPMC being a long-chained, non-ionic polymer, the bioadhesion is either attributable to formation of physical bonds or hydrogen bonding with the mucus components. The increase in bioadhesion with an increase in concentration was expected. The increased sites for bond formation can explain the increase in bioadhesion with an increase in concentration.

Carbopol 974-P-NF is a cross-linked, anionic, hydrophilic polymer. In solution, it tends to disentangle because of its partially ionized carboxylic acid groups, which lead to bioadhesion. Earlier work with Carbopol polymers has clearly indicated that it is the availability of these groups that determines bioadhesion (25–28). The results obtained with tablets containing Carbopol as the controlled-release bioadhesive polymer show no significant change in the bioadhesive performance with change in concentration. This particular trend can be attributed to the fact that at all three concentrations, the volume of the buffered solution available for wetting was the same. As a result the number of ionized groups available for bond formation did not differ significantly at any of the concentrations used. Because for polyacrylic acids, bioadhesion is predominantly a function of the number of anions available for bond formation, the extent of bioadhesion did not change with concentration.

Smart and coworkers (14) have compared the bioadhesive strength of Carbopol 934 with a variety of other polymers and concluded that Carbopol 934 is a stronger bioadhesive than is Polyox or Methocel. Because Carbopol 974P NF is similar to Carbopol 934, except that it has lower organic solvent residues making it safer for oral use, similar results were expected. Contrary to this, tablets containing Polyox WSRN-303 and Methocel K4M have shown higher bioadhesion than did tablets containing Carbopol 974P NF. Decreased availability of free carboxylic acid groups attributable to interaction with ddI may be the reason for reduced bioadhesion in addition to incomplete hydration and, hence, incomplete ionization of the carboxylic acid group leading to diminished bioadhesion.

CONCLUSION

In conclusion, the bioadhesive and release properties of a controlled-release tablet for ddI alter remarkably with the polymer system selected. Polyox WSRN-303 and Methocel K4M are suitable for development of oral sustained-release bioadhesive tablets for ddI. The use of Carbopol 974P NF in bioadhesive formulations of ddI seems to be very limited.

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