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Comparison of Aloe Vera Gel and Aloe Vera Powder on Physical Properties of Ranitidine Mucoadhesive Microgranules

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Abstract

Aloe vera product is well known for medicinal, cosmetic properties, and polymer for pharmaceutical industry. Aloe vera gel may be employed to effectively deliver poorly absorbable drugs through the oral route of drug administration. Ranitidine hydrochloride is a drug of choice in the treatment of ulcer. The drug has a short biological half-life of approximately 2–3 hours, thus a sustained release dosage form of ranitidine HCl is desirable. The aim of this study was to compare Aloe vera gel and Aloe vera powder as polymer mucoadhesive. The obtained results indicated that aloe vera powder has physical properties better than aloe vera gel. Drying process of aloe vera powder is important to improve their stability which performed by less of moisture content, increase of flow rate, swelling index, in vitro mucoadhesive, and dissolution. Aloe vera powder is a suitable polymer for local delivery in the gastrointestinal tract.

Key words: aloe vera, microgranules, ranitidine HCl, mucoadhesive polymer, gastrointestinal tract

Introduction

Aloe vera (*Aloe vera* (L.) Webb) is a perennial plant of the Aloeaceae family, well known for its succulent leaves and the medicinal and cosmetic properties of the gel obtained from them [1]. The gel extracted from the parenchymal tissue of the plant is composed of several potentially active constituents (soluble sugars, polysaccharides, salicylic acids, proteins, minerals, etc.) and thereby has been used as topical agent for the treatment of different skin disorders [2].

In the present study, ranitidine hydrochloride was selected as the model [3]. Ranitidine hydrochloride is a competitive inhibitor of histamine H2-receptors, drug of choice in the treatment of duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome (ZES), gastroesophageal reflux disease (GERD), and erosive esophagitis [4]. The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. The drug has a short biological half-life of approximately 2–3 hours, an absolute bioavailability of only 50%, and it is absorbed only in the initial part of the small intestine. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 hours but not up to 10 hours. An alternative dose of 300 mg leads to plasma fluctuations; thus a sustained release dosage form of ranitidine HCl is desirable [5].

There are a number of approaches that can be used to prolong gastric retention time, one of them is polymeric mucoadhesive systems. Aloe vera gel can act as natural polymer mucoadhesive in many biomedical applications, including drug delivery systems because of their polysaccharide contents [6]. This substance can be found in the parenchymal tissues of Aloe vera[7] , but it has disadvantages of physicochemical properties, such as sensitive to heat, light, air, and easy to oxidation [8]. Aloe vera gel may be employed to effectively deliver poorly absorbable drugs through the oral route of drug administration. Furthermore, the dried powder obtained from Aloe vera gel was successfully used to manufacture directly compressible matrix type tablets. These matrix type tablets slowly released a model compound over an extended period of time and thereby showing potential to be used as an

excipient in modified release dosage forms [9].

The objective of this study is to compare Aloe vera gel and Aloe vera powder as polymer mucoadhesive. Formulated microgranules were characterized for its flow rate, moisture content, swelling index, dissolution, and particle size using SEM (Scanning Electron Microscopy). Biological activities based on mucoadhesive strength using gastric mucosa from male white rats Wistar strain.

Materials And Methods

The materials used were Aloe vera (*Aloe vera* (L.) Webb), aqua destilata, dextrin, FDC green, ethanol 96%, natrium chloride (technical grade), ranitidine hydrochloride, polyvinylpyrrolidone K-30, lactose (pharmaceutical grade), acid hydrochloride (analytical grade), and gastric mucosa from male white rats Wistar strain.

The instrumens used were analytical scales, ceramic mortar, sieve no. 30 and 40 mesh, pH meter (Hanna instrument), moisturemeter (G-Won Hitech Co.LDT, RRC), stopwatch, spectrophotometer UV-Vis mini 1240 (Shimadzu), dissolution apparatus type I basket (Veego VDA 6-DR), freeze dryer, and Scanning Electron Microscopy (Biometrics: SEM-CS491Q/790Q).

Processing of Aloe vera

The potential use of Aloe vera products often involves some types of processing, like heating, dehydration, and grinding. Unfortunately, because of improper processing procedure aloe products contain very little or virtually no active ingredients, so it has become important to evolve a better method of processing aloe products [10].

When Aloe vera (*Aloe vera* (L.) Webb) has harvested, it contains dirt and other impurities. The yellow fluid secretion from the harvested leaves should be completely removed from the leaf for its processing and purity of products. The leaves were heated by water (at a temperature of 70^{o}C for 10 minutes) to stop the enzymatic reaction. This stuff was blended and filtered to get aloe vera gel [11].

Aloe vera powder were obtained from drying the aloe vera gel using freeze dryer (at a temperature of 0^{o}C and pressure of 4,58 torr) by adding dextrin 15%. Next, the obtained dried powder were sieved through the set of sieves and calculated their yield.[8] Both gel and powder were used as polymer of mucoadhesive microgranules.

Microgranules were prepared in at least 6 batches in a ceramic mortar by the modified wet granulation technique. Ranitidine HCl, aloe vera gel or aloe vera powder, Carbopol 934P, PVP K-30, FDC green, and lactose were weighted (Table 1), then blended and mixed thoroughly. Next, the proper amount of 5% PVP K-30 in ethanol (and FDC green) was gradually added to moisten the powders.

Formulation of Microgranules Containing with Ranitidine HCl

Table 1. Composition of various microgranules formulations

Ingredients (/tablet)	F1	F2	F3	F4	F5	F6
Ranitidine HCl (mg)	300	300	300	300	300	300
Aloe vera gel (%)	4	6	8	-	-	-
Aloe vera powder (%)	-	-	-	4	6	8
Carbopol 934P (%)	15	15	15	15	15	15
PVP K30 5% (mL)	11	11	11	11	11	11
FDC Green (%)	0,25	0,25	0,25	0,25	0,25	0,25
Lactose (%)	ad 100	ad 100	ad 100	ad 100	ad 100	ad 100

The wet granules were sieved no 30 and 40 mesh, then dried (at a temperature of 35^{o}C for 25 minutes). The dried granules were tested for physical properties including flow rate, moisture content, swelling index, in vitro mucoadhesive, dissolution efficiency, and particle size using SEM (Scanning Electron Microscopy). The data were analyzed by analysis of variance (ANOVA) followed by post hoc test, with the level of significance set at $P < 0.05$.

Result And Discussion

Aloe vera plants products are biologically active and hence their processing needs great care. The time, temperature, and sanitation are the prime requirement for processing to put the Aloe vera plant products in active form [10]. Aloe vera has susceptible to microbial spoilage as well as enzymatic and oxidation reactions. However, contact with the air will increase the oxidation reactions, results yellow-brownish granules both made from aloe vera

gel and powder (Fig 1). Dehydration of samples is necessary to improve their stability and less susceptible to spoiling during storage[13]. Freeze drying method is the best choice to dehydration the sample due to lower temperature and pressure (0^oC and 4,58 torr). The dried samples were sieved through no. 60 mesh, characterized by loose powder, white-brownish, odorless, and tasteless.

Figure 1. Ranitidine microgranules

Six batches of microgranules were added carbopol 934P as mucoadhesive polymer. Carbopol 934P was selected as a copolymer for the preparation of microgranules owing to its mucoadhesive properties and it may give better synergistic effect for the treatment of ulcer. It was expected that improved adherence to the mucosa would both prolong gastric residence and result in more localized drug release [14] , shown in Table 2.

Table 2. Physical Properties of Ranitidine Microgranules

	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Flow rate (g/sec)	11.42 ± 0.08	8.99± 0.08	8.35± 0.03	15.36± 0.61	13.85 ± 0.25	12.49 ± 0.28
Moisture content (%)	4.40 ± 0.12	3.82 ± 0.12	3.43 ± 0.14	0.48 ± 0.03	0.63 ± 0.03	0.70± 0.03
Swelling index (%)	380.05 ± 12.55	446.22 ± 18.09	552.01 ± 17.81	297.20 ± 87.72	414.8 ± 35.34	555.60 ± 44.44
In vitro mucoadhesive (%) 5^{th} min 10^{th} min	 98 ± 2.74 96 ± 2.24	 98 ± 2.7386 97 ± 2.74	 99 ± 2.24 98 ± 2.74	 81.6± 2.19 71.2± 3.35	 86.4± 2.19 80± 2.83	 90.4± 2.19 86.4± 2.19
Dissolution efficiency (%)	72.26 ± 0.42	74.79± 0.66	77.47 ± 1.19	75.59 ± 9.04	77.89 ± 6.25	79.50 ± 9.53
Particle size (µm)	566.14	679.57	732	789.75	681	826.67

Notes:
FI = ranitidine microgranules with 4% of aloe vera gel
F2 = ranitidine microgranules with 6% of aloe vera gel
F3 = ranitidine microgranules with 8% of aloe vera gel

F4 = ranitidine microgranules with 4% of aloe vera powder
F5 = ranitidine microgranules with 6% of aloe vera powder
F6 = ranitidine microgranules with 8% of aloe vera powder
Mean ± SD, n = 5

Microgranules Size and Shape Morphology

Photomicrographs (x 50 magnifications) of dried microgranules are shown in Fig.2. The shape of microgranules demonstrated in light microscope is amorphous and the morphology of the microspheres was examined by SEM (Scanning Electron Microscopy). The SEM analysis revealed that the microparticles prepared in this study were mostly spheres with rough surfaces. All batches fit up the requirements of particle size, which is between 425-850 µm[15], shown in Table 2.

Each batch of ranitidine microgranules was ordered into amorphous state. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process [16].

Flow Rate

Based on Table 2, all batches were formulated by aloe vera gel have lower flow rate than aloe vera powder. Batch F3 has the lowest flow rate of 8.35 g/sec because this batch contains high concentration of aloe vera gel (8%). These results correlate to moisture content, proved by 3.43% for moisture content. However, only batches F2 and F3 did not fulfill the requirements of flow rate, which should be more than 10 seconds of 100-gram granules to flow or more than 10 g/sec, its usually known as free flowing properties [17]. Statistical analysis was performed using the analysis of variance (ANOVA), explain that all batches have significant comparison due to the different of aloe vera kinds and concentrations.

Swelling Index

Ranitidine microgranules were placed in a basket, to measure the increase in area due to swelling of the microgranules. Nine hundred mL of pH 1.2 HCl medium was poured into the dissolution apparatus type I. An increase in the weight of the microgranules was noted in 5

and 10 minutes, then the weight was calculated. The swelling index was calculated by using the following formula,

$$\%S = \frac{Wt - Wo}{Wo} x100\%$$

Where, % S = swelling index, Wt = the weight of swollen microgranules after time t, and Wo = weight of microgranules at zero time [18].

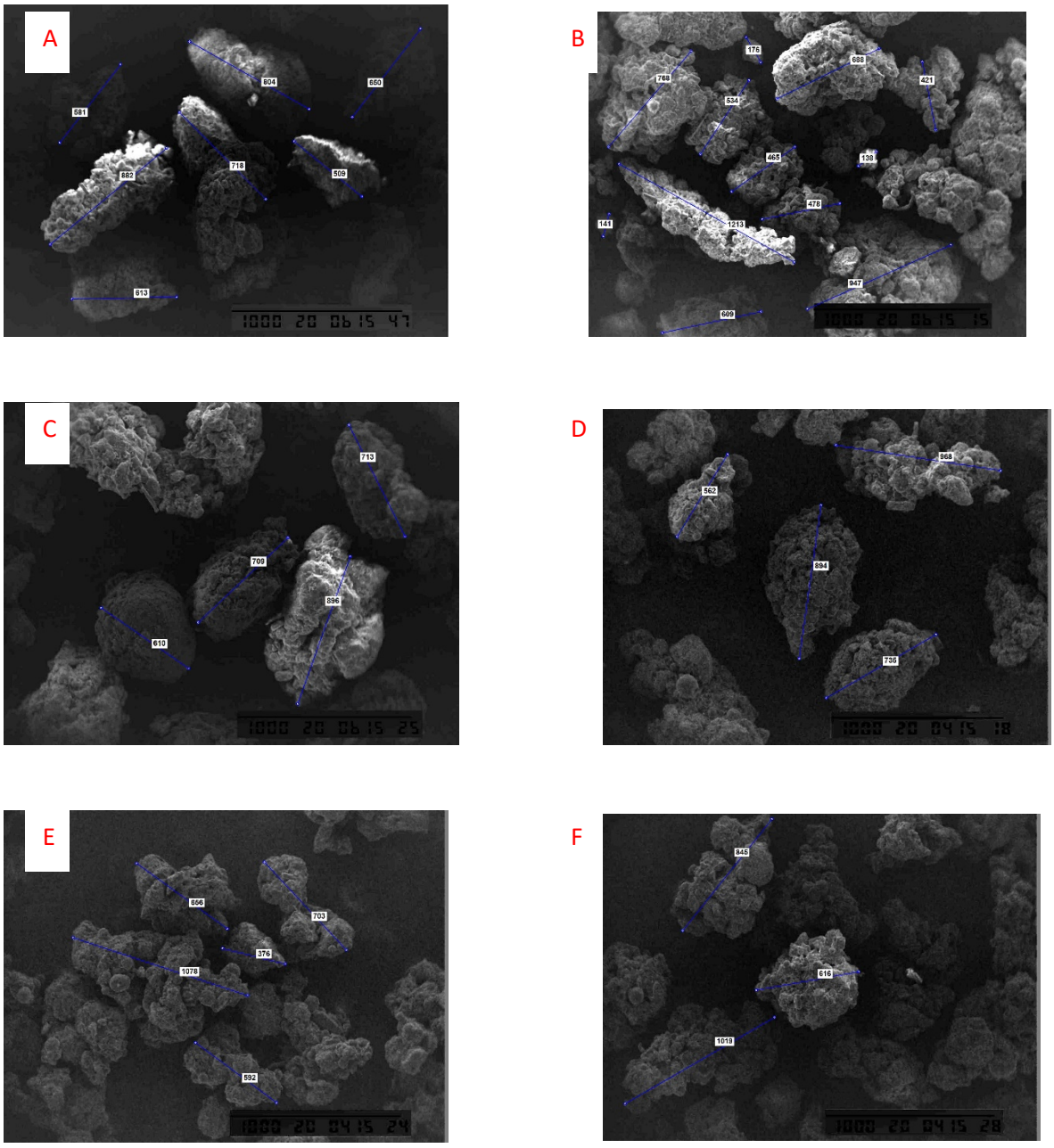

Figure 2. Microscopic images of ranitidine microgranules: batch F1 (A), batch F2 (B), batch F3 (C), batch F4 (D), batch F5 (E), and batch F6 (F)

The drug loaded microgranules were showing the most swelling index in batch F6, which contain aloe vera powder 8% and carbopol 934P 15% (Fig. 3). Aloe vera powder has strong absorption than aloe vera gel because its contain lower water content due to drying process. The more concentration of aloe vera powder, the more swelling index because of the more water absorption. In acidic medium, carbopol 934P are in a collapsed form due to hydrogen bonding, which supporting the swelling of microgranules [19].

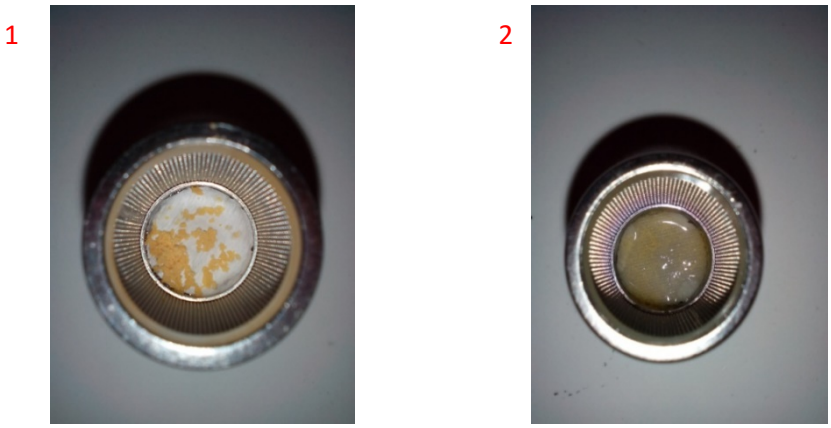

Figure 3. Swelling index of ranitidine microgranules (1: initial, 2: final)

In vitro Mucoadhesive

The results of in vitro mucoadhesive tests are shown in Fig. 4 where the microgranules exhibited excellent mucoadhesive properties. After 5 min and 10 min, all particles are found to be attached to the gastric. This may be due to the formation of strong gel which penetrate deeply into the molecules of mucin and show good mucoadhesives. Formulation using aloe vera gel performed higher mucoadhesive better than aloe vera powder, but has a lower swelling index. Another polymer which affects the mucoadhesive strength is carbopol 934P and it has a positive effect on mucoadhesive strength, as shown in Table 2 and Figure 4.

Mucoadhesion occurs when mucosal epithelium bioadhesive interactions take place primarily with the mucous layer. The mechanism of mucoadhesion is generally divided into two steps: the contact stage and the consolidation stage. The first stage is characterized by the

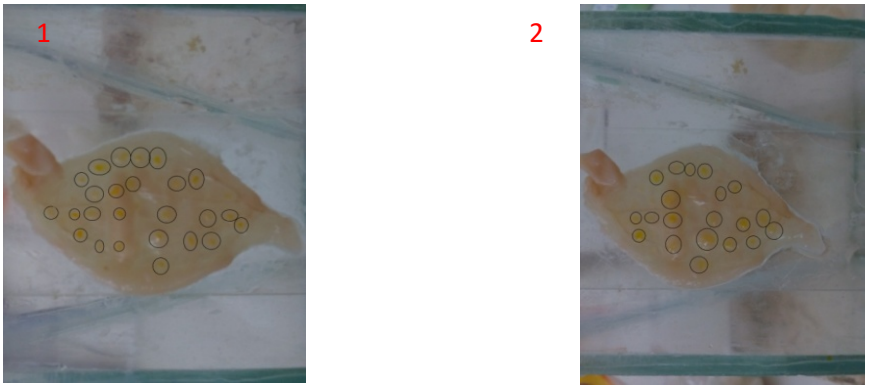

Figure 4. In vitro mucoadhesive of ranitidine microgranules (1: initial, 2: final)

contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucous layer. In the consolidation step, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak Vander Waals and hydrogen bonds [20].

Mucoadhesion is a complex process and numerous theories have been proposed to explain the mechanism involved. These theories include wetting and diffusion theories. Firstly, the wetting theory, which is based on the ability of mucoadhesive polymers to spread and develop intimate contact with the mucous layers, and secondly, the diffusion theory proposes physical entanglement of mucin strands and the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate [3,21] shown in Fig 5. Analysis by ANOVA resulted significant different among six batches because of their different kinds and concentration of aloe vera. Batch F6 containing the highest amount of aloe vera powder (8%) show the best formulation of ranitidine mucoadhesive microgranules.

Dissolution Studies

In the pharmaceutical industry, dissolution is defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. ie. mass transfer from the solid surface to the liquid

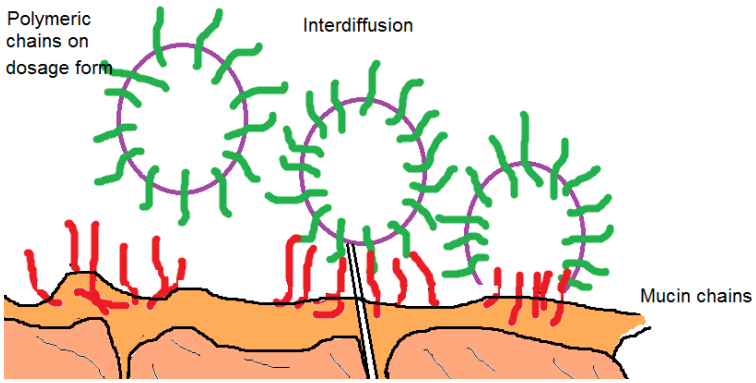

Figure 5. Mucoadhesive mechanism

phase. Intrinsic dissolution rate can be defined as rate of dissolution pure pharmaceutical active when conditions such a pH, surface area, temperature, agitation, rate and ionic strength of dissolution media kept constant [22].

Dissolution studies are done using the acid medium (simulated gastrointestinal fluid). This parameter has advantages to estimate the bioavailability and bioequivalency of ranitidine HCl. Testing of dissolution was done by measuring the absorbance at 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 minutes with spectrophotometer UV-Vis.
The release standard of ranitidine HCl was 20-50% within 120 minutes and 45-75% within 480 minutes [23]. Only batch F1 and F2 was fulfilling the requirements because of the polymers. Aloe vera can role as thicker barrier surrounding this microgranules, causing the lower release of ranitidine HCl [7].

Aloe vera powder and carbopol 934P are hydrophilic polymers. Monolithic matrix systems were occurred when using hydrophilic polymers, which swell on hydration and dissolve to release the drug. This mechanism includes erosion, diffusion, polymer relaxation or a combination. On contact with water a hydrophilic matrix increases in size due to the entry of the solvent. This then allows the polymer to swell up forming a barrier to drug release. The drug particles would then move through this gel layer via diffusion or erosion of the gel eventually allowing drug to be released [24].

Table 3. R values and slope values of ranitidine microgranules

Batches	R values			Slope values		
	Zero order	First order	Higuchi	Zero order	First order	Higuchi
F1	0.8819	0.6697	**0.9228**	0.4204	0.0053	9.8331
F2	0.8868	0.7506	**0.9289**	0.5209	0.0045	12.2249
F3	0.8707	0.7436	**0.9095**	0.6617	0.0046	15.6082
F4	0.9154	0.8350	**0.9613**	0.8637	0.0039	22.9366
F5	0.9052	0.8590	**0.9438**	0.7636	0.0034	20.1354
F6	0.8244	0.7824	**0.8905**	0.5999	0.0029	16.3889

Kinetic models

Mathematical models such as zero-order, first-order, and Higuchi's models are usually used to describe the kinetics of the drug release from the test formulation. Representative regression coefficients (R) obtained by fitting experimental release data to distinct models are shown in Table 3. The R value is the largest when fitted to the Higuchi's model as opposed to the other model, which indicates a Higuchi's model that the drug release is controlled by diffusion mechanism [25]. In the dissolution medium, firstly microgranules shows swelling of polymer and burst release of drug and after that combination of aloe vera and carbopol 934P acts as release retardant polymer and gives the release of drug in a sustained manner.

Conclusion

Aloe vera powder has physical properties better than aloe vera gel. Drying process of aloe vera powder is important to improve their stability and less susceptible to spoiling during storage, which performed by less of moisture content, increase of flow rate, moisture content, swelling index, in vitro mucoadhesive, and dissolution. Ranitidine HCl release followed better Higuchi model than the zero order and first order kinetic models, which confirm the monolithic matrix systems to ensure prolonged release of ranitidine HCl. The obtained results indicate that aloe vera is a suitable polymer for developing a sustained-release dosage form of

ranitidine HCl for local delivery in the gastrointestinal tract.

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