ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

The Effect of Combination of Methacrylic Acid Copolymer L Type and S Type 0n the Physical and Chemical Polymer Properties

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ABSTRACT

The combination of methacrylic acid copolymers L-type and S-type in development of novel drug delivery system (NDDS) has been hold to modify the release pattern of drug. This combination especially for achieving dosage form release active substances in intestine. Physical and chemical properties of this copolymers has an important things because it can influence the quality of dosage form. Each of copolymers has different properties, so the combination will achieve the best formula. Methacrylic acid copolymer L-type has a number of methacrylic acid 49.6% and low viscosity 89 Mpa.s whereas methacrylic acid copolymer of S-type has a number of methacrylic acid 28.8% and a high viscosity 162 Mpa.s. To investigate the effect of the copolymer combination on the physical and chemical properties, the viscosity, acid number and pH of the matrices combination were then investigated. The combination of methacrylic acid copolymers L-type and S-type are: 10 : 0; 8 : 2; 6 : 4; 5 : 5; 4 : 6; 2: 8; and 0 : 10. The result showed that the increasing proportions of S-type (formula 1 to formula 7), increased the viscosity and pH, and decreased acid value.

Keywords: Copolymer methacrylic acid L-type and S type, Viscosity, Acid Value, pH.

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ISSN: 0975-8585

INTRODUCTION

Pharmaceutical excipients has important role in pharmaceutical formulation because it will affect the behavior and quality of drug product. Polymer is a major part of pharmaceutical formulations and tend to improve release pattern. Copolymer methacrylic acid as a gastro-resistance and GI targeting, because it protects the active ingredient from gastric fluid and release drug in ithe intestine. Methacrylic acid copolymer L-type and S-type suitable for pharmaceutical coating material which has a target action in intetstin. Methacrylic acid copolymer is an anionic polymer soluble at alkaline pH and insoluble at acidic pH. The copolymer has advantages when used as a coating of enteric coated preparations, increasing the effectiveness of drugs, is stable in storage, and protects the active ingredients from the environmental damage (Jain, 2008; McGinity, 2008).

Copolymer methacrylic acid L-type and S- type are the preferred choices of coating polymers. They enable targeting specific areas of the intestine. These anionic eudragit grades dissolve at rising PH values. In addition, different grades can be combined with each other, making it possible to adjust the dissolution pH and thus to achieve required GI targeting for drug (Sonje&Chandra, 2013). Copolymers offers valuable advantages for enteric coatings include pH-dependent drug release, increase in drug effectiveness, good storage stability, colon targeting and protection of actives sensitive to gastric fluid.

Meahcrylic acid copolymers L-type and S-type are copolymer based on methacrylic acid and ethyl acrylates. These are anionic, white free flowing powder with a weight average molar mass of approximately 125,000 g/mol .The various characteristics of eudragit L and eudragit S include effective and stable enteric coatings with a fast dissolution in the upper bowel, granulation of drug substances in powder form for controlled release, site-specific drug delivery in intestine by combination with eudragit S grades, variable release profiles. The process of trapping, protection, andrelease of the active ingredient by the methacrylic acid copolymer is influenced chemical properties and physical properties of the material making up the microparticle, the pH and the amount of carboxylate groups (acid number). Compounds weak acid at pH less 2 units of pK can not ionize. When pH = pK a price will be a 50% ionization, and when the pH value is greater than 2 units will occur ionization pK a perfect (Attwood and Florence, 2008).

The ionization process occurs as a result of the release of H atoms in the OH groups that do not form hydrogen bonds. The lower the pH value, the less the ionization occurs and the greater number of hydrogen bonds. The number of hydrogen bonds also depend on the chemical properties of the others, namely the number of carboxylic groups, small or large value of the acid number, the higher the price the acid number, produces the number of hydrogen bonds that more and more. The occurrence of hydrogen bonds are also influenced by the distance and angle between the atoms forming hydrogen bonds. (Marechal, 2007). The number of hydrogen bonds will affect the quality of the microparticles. The more hydrogen bonds are formed closer the surface so that the process of shrinkage due to drying can be avoided and the particle size becomes large and the greater the efficiency of trapping and power protection, but the lower the release of the active ingredient (Binder and Zirbs, 2007; Yeo and Park, 2014)

Physical properties of the constituents of microparticles that affect the process of trapping, protection and release of the active ingredient is the viscosity. The higher the viscosity of the material making up the microparticle, the larger the particle size, the greater the efficiency of trapping and power but the lower discharge protection (Maghsoodi 2009; Tiwari et al., 2009; Auda et al., 2010). Methacrylic acid copolymer L type has a large amount of methacrylic acid (49, 6%) and low viscosity (89 mPa.s). While the S-type has a small amount of methacrylic acid (28, 8%) and a large viscosity (162 mPa.s) (McGinity, 2008). The nature of chemical physics methacrylic acid copolymer type L and type S relied upon by previous researchers to optimize the formula by combining methacrylic acid copolymer L type and S type (Khan, et al,. 2006; .Nishit, et al., 2011). Microparticles with a pulsatile release that uses a matrix of methacrylic acid copolymer L type and S type can be applied to the active ingredient with a target action in the intestine but suffered damage in the stomach, for example, Lactobacillus acidophilus.

ISSN: 0975-8585

MATERIAL AND METHODS

Material

Methacrylic Acid Copolymers L-type, Methacrylic acid copolymerr S-type (PT. Waris); Isopropanolol (Merck, Pharmaceutical grades); NaOH (Merck, Pharmaceutical grades)

Test of chemical - physical properties of methacrylic acid copolymer L type and S type

Test of chemical properties (pH and acid number) and physical properties (viscosity) are perform on the copolymer solution in isopropanol. Weighed 0.5 grams of a mixture of methacrylic acid copolymer type L and type S, dissolved in a solvent mixture of 60 ml isopropanol and 40 ml of water and stirred at a temperature of 50 °C for 30-60 minutes. Measured the pH, acid number and viscosity.

The test of acid number of solution Acid Methacrylate Copolymer L type and S type measurement

The test were carried out with pH titration method by observing changes in pH and the equivalence point titration is determined by the point at the time of stepping pH were great. Volume equivalence point is calculated based on the second derivative curve. Copolymer solution in isopropanol was titrated with NaOH 0.5 N.

1 ml of 0.5N NaOH solution equivalent to 43 045 mg of methacrylic acid units.

Numbers acid = mg KOH required to neutralize the acid groups of 1 gram of dry matter

Acid number = Unit methacrylic acid x 6.517 ..... (1)

The test of the pH of methacrylic acid copolymer L type and S type

Copolymer solution in isopropanol-water (6: 4) the pH is determined by means of pH meter SCHOTT glass mainz types that have dikaliberasi CG 842 uses the standard buffer solution.

The test of solution viscosity of acid methacrylate copolymer L type and S type

Copolymer solution in isopropanol prior density is determined in the following manner: empty pycnometer weighed at a temperature of 27.5 ° C. Samples were inserted into the pycnometer to the brim and weighed at the same temperature. Density of the solution is calculated by the formula:

$$\rho = (\text{weight of pycnometer + content}) - (\text{weight of empty pycnometer}) / \text{Volume} \quad \ldots\ldots (2)$$

ρ = density of the solution (g / ml)

Viscosity test is done by means of Ostwald viscometer. Before determining the viscosity must first be determined density of the solution by using a pycnometer. The solution is passed through a pipe to r space fully occupied. The solution is sucked through the pipe b to climb over the line m. Suction is stopped and let the solution was allowed to go down to line n required for the solution to flow from line m to line n

.

$$\eta = t \times \rho \quad \ldots\ldots (3)$$

(η = viscosity (cp) ; ρ = density (g / ml))

RESULT AND DISCUSSION

In the test the acid number, obtained the largest number of acid methacrylic acid copolymers are owned by a single L-type, ie, 301.48. The combination of methacrylic acid copolymer L type with S type has the acid value is smaller than a single L-type, and most minor methacrylic acid copolymers are owned by a single S-

type, ie, 186.95. If the acid number copolymer both types are compared, then obtained the acid value of type S = 62.01% compared to the acid number of type L (Table 1). The acid number is the amount of KOH required for neutralizing the carboxylic group in the copolymer. Thus the acid number depending on the number of carboxylate groups in the copolymer. It is linear with the data content of the carboxylic group of type S (28.8%) and the type of L. (58.06%) (Attwood and Florence, 2008). The results of MANOVA analysis (α = 0.05) acid number obtained significancy price 0.00 indicating a significant difference between the acid number between formula, so necessary to test posthoc LSD. Posthoc LSD test results showed a decrease in the price of the acid number with no significant differences between methacrylic acid copolymer L type single or a combination thereof. Numbers acid copolymer L-type single and combination with S type ratio of 8: 2, did not give significant differences. Newly acquired significant differences in combination with the ratio of 6: 4. This phenomenon is caused because of methacrylic acid copolymer of S type has the acid number 62.0% compared to the L type , then in order to influence the price decrease significantly acid number, required the addition of S-type copolymer in significant amounts.

Table 1. Results of acid number measurement solution methacrylic acid copolymer L type- S type (n = 3)

Combination of Copolymer	Replication I	Replication 2	Replication 3	Average ±SD
L:S=10:0	310,21	291,57	302,65	301.48 ± 9.37
L:S=8:2	285,83	291,57	264,66	280.69 ± 14.17
L:S=6:4	254,68	249,47	243,02	249.05 ± 23.78
L:S=5:5	248,17	248,17	232,53	242.96 ± 9.03
L:S=4:6	244,78	244,26	239,45	239.45 ± 8.78
L:S=2:8	202,28	201,77	202,50	202.97 ± 1.76
L:S=0:10	192,64	181,30	186,95	186.95 ± 5.67

Differences in the number of carboxylic groups also result in differences in pH and viscosity of the copolymer. The more carboxylate, the more H + ions are removed, so that the lower pH. The pH test results methacrylic acid copolymer L type single most low- and methacrylic acid copolymer S-type single highest compared copolymer pH combination (Table 2).

Table 2. Results of pH measurement solution methacrylic acid copolymer L type-S type (n = 3)

Combination of Copolymer	Replication I	Replication 2	Replication 3	Average
L:S=10:0	3,95	4,01	4,26	4.07 ± 0.16
L:S=8:2	3,82	4,06	4,36	4.08 ± 0.27
L:S=6:4	3,96	4,15	4,45	4.18 ± 0.25
L:S=5;5	3,99	4,21	4,47	4.22 ± 0.24
L:S=4:6	3,98	4,36	4,46	4.27 ± 0.23
L:S=2:8	4,14	4,45	4,52	4.37 ± 0.21
L:S=0:10	4,21	4,59	4,61	4.47 ± 0.23

Viscosity test results obtained from the price of methacrylic acid copolymer solution viscosity lowest type L and methacrylic acid copolymer solution viscosity highest type S (Table 3). The results of MANOVA analysis (α = 0.05) obtained significancy price pH and viscosity of 0.375 and 0.369 respectively, ensuring there are no significant differences in the price of the viscosity and pH of the solution copolymers. Although acid number significant difference, but the difference was not significantly different pH, as methacrylic acid is a weak acid so that the pH value also depends on the pK and the degree of ionization, such as the following formula: $pH = pKa + Log [A^-]/[HA]$.

ISSN: 0975-8585

Table 3. Results of viscosity measurement solution methacrylic acid copolymer L type- S type (n = 3)

Combination of Copolymer	Replication I	Replication 2	Replication 3	Average
L:S=10:0	0,218	0,218	0,274	0.256 ± 0.03
L:S=8:2	0,251	0,251	0,284	0.284 ± 0.27
L:S=6:4	0,266	0,266	0,293	0.293 ± 0.25
L:S=5:5	0,268	0,268	0,297	0.297 ± 0.24
L:S=4:6	0,270	0,270	0,300	0.300 ± 0.23
L:S=2:8	0,269	0,269	0,308	0.308 ± 0,21
L:S=0:10	0,270	0,270	0,310	0.310 ± 0.23

Table 4. Recapitulation posthoc test LSD acid value methacrylic acid copolymer solution of L type and S-type on various comparison with solvent isopropanol

GROUPS	F1	F2	F3	F4	F5	F6	F7
F1		+	+	+	+	+	+
F2	+		+	+	+	+	+
F3	+	+		-	-	+	+
F4	+	+	-		-	+	+
F5	+	+	-	-		+	+
F6	+	+	+	+	+		+
F7	+	+	+	+	+	+	

CONCLUSION

An increasing proportion of acid methacrylate copolymer S type will increase the pH and viscosity and decrease the acid number of copolymer solution.

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