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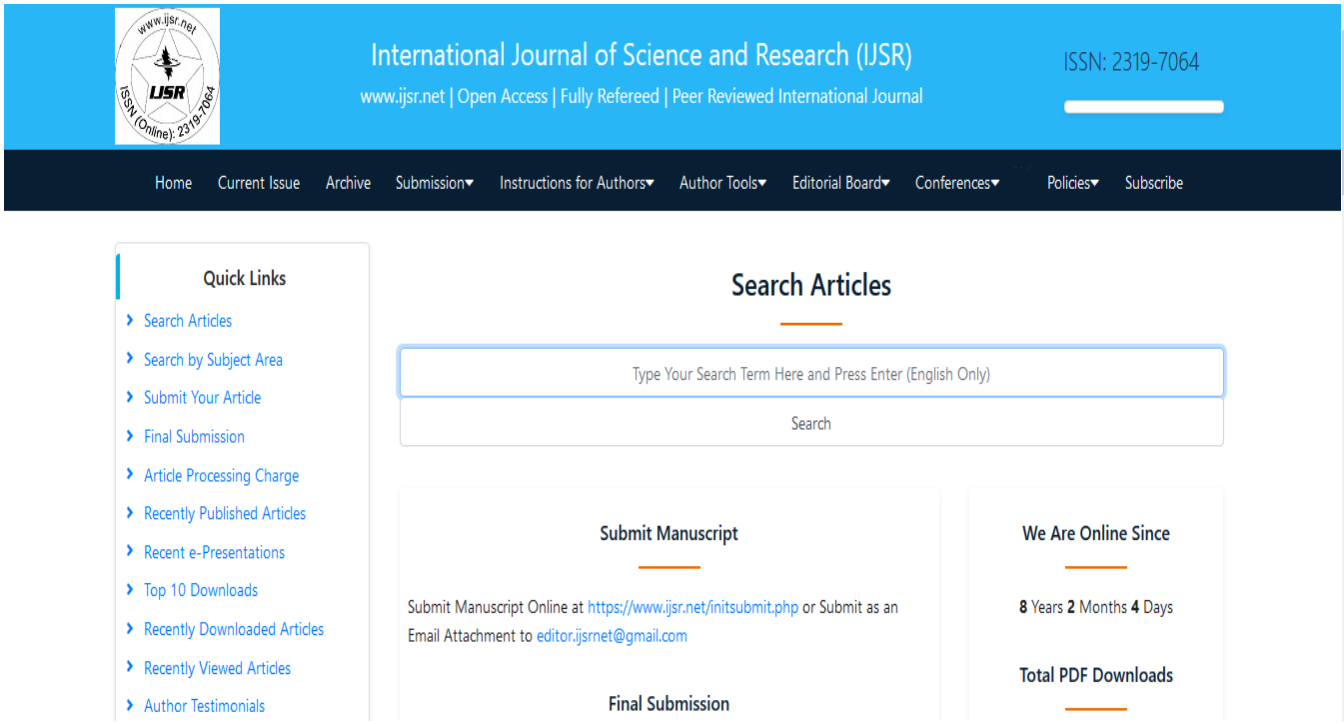
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Dissolution Profile Mucoadhesive Microgranules of Ranitidine HCL using Polymer Combination of Aloe Vera Powder (Aloe vera L.) and Carbopol 934P On AIF and SIF Media with a Line of Identification Approach

Endang Diyah Ikasari, Intan Martha Cahyani

Short Research Article

DISSOLUTION PROFILE MUCOADHESIVE MICROGRANULES OF RANITIDINE HCl USING POLYMER COMBINATION OF ALOE VERA POWDER (Aloe vera L.) AND *CARBOPOL* 934P ON AIF AND SIF MEDIA WITH A LINE OF IDENTIFICATION APPROACH

ABSTRACT

There are several factors that influence dissolution test in vitro such as dissolution media. The AIF media (Atrial Intestinal Fluid) and the SIF media (Simulated Intestinal Fluid) media are among the media that can be used in the dissolution test. Mucoadhesive microgranule of ranitidine HCl using a combination polymer of aloe vera powder and *carbopol* 934P that expands maximally at pH 7.8. The purpose of this study was to determine the dissolution profile of mucoadhesive microgranule of ranitidine HCl in AIF (*Atrificial Intestinal Fluid*) pH 7.8 and SIF (*Simulated Intestinal Fluid*) pH 7.8 with a line of identification approach. The method of making granules used is wet granulation. Data analysis using *Statistic Product and Service Solution* (SPSS) 16.0 with T-Test. The test results showed that the dissolution profile of AIF media followed Higuchi model while in SIF media following release model of order 1. Mechanism of release of mucoadhesive microgranule of ranitidine HCl on SIF media was better than AIF media. Media type significantly influence dissolution test.

Key words: Carbopol 934P, AIF media, SIF media, ranitidine HCl, aloe vera powder

1. INTRODUCTION

Ranitidine is a class of Biopharmaceutics Classification System (BCS) class III which has high solubility and low permeability (Reddy and Karunakkar, 2011). The dosage form of mucoadhesive microgranule is one way to increase the low permeability of ranitidine HCl. The mucoadhesive dosage form is strongly influenced by the ability of the polymer to expand (Miranda, et.al, 2009), The polymers used in the mucoadhesive dosage form of ranitidine HCl are a combination of aloe vera polymer 27.34% and *carbopol* 934P 7.62% (Revita, 2015). Lutfiani (2016), suggests that mucoadhesive microgranule of ranitidine HCl undergoes a slow drug release at pH 7.8 because the gel expands optimally so that the release rate of the drug can be controlled. Many factors that influence dissolution test in vitro include dissolution media. SIF (*Simulated Intestinal Fluid*) and AIF (*Atrificial Intestinal Fluid*) are media that can be used to produce dissolution profile of mucoadhesive microrogranule of ranitidine HCl (Dewi *et al*., 2017).

SIF media (*Simulated Intestinal Fluid*) has been widely used as a dissolution medium to determine the release of the active substance of a drug. Kumar et al. (2011)

suggests that the process of development and erosion of alginate polymers can be observed on SIF media at pH 7.4. The release of cefuroxime salts on SIF media can also be seen rapidly for 30 minutes for initial dosage and followed by a slower release for the next 150 minutes (Ofokansi and Aikau, 2007). AIF (*Atrificial Intestinal Fluid*) is a dissolution medium containing physiological salts such as Na. diclofenac, $MgCl_2$, $CaCl_2$, KCl, NaCl, and $NaHCO_3$. The use of physiological salts corresponds to the electrolyte composition of the intestinal fluid, thus illustrating the actual condition of the intestinal fluid (Ririn *et al*., 2015). AIF media contains pancreatin enzymes in which this enzyme contains amylase and lipase. Amylase serves to break down carbohydrates into simple sugars whereas lipase breaks down fat into fatty acids and glycerol. Enzyme activity may affect the physical and chemical characteristics of a drug. The aim of this research is to know dissolution profile difference and release mechanism of ranitidine HCl on microgranule dosage form on AIF and SIF media with line of identification approache complications.More complications would be due to the potentially greater disparity between two media dissolution than between any single media.

2. MATERIALS AND METHODS

The materials used in this research are aloe vera gel from Demak district, Central Java, aqua distillate, material with technical grade (96% ethanol, sodium hydroxide (Merck KGaA), sodium chloride, and maltodextrin), pharmaceutical grade ranitidine HCl (SMS Pharmaceuticals), PVP K-30 (BASF The Chemical Company), *Carbopol* 934P (Shree Chemicals) and lactose (Leprino Foods), potassium dihydrogen phosphate (Merck KgaA), and pancreatin enzyme (Oxford Lab).

The instruments used are the analytical balance (Shimadzu), digital balance, mesh number 30, 40, and 50, glassware, blender, freeze dryer (Labconco), basket type dissolution tester (Veego VDA 6-DR), spectrophotometer UV-Vis 1280 (Shimadzu), kuvet and pH meter (Hanna Instrument).

Aloe vera washed with water and then cut into pieces and the skin is peeled to obtain a clear colored aloe vera gel. Heating temporarily (blanching) on aloe gel is done by soaking the gel in water temperature of 70^{o}C for 10 minutes. The gel is then filtered, and blended to form aloe vera slurry. A 15% maltodextrin is weighed from the weight of the aloe vera and then added to the aloe vera slurry, stirred until it becomes homogeneous. Aloe vera slurry is dried using freeze dryer at temperature

(-45^{o}C). The dried aloe vera result was sieved using sieve with mesh number 50 to obtain aloe vera powder. Ranitidine HCl microgranules are made by wet granulation method. The mucoadhesive microgranule formula of ranitidine HCl is as follows:

Ranitidine HCl		50%
Aloe vera powder		27,34%
Carbopol 934P		7,62%
Sol. PVP K-30 1% in ethanol		0,17 ml
FDC green		0,3%
Lactose	until	600 mg (Revita, 2015).

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 composed by PVP K30 is added with 96% ethanol, stirred until dissolved and homogeneous. A 1% PVP K30 solution was added FDC green, stirred until homogeneous. Ranitidine HCl is mixed with aloe vera powder, *Carbopol* 934P, and lactose, mashed and stirred until homogeneous. The powder mixture is added with a 1% PVP K30 solution of 0.17 ml to form a wet mass. The wet mass formed is then sieved with 30 and 40 a mesh number. The granules are then dried in a drying cupboard for approximately 15 minutes. The granules are sieved again using the same sieve as above. For each replication conducted dissolution test with a sample of 600 mg put in the basket type tool and dissolved for 50 rpm for 6 hours using two different media and testing replication of five times.

3. RESULTS AND DISCUSSION

Dissolution test is the process of dissolving a chemical substance or drug compound from solid dosage form into a certain medium (Ansel, 2005). Dissolution was used as an initial step to determine the bioavailability of a dosage form prior to the in vivo drug release testing.

TABLE 1: DISSOLUTION CONTENT OF MUCOADHESIVE MICROGRANULES OF RANITIDINE HCL

Time (minute)	Average Dissolution Content of Microgranules Ranitidine HCl (%)	
	AIF	SIF
0	0.00 ± 0.00	0.00 ± 0.00
30	24.92 ± 0.30	14.35 ± 0.97

60	30.35 ± 0.29	22.86 ± 0.67
90	46.68 ± 1.12	34.77 ± 0.86
120	**59.07 ± 0.63**	**45.40 ± 0.39**
150	64.30 ± 0.21	53.58 ± 0.97
180	67.50 ±0.48	57.28 ± 0.21
210	70.39 ± 0.69	60.36 ± 0.03
240	**73.12 ± 0.71**	**64.70 ± 0.09**
270	80.24 ± 0.95	69.27 ± 0.02
300	85.50 ± 1.20	73.58 ± 0.08
330	90.71 ± 1.41	77.21 ± 0.09
360	**95.24 ± 0.75**	**79.24 ± 0.31**

Based on Table 1 it can be seen that the dissolution content is influenced by the type of media. AIF media results in a greater percentage of dissolution content compared to SIF media. Dissolution test is influenced by the expanding power of the polymer used. Aloe vera powder is a hydrophilic polymer, while *carbopol* 934P is a hydrogel polymer. When both are in contact with water, a hydrated matrix layer will be formed. This outer layer will erode to become dissolved (Sari, 2009). Lutfiani (2016) suggests that the expanding power of granule with the best combination of aloe vera polymer and *carbopol* 934P is at pH 7.8. In AIF media pH 7.8 there is an enzyme that can interfere with the expansion process and the inherent ability of the polymer in the dosage form. Pancreatin enzymes contains amylases that can damage carbohydrate content in both polymers. Non-fluid and well-attached gels cause the release of drugs to become larger because the polymer can not hold drug release process in the dosage form. In contrast, the polymer in the SIF medium can expand completely so that drug release becomes smaller as the polymer can hold the drug release from its dosage form. Dissolution test in Figure 1 shows the release profile of ranitidine HCl on AIF media is greater than in SIF media but, drug release is linear with percentage of release which keep increasing. The dissolution test statistic data obtained showed significantly different result with significance value 0.000 (significant data condition is ≤ 0.05) which means media difference influence ability of dosage to release active substance.

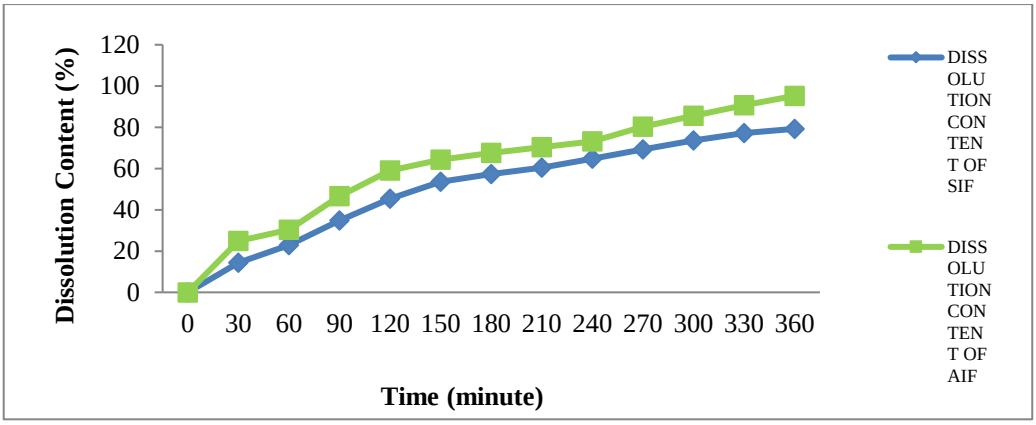
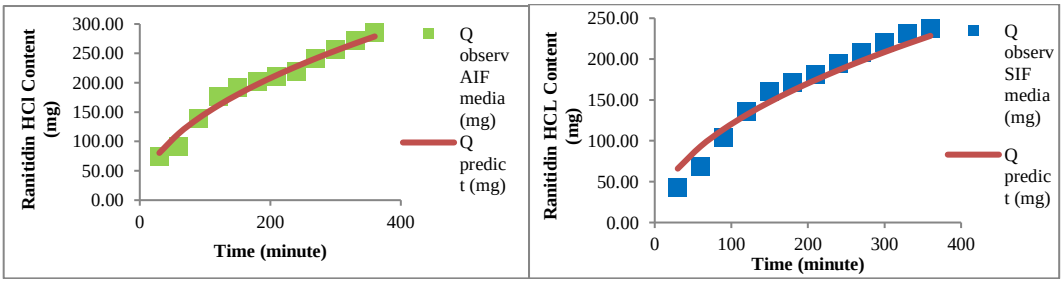


FIG. 1. DISSOLUTION PROFILE MUCOADHESIVE MICROGRANULES OF RANITIDINE HCL

The release of the active substance of a dosage form which release has been modified can be obtained using the zero order reactions, first order, Higuchi model and Michaeles Menten model. According to Figure 2, the kinetics of ranitidine HCl release in muoadhesive microgranulic dosage form on AIF media followed the Higuchi model by diffusion of the matrix while in SIF media following the first order release kinetics which is drug release based on active substance concentration. This indicates that the media type affects the kinetics of the release of the active substance of a dosage form.



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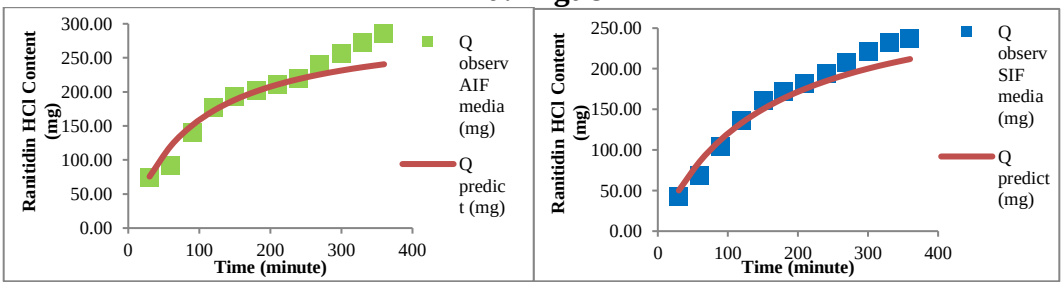

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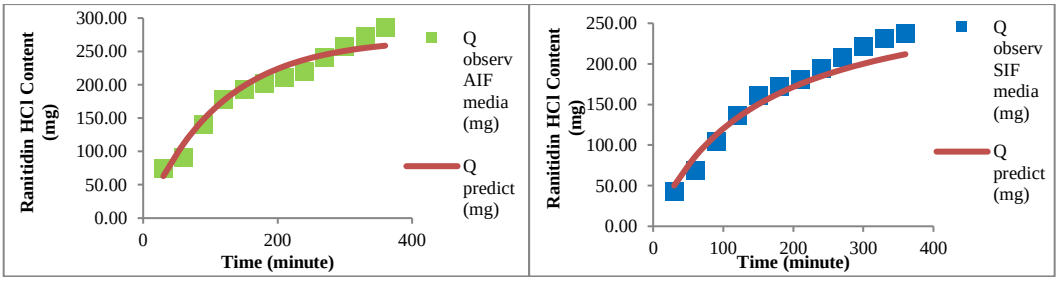

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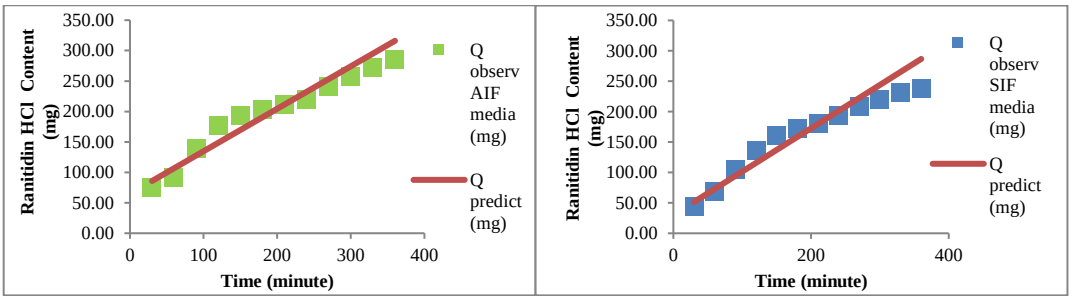

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FIG. 2. RELEASE KINETICS MUCOADHESIVE MICROGRANULES OF RANITIDINE HCL

In this study, the drug release of ranitidine HCl tablets were tested in two different *in vitro* pH environments in order to correlate *in vitro* drug release. As shown in figure 2, in SIF, for most formulations tested, the dissolution was slower as compared to that at AIF. Ranitidine HCl is a basic compound with pKa of 12.4; practically drug release is increased at acidic pH due to increased solubility. Also, the UV absorption spectrum of ranitidine HCl varies with pH, which may cause differences in drug release at different pH. It has been reported that drug release studies on ranitidine HCl tablets sourced from different territories often showed inconsistent drug release characteristics.

CONCLUSION

Based on the results of the study, there was a difference in dissolution profile and mechanism of the release of mucoadhesive microgranules containing ranitidine HCl, that is on AIF media the release of active substance greater than SIF media. The media type affects the release kinetics of the active substance of a dosage form wherein the release kinetics of the mucoadhesive microgranules of ranitidine HCl on the AIF medium follows the Higuchi model while in the SIF medium follows the first order release kinetics**.**

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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