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THE EFFECT OF ALOE VERA POWDER (*Aloe vera* (L.) Webb) ON PHYSICAL PROPERTIES OF MUCOADHESIVE MICROGRANULES CONTAINING RANITIDINE HYDROCHLORIDE

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ABSTRACT

Ranitidine hydrochloride is a competitive inhibitor of histamine H2-receptors, 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 formulate and in vitro evaluate microgranules with ranitidine HCl. Microgranules were prepared by the wet granulation method using aloe vera powder as bioadhesive polymer. Increasing concentration of aloe vera powder results decreasing of flow rate, improving of moisture content, swelling index, in vitro bioadhesive, and dissolution efficiency. The obtained results indicated that aloe vera powder is a suitable polymer for developing a sustained-release dosage form of ranitidine HCl for local delivery in the gastro intestinal tract.

KEYWORD: Aloe vera powder, microgranules, ranitidine HCl, bioadhesive polymer, gastro intestinal tract.

INTRODUCTION

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.[1] 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.[2]

There are a number of approaches that can be used to prolong gastric retention time, one of them is polymeric bioadhesive systems. Aloe vera gel can act as natural polymer bioadhesive in many biomedical applications, including drug delivery systems because of their polysaccharide contents.[3] This substances can be founded in the parenchim tissues of Aloe vera,[4] but it has disadvantages of physicochemical properties, such as sensitive to heat, light, air, and easy to oxidation. Therefore, it is important to make a good stability using freeze drying method.[5]

The objective of this study is to prepare gastro retentive mucoadhesive microgranules of ranitidine HCl, to release the drug in a controlled manner and to optimize the release profile and bioadhesion of the system. Formulated microgranules were characterized for its flow rate, moisture content, swelling index, dissolution efficiency, and particle size using SEM (Scanning Electron Microscopy). Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the gastro intestinal tract.[6]

MATERIALS AND METHODS

The materials used were aloe vera powder (*Aloe vera* (L.) Webb), aquadestilata, dextrin, FDC green, ethanol 96%, natrium chlorida, ranitidine hydrochloride, polyvinilpyrolidon K-30, carbopol 934P, lactosum, acid hydrochloride, and gastric mucosa from male white rats Wistar strain.

The instrumen used were analytical scales, ceramic mortar, sieve no. 30 and 40 mesh, pH meter (Hanna instrument), moisturemeter (G-Won Hitect 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).

Preparation of Aloe Vera Powder

Aloe vera (*Aloe vera* (L.) Webb) which has been identified were washed, then cutted, and peeled. This stuff were heated by water (at a temperature of 70^{o}C for 10 minute) to get aloe

vera gel. The gel was filtered and blended into aloe vera pulp, then dried 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.[5]

Formulation of Microgranules Containing with Ranitidine HCl

Table 1. Composition of various aloe vera powder microgranules formulations

Batches	Ranitidine HCl (mg)	Aloe vera powder (%)	Carbopol 934P (%)	PVP K30 5% (mL)	FDC Green (%)	Lactosum (%)
F1	300	4	15	11	0,25	ad 100
F2	300	6	15	11	0,25	ad 100
F3	300	8	15	11	0,25	ad 100

Microgranules were prepared in at least 3 batches in a ceramic mortar by the modified wet granulation technique. Ranitidine HCl, aloe vera powder, carbopol 934P, PVP K-30, FDC green, and lactosum 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. The wet granules were sieved no 30 and 40 mesh, then dried (at a temperature of 35^{o}C for 25 minute). The dried granules were tested for physical properties including flow rate, moisture content, swelling index, in vitro bioadhesive, dissolution efficiency, and particle size using SEM (Scanning Electron Microscopy). The data were analysed 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 gel has susceptible to microbial spoilage as well as enzymatic and oxidation reactions. However, contact with the air will incerase the oxidation reactions, results yellow-brownish gel. Dehydration of samples is necessary to improved their stability and less susceptible to spoiling during storage.[7] Freeze drying method is the best choice to dehydration the sample due to lower temperature and pressure (0^{o}C and 4,58 torr). The dried samples were sieved through no. 60 mesh, characterized by loose powder, white-brownish, odorless, and tasteless (Fig. 1). Yield of 6,52% aloe vera powder were calculated by weighing dried samples (436 gram) and referring it to the initial amount of aloe vera gel (6,6872 kg).

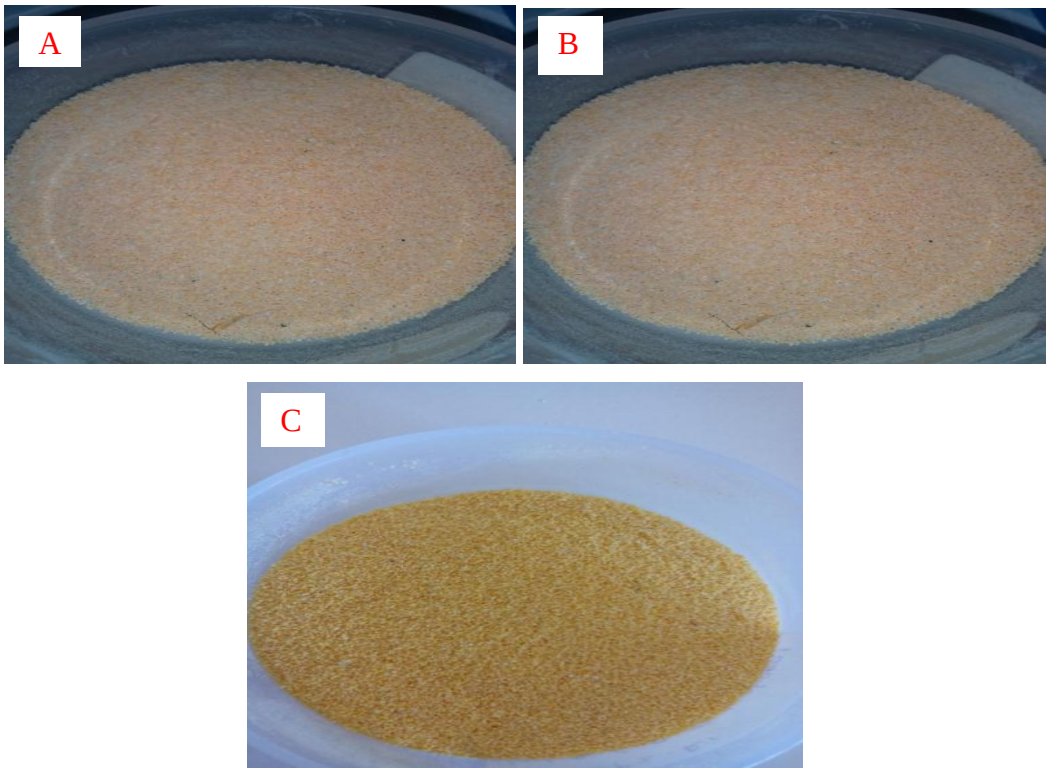


Figure 1. Ranitidine microgranules: batch F1 (A), batch F2 (B), and batch F3 (C)

Three batches of microgranules were formulated by aloe vera powder and carbopol 934P as bioadhesive 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,[8] shown in **Table 2**.

Table 2. Physical Properties of Ranitidine Microgranules

Physical properties	F1	F2	F3
Flow rate (g/sec)	15.3560 ± 0.6103	13.8540 ± 0.2488	12.4984 ± 0.2829
Moisture content (%)	0.48 ± 0.0274	0.63 ± 0.0274	0.70± 0.0354
Swelling index (%)	297.2 ± 87.7236	414.8 ± 35.3406	555.6 ± 44.4414
In vitro bioadhesive (%)			
5^{th} minute	81.6± 2.1909	86.4± 2.1909	90.4± 2.1909
10^{th} minute	71.2± 3.3466	80± 2.8284	86.4± 2.1909
Dissolution efficiency (%)	75.59 ± 9.0375	77.89 ± 6.2546	79.50 ± 9.5278
Particle size (µm)	7.04 ± 3.1457	5.6429 ± 1.7069	2.8664 ± 3.0189

Notes:

FI= ranitidine microgranules with 4% of aloe vera powder.

F2= ranitidine microgranules with 6% of aloe vera powder.

F3= ranitidine microgranules with 8% of aloe vera powder.

Mean ± SD, n = 5

Microgranules Size and Shape Morphology

Photomicrographs (x 1000 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 scanning electron microscopy. Batch F1, F2, and F3 has particle size of 7.04 µm, 5.6429 µm, and 2.8664 µm for 1000 magnifications, whereas 789.75 µm, 681 µm, and 826.6667 µm for 50 magnifications, respectively. All batches fit up the requirements of particle size, which is between 425-850 µm.[9]

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.[10]

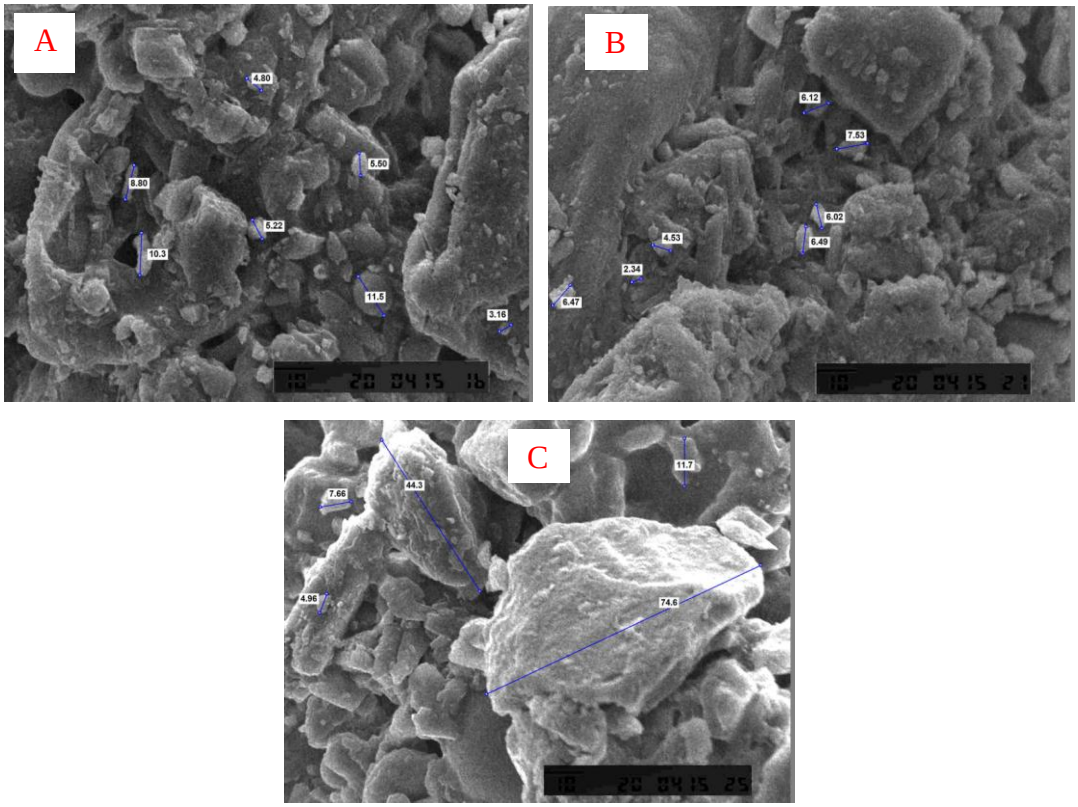


Figure 2. Microscopic images of ranitidine microgranules: batch F1 (A), batch F2 (B), and batch F3 (C)

Flow Rate

Based on table 2, F1 has flow rate of 15.3560 g/sec compared to F2 (13.8540 g/sec) and F3 (12.4984 g/sec). This results correlate to moisture content, proved by batch F1 which has the fastest flow rate due to the lowest moisture content. All batches fulfill the requirements of flow rate, which is not more than 10 second of 100 gram granules to flow or more than 10

g/sec, its usually known as free flowing properties.[11] Statistical analysis was performed using the analysis of variance (ANOVA), explain that all batches has significant comparison due to the different of aloe vera powder concentration.

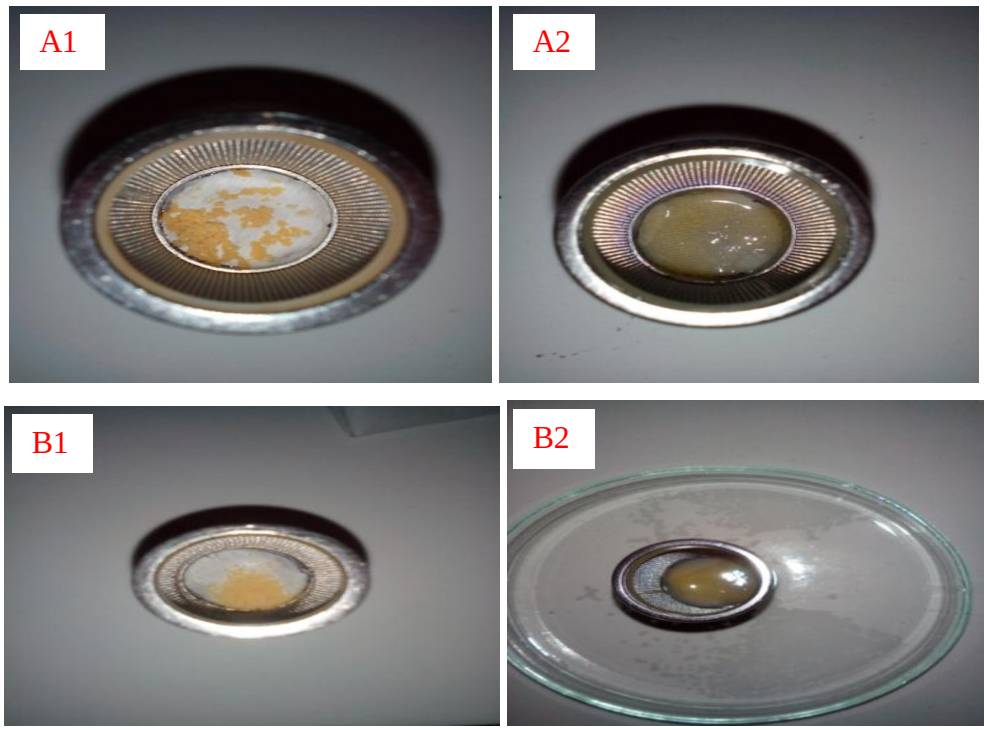
Swelling Index

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 minute, 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.[12]

The drug loaded microgranules were showing the most swelling index in batch F3, which contain aloe vera powder 8% and carbopol 934P 15% (Fig. 3). 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.[13]



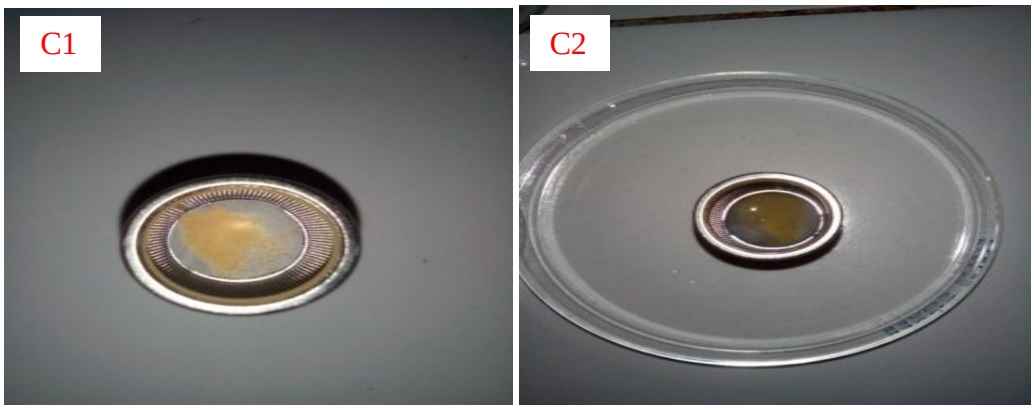
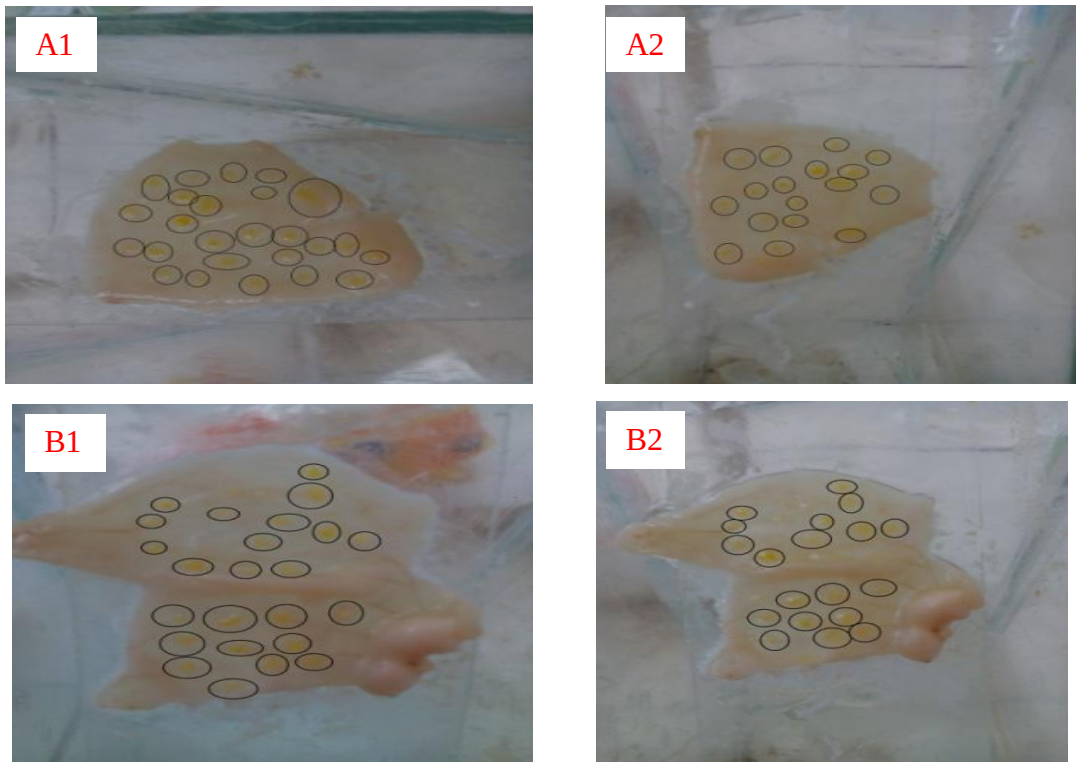


Figure 2. Swelling index of ranitidine microgranules: batch F1 (A1: initial, A2: final), batch F2 (B1: initial, B2: final) and batch F3 (C1: initial, C2: final)

In vitro Bioadhesive

When designing a bioadhesive properties, it is more important to guarantee its adhesivity to the mucosa. Mucoadhesive strength was found to be directly proportional to the concentration of aloe vera powder. This may be due to the formation of strong gel which penetrate deeply into the molecules of mucin and show strong bioadhesion. Thus batch F1 which contain lowest amount of aloe vera powder show lowest mucoadhesivity while F3 containing highest amount of aloe vera powder show highest mucoadhesive strength. 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**.



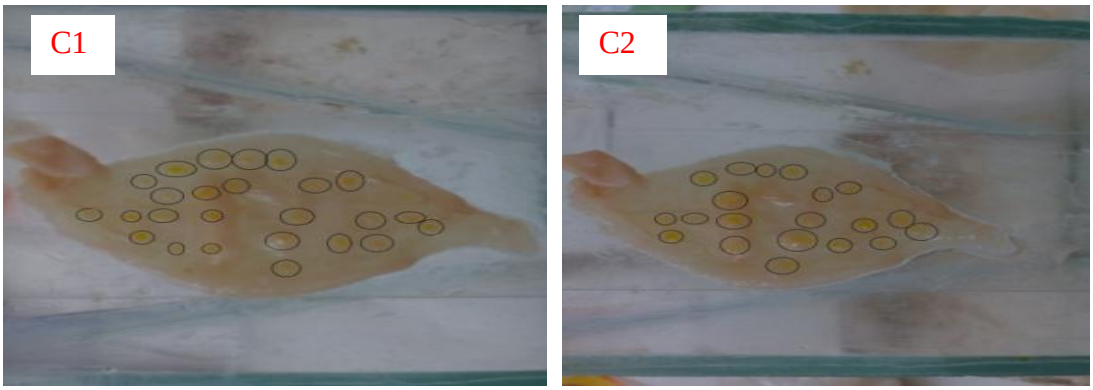


Figure 4. In vitro bioadhesive of ranitidine microgranules: batch F1 (A1: initial, A2: final), batch F2 (B1: initial, B2: final) and batch F3 (C1: initial, C2: final)

Bioadhesive mechanism of ranitidine HCl loaded microgranules can be explained by wetting and diffusion theories. Firstly, the wetting theory, which is based on the ability of bioadhesive 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.[14] Analysis by ANOVA resulted significant different among three batches because of their different concentration of aloe vera powder.

Dissolution Efficiency

The dissolution efficiency was used to find out the ability of drug dissolved in acid and base medium (gastric, duodenum, or ileum). This parameter has advantages to estimate the bioavailability and bioequivalency of drug. Microsize of granules was expected to improve the dissolution and to achieve the plasma concentration of ranitidine HCl.[15] Testing of dissolution was done by measuring the absorbance at 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 minute with spectrophotometer UV-Vis.

The release standard of ranitidine HCl was 20-50% within 120 minute and 45-75% within 480 minute,[16] whereas all batches did not fill up this requirement because of the effect of polymers. Based on **Table 2**, batch F3 has the lowest dissolution efficiency. The higher concentration of aloe vera powder make the thicker barrier surrounding this microgranules, causing the lower release of ranitidine HCl.

Aloe vera powder and carbopol 934P act as hydrophilic polymers. Monolithic matrix systems was occured when using hydrophilic polymers, which swell on hydration and dissolve to release drug. This mechanism include 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.[17]

Kinetic models

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	0,9154	0,8350	**0,9613**	0,8637	0,0039	22,9366
F2	0,9052	0,8590	**0,9438**	0,7636	0,0034	20,1354
F3	0,8244	0,7824	**0,8905**	0,5999	0,0029	16,3889

The dissolution kinetics of all batches were applied to various dissolution models such as zero order, first order, and Higuchi. The best fitted model gives the highest R value (Table 3). Thus, Higuchi model fits best for the dissolution data of all batches as it showed the highest value for R which indicate that the drug release from a system in controlled manner.[18] In the dissolution medium, firstly microgranules shows swelling of polymer and burst release of drug and after that combination of aloe vera gel and carbopol 934P acts as release retardant polymer and gives the release of drug in sustained manner.

CONCLUSION

Aloe vera powder (*Aloe vera* (L.) Webb) can be used to formulate microgranules for the prolonged delivery of ranitidine HCl. The increasing concentration of aloe vera powder results decreasing of flow rate, improving of moisture content, swelling index, in vitro bioadhesive, and dissolution efficiency. The drug release followed better Higuchi model than the zero order and first order kinetic models, which confirm the monolithic matrix systems to achieve controll release dosage form.

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