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PHYSICAL CHARACTERISTICS AND STABILITY MUCOADHESIVE MICROGRANULES OF RANITIDINE HCL WITH ALOE VERA POWDER POLYMER AND CARBOPOL 934P IN TEMPERATURE 2°C AND 25°C

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ABSTRACT

Ranitidine HCl has low stability due to its hygroscopic. Stability tests need to determine the changes physical and chemical stability that occur during storage against. A study was conducted to determine the effect of storage temperature (2°C and 25°C) on the stability of the mucoadhesive microgranules ranitidine HCl over a period of 3 months. The mucoadhesive polymer used was a combination of aloe vera powder and carbopol 934P. Aloe vera powder was made by dried process using freeze dryer at -45ºC. The method of making granules used is wet granulation. The parameters tested included moisture, flow rate, flux, mucoadhesive power in vitro, dissolution, permeation, and SEM (Scanning Electron Microscopy). Data analysis using Statistic Product and Service Solution (SPSS) 16.0 with one way ANOVA test. The test results was showed that temperature and storage time affect the stability of microgranules because the release rate constant is significantly different throughout the test. Storage of microgranules stable at 2°C, because from 0 to 3 months which shows different results are not significant.

KEYWORDS: *Carbopol* 934P, mucoadhesive microgranules, ranitidine HCl, stability, aloe vera powder.

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. 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] This drug belongs to the class III Biopharmaceutics Classification System (BCS) which has high solubility and low permeability.[3]

There are a number of approaches that can be used to prolong gastric retention time, one of them is polymeric bioadhesive systems. Studied by Maru and Singh,[4] aloe vera gel can act as natural polymer bioadhesive in many biomedical applications, including drug delivery systems because of their polysaccharide contents. Ways to improve bioavailability were made with mucoadhesive preparations with a combination of aloe vera polymer 27.34% and carbopol 934P 7.62%.[5] The preparation of ranitidine HCl with the stability field given the hygroscopic and aloe vera that are sensitive to heat, light, air and are easily oxidized. Based on the above, a study was conducted to determine the effect of storage temperature (2°C and 25°C) on the stability of the mucoadhesive ranitidine HCl for a period of 3 months. The parameters tested were physical characteristics, dissolution, and permeation.

MATERIALS AND METHODS

The materials used are aloe vera gel, aqua distillata, 96% ethanol, sodium hydroxide (Merck KGaA), sodium chloride, maltodextrin, ranitidine HCl (SMS Pharmaceuticals, PVP K-30 (BASF The Chemical Company), carbopol 934P (Shree Chemicals), lactose (Leprino Foods), potassium dihydrogen phosphate (Merck KgaA), intestinal mice rats Wistar strain, cellophane membrane.

The instruments used are analytical balance (Shimadzu), digital balance sheet, blender, freeze dryer (Labconco), Stainless Steel, Moisturemeter (Shimadzu), Basket Vester 6-DR dissolution tester, UV- Vis 1280 (Shimadzu), Franz diffusion tool, Stirer, pH meter (Hanna Instrument), Scanning Electron Microscopy (Jeol T-300, Japan).

Processing of Aloe vera

Aloe vera (Aloe vera (L.) Webb) which has been identified were washed, then cutted, and peeled. The aloe

vera was heated by water (at a temperature of 70°C for 10 minutes) to get aloe vera gel.[6] The gel was filtered and blended into aloe vera pulp, then dried using freeze dryer (at a temperature of 0°C and pressure of 4.58 torr) by adding dextrin 15%. Next, the obtained dried powder were sieved through the sieve no 60 mesh.[7] The characteristics were tight, white-brownish, odorless, tasteless, and loose powder.[8] From 6.6872 kg aloe vera pulp were obtained 436 grams of aloe vera powder, therefore the yield was 6.52%.

Formulation of Mucoadhesive Microgranules Containing with Ranitidine HCl

Ranitidine HCl	50%
Aloe Vera Powder	27,34%
Carbopol 934P	7,62%
Sol. PVPK-30 1% in ethanol	0,17 ml
FDC *green*	0,3%
Lactose	600 mg[5]

Ranitidine HCl microgranules are made by wet granulation method. Ranitidine HCl, aloe vera powder, carbopol 934P, PVP K30, FDC green, and lactose are weighed according to calculated weights. A 1% PVP K30 solution was prepared by PVP K30 added with 96% ethanol, stirred until dissolved and homogeneous. PVP K30 solution was added FDC green, stirred to homogeneous. Ranitidine HCl is mixed with aloe vera powder, Carbopol 934P, and lactose, stirred until homogeneous. The powder mixture was added with a 1% PVP K30 solution of 0.17 ml to form a wet mass. The wet mass formed is then sieved with a mesh of 30 and 40 mesh. The granules are then dried in a drying cupboard for approximately 15 minutes.[9] Some microgranules are stored at 2°C and 25°C, then each one is tested at 1, 2 and 3 months.

Tests performed on microgranule preparations include moisture content by weighing 500 mg samples inserted in a moisture meter measured at 70°C.[10] Flow rate by inserting 10 grams of sample into flow time funnel. Power expanded by introducing 50 mg of sample into a petri dish containing phosphate buffer media of pH 7.8 by 10 ml for 3 hours, change between weight before development and after development was measured.[11] Mucoadhesive in vitro by eluting samples that have been attached to tissue with phosphate buffer media for 10 minutes at 22 ml / min.[12] Dissolution test with dissolution tester basket type as much as 600 mg sample is put into phosphate buffer media pH 7.8 then rotor ignited with speed 50 rpm for 6 hours.[13] SEM (Scanning Electron Microscopy) by firing the surface of gold-coated objects using high-energy electron beams. Permeation using vertical Franz diffusion cells.

RESULTS AND DISCUSSION

This study was conducted to determine the stability of ranitidine HCl mucoadhesive microgranules in cold temperature storage (2°C) and room temperature (25°C) for a period of 3 months which included testing moisture content, flow rate, flux, mucoadhesive in vitro, SEM, dissolution and permeation.

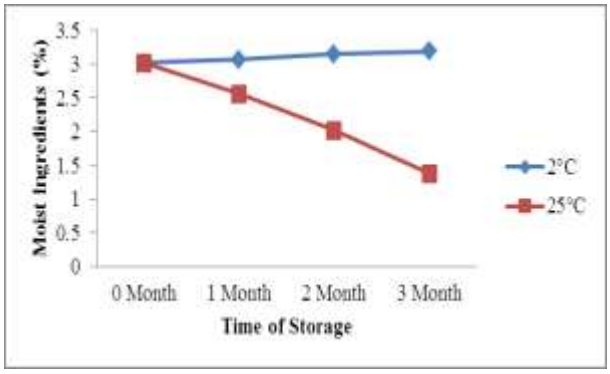

Fig. 1. Effect of storage time on moist ingredients mucoadhesive mirogranules of ranitidine HCL.

Fig. 1 shows that the storage temperature affects the results of the moist moisture content of the microgranules, at a temperature of 2°C the moist moisture content is relatively stable and in accordance with the requirements according is 2 - 4%[14] whereas at 25°C there is a decrease in moist evaporation of moisture will be greater if the temperature is increased so that the results obtained are not in accordance with the requirements.

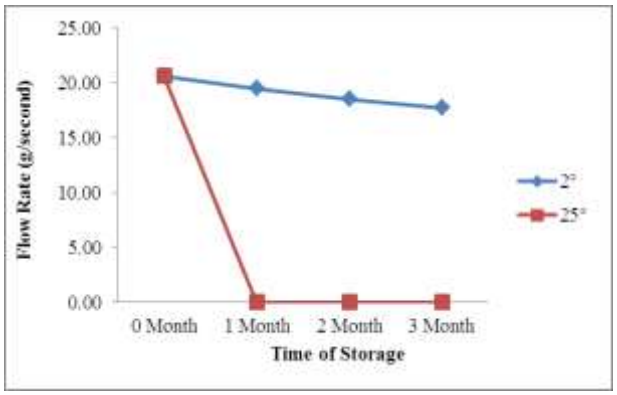

Fig. 2: The effect of storage time on mucoadhesive flow rate mucoadhesive microgranules of ranitidine HCL.

Based on Fig. 2, it appears that only storage at a temperature of 2°C corresponds to a good flow rate requirement of over 10 grams/sec,[15] so it can be concluded that storage at 2°C does not affect the stability of the mucoadhesive microgranules ranitidine HCl. At 25°C the test cannot be performed because the physical form of the sticky and clot microgranules does not allow it to be inserted into the flow funnel.

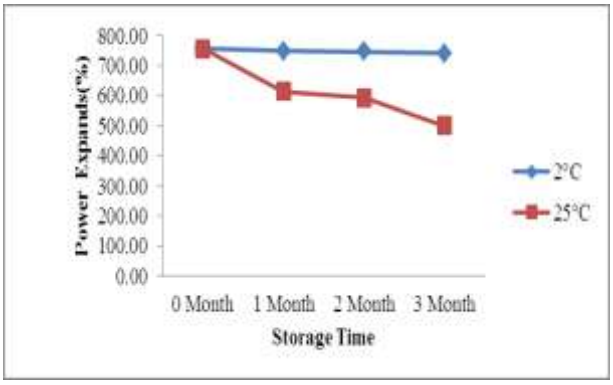

Fig. 3: Effect of storage time on power expand mucoadhesive microrogranules of ranitidine HCL.

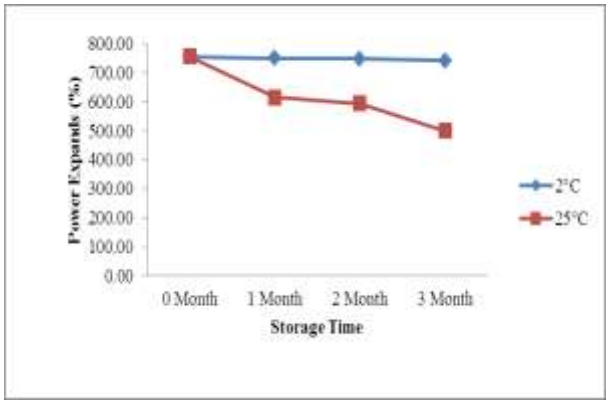

Fig. 4: Effect of storage time on mucoadhesive in vitro muco¬adhesive microgranules of ranitidine HCL.

The results of the expanded and mucoadhesive power tests in vitro in Fig. 3 and 4 are interconnected, the lower the storage temperature the higher the power of the microgranules expand, this results in the ability to attach the microgranules to increase as the higher the percentage of the polymer expands the power, the more water is absorbed so that water from the mucus also absorbed. Mucus dehydration strengthens the adhesive bond between the polymer and the intestine, allowing expanded and mucoadhesive power at storage temperature of 2°C higher than storage temperature of 25°C.

Based on the literature, microgranules have a range of 1-1000 µm,[16] whereas the results of microcranules mucoadhesive ranitidine HCl test obtained size 678.5 µm for storage for 3 months at 2°C with 50x magnification it can be concluded that the storage temperature of 2°C corresponds with the literature. Testing at 25°C does not produce particle size data because the physical condition does not form a microgranules anymore and forms a sticky mass.

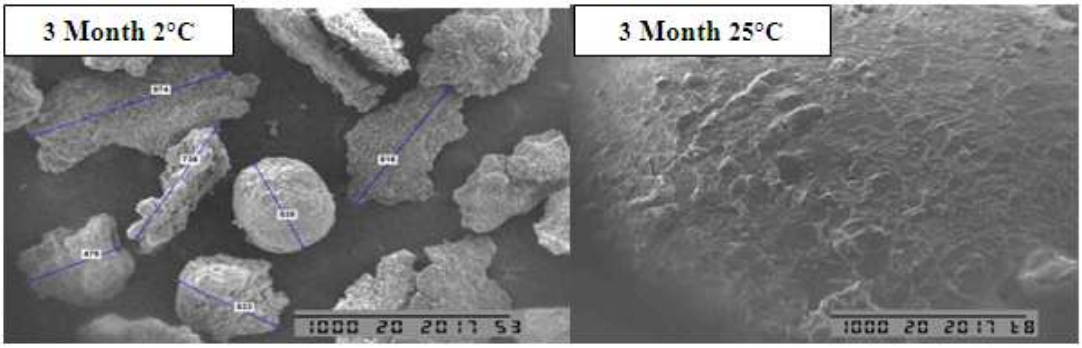

Fig. 5: Mucoadhesive microgranules of ranitidine HCL with SEM

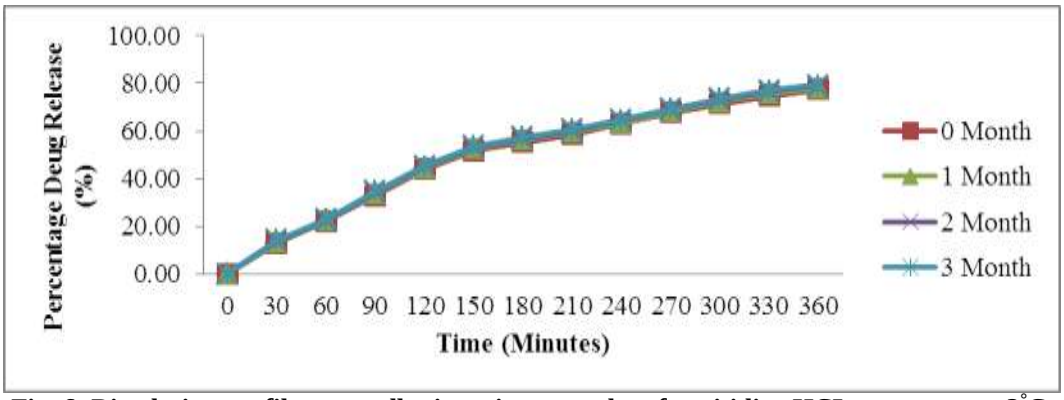

Fig. 6: Dissolution profile mucoadhesive microgranules of ranitidine HCL temperature 2°C.

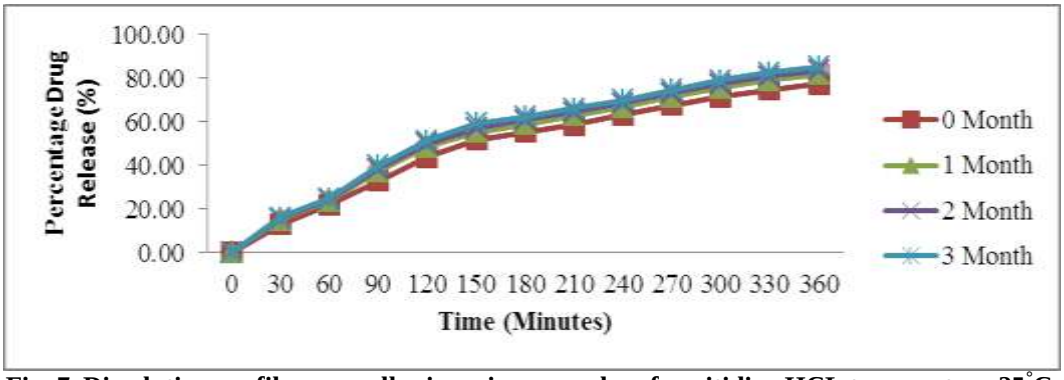

Fig. 7. Dissolution profile mucoadhesive microgranules of ranitidine HCL temperature 25°C.

The higher the temperature and length of storage time the higher is also the dissolved content of the mucoadhesive microgranules ranitidine HCl because with the increase in temperature for 3 months storage, resulting in damage to aloe vera polymer and decrease the stability of carbopol polymer. Damage to the polymer causes the release of ranitidine HCl to become uncontrolled and levels are higher.

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In Fig. 8, it is seen that at 2°C the amount of the diffused drug is relatively stable during the 3 month sustained, at 25°C. the longer the storage time the higher the percentage of permeation. An increase in the percentage permeation of the mucoadhesive HCl caused by the ability of the polymer to function as a barrier is less than optimal because of the influence of air, light and heat so that ranitidine HCl can penetrate the membrane. The more damaged the microgranules polymer the ability to inflate it becomes smaller so it cannot resist the release of the active substance.

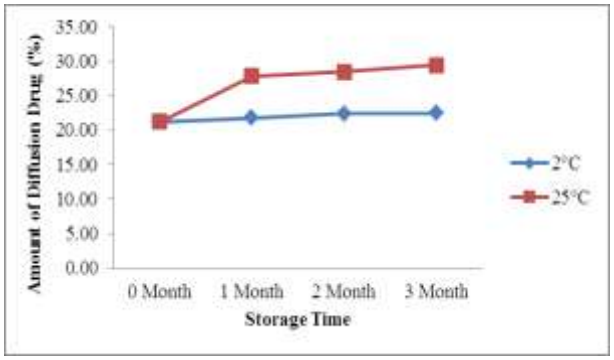

Fig. 8: Influence of storage time on permeation of mucoadhesive microgranules of ranitidine HCL.

The effect of storage on the physical stability of the mucoadhesive microgranules of ranitidine HCl can be observed from the color changes seen in Figure 9. At 2°C temperature storage does not change color and shape, whereas at 25°C storage occurs a change of color from light green to light brown and dark brown as well as texture of microgranules become sticky and clot. The color changes that occur due to the instability of aloe vera polymer to heat, light and air and easily oxidized because of the presence of metal compound (magnesium) in aloe vera flour, the presence of contact with air (oxygen) will also accelerate the occurrence of oxidation processes that result in flour brown aloe vera and known as "Browning reaction".

Fig. 9: Physical characteristics of mucoadhesive microgranules of ranitidine HCL.

Table 1: Statistical test result of mucoadhesive microgranules testing ranitidine HCL.

Test	Assymp. Sig	Requirement	Results
Moist Ingredients	0,000	Data is Significant if Assymp. Sig ≤ 0,05	Significantly Different
Flow Rate	0,000		Significantly Different
Power Expands	0,000		Significantly Different
Mucoadhesive in vitro	0, 001		Significantly Different
Dissolusion	0,000		Significantly Different
Permeation	0,000		Significantly Different

Table 1 is the result of statistical analysis of rate change constant at temperature of 2°C and 25°C, it can be concluded that the storage temperature affects the stability of the mucoadhesive microgranules ranitidine HCl because the rate of release release in the statistical test shows significantly different results throughout the test.

CONCLUSION

1. The storage temperature affects the stability of the mucoadhesive microgranules of ranitidine HCl, since the rate constant of release on statistical tests shows significantly different results in all tests of both physical characteristics, dissolution, and permeation.
2. Time affects the stability of the mucoadhesive microgranules of ranitidine HCl, since all tests show significantly different results between storage times.

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