Synthesis and application of aqueous stomach aminoalkyl methacrylate copolymer

Liangchen Xing\textsuperscript{1}, Mengmeng Zhou\textsuperscript{2}, Xiaoqi Chen\textsuperscript{2, *}, Haijun Zhou\textsuperscript{2}, Yantao Li\textsuperscript{2}

\textsuperscript{1}Hebei University of Science and Technology, Shijiazhuang, China
\textsuperscript{2}Institute of Energy Source, Hebei Academy of Sciences, Shijiazhuang, China

*Corresponding author e-mail: cxq198508@163.com

Abstract. A series of stomach cating aminoalkyl methacrylate copolymer emulsions containing large number of tertiary amino groups in molecular side chain were prepared throughl emulsion polymerization, which take dimethylaminoethyl methacrylate, methyl methacrylate and butyl methacrylate as main raw materials. The properties of the emulsions were characterized by Fourier transform infrared spectroscopy (FT-IR) and differential scanning calorimetry (DSC). And effects of monomer mass ratio and emulsifier system on the properties of emulsions polymerization were also discussed. The results showed that the emulsion performance was stable when the amount of emulsifier was 4.5wt\% taking cationic and non-ionic composite emulsifier as emulsifying system. At the same time, it has excellent moisture resistance and stable performance when used in pharmaceutical coating materials.

1. Introduction

The pharmaceutical acrylic resins are copolymers of methacrylic acid, methacrylic acid acrylic acid, acrylate or other esters. Acrylic resin developed rapidly because it has a shorter working time, lower cost, and easier operation than natural film materials, even though it has not used as film coating materials for a long time. Due to some special properties of the drug and medical needs, some drugs must be used and absorbed in the stomach acid environment [1-3].

Thus, the stomach eating materials will be a necessity in order to avoid the release of the oral cavity, esophagus and other parts, without affecting the drug dissolution time. Dimethylaminoethyl methacrylate (DM) is an important acrylate derivative, because the molecular structure contains a tertiary amine group, which has strong hydrophilicity and has a larger swelling property in a neutral or alkaline environment. While it has little solubility and easier to soluble in weakly acidic aqueous solution. Then stomach coating materials can be prepared by using above characteristic [4-5].

In this paper, stomach cationic aminoalkyl methacrylate copolymer emulsion was prepared by conventional emulsion polymerization process, taking dimethylaminoethyl methacrylate, methyl methacrylate and butyl methacrylate as main raw materials and a tertiary amine group is introduced into the molecular chain. The effects of monomer ratio, emulsifier system and initiator system on the polymerization performance of the emulsion and the dissolution of the material in artificial gastric juice were discussed.
2. Experimental

2.1. Materials

The raw materials are as follows: Methyl methacrylate (MMA, purity >99.5%) was supplied by Shandong Chuangying Chemical Co., Ltd. Butyl methacrylate (BMA, purity >99.5%), cetyltrimethylammonium bromide (CTAB, analytically pure) and indophenol polyoxyethylene ether (OP-10, content >99%) were obtained from Tianjin Yongda Chemical Reagent Co., Ltd. Dimethylaminoethyl methacrylate (DM, purity >99.9%) was bought from Wuxi Xinyu Chemical Co., Ltd. Propylene oxypropyl alkylphenol polyether sulfate (V-20S, content 49~52%), allyl ether hydroxy phosphate (UCAN-III, content >43%) and special alkyl alcohol polyether type non-ionic (EO=40) emulsifier (EFS-4070)(content 69~71%) were donated by Shanghai Zhongyou Fine Chemical Co., Ltd. Potassium Persulfate (analytically pure) was supplied from Tianjin Bodi Chemical Co., Ltd. Deionized water was commercially available.

2.2. Preparation of pH-sensitive aminoalkyl methacrylate copolymer emulsion

The emulsifier and deionized water were added into four-necked flask with thermometer, condenser, and mechanical agitation. And the mixture of DM, MMA and BMA with a certain mass ratio was slowly added to the system. The initiator aqueous solution was added after 1 hour's pre-emulsification. Then the residual initiator is added when the temperature rises to 78~80℃. The drip acceleration is controlled by a peristaltic pump and the temperature is kept for 1 hour after the drip is added. The pH sensitive cationic aminoalkyl methacrylate copolymer emulsion with content of 30% was obtained after cooling to room temperature and filter.

2.3. Characterization

The glass transition temperature (Tg) of the aminoalkyl methacrylate copolymer was tested on differential scanning calorimeter (DSC) under nitrogen atmosphere, with heating rate of 10℃/min. The molecular structure of the aminoalkyl methacrylate copolymer was measured by Fourier transform infrared spectroscopy (FT-IR). Determination of filtrate: the prepared emulsion was filtered and dried to a constant weight (m₁) at 105℃. And the theoretical solid content is m, a product filtrate amount was (m₁/m)*100%. Determination of emulsion viscosity was tested on NDJ-79 digital rotary viscometer (test with the second unit test cartridge).

3. Results and discussion

3.1. Molecular structure of aminoalkyl methacrylate copolymer

In this paper, DM, MMA and BMA were used as main raw materials to obtain aminoalkyl methacrylate copolymer containing tertiary amino groups in the molecular chain by addition polymerization. The reaction process is shown in Fig. 1 and the FT-IR spectra of aminoalkyl methacrylate copolymer was shown in Fig. 2.

Figure 1. Synthesized procedure of aminoalkyl methacrylate copolymer
It can be seen from Figure 2, the C-H vibration characteristic absorption peaks of methyl and methylene appeared at 2953 cm\(^{-1}\), 2930 cm\(^{-1}\) and 2822 cm\(^{-1}\). And the stretching vibration peak of 1723 cm\(^{-1}\) was correspond to C=O. The vibration frequency of the C-O-C group and C-N group of the tertiary amine group were both appeared in 1210 cm\(^{-1}\)~1070 cm\(^{-1}\). And a large-area of characteristic absorption peak appears in this band region, which is caused by the overlapping of the characteristic absorption peaks of the C-O-C group and the C-N group. In addition, no absorption peak of C=C group at 1638 cm\(^{-1}\) was found.

The above data show that aminoalkyl methacrylate copolymer is successfully synthesized.

3.2. Effect of monomer mass ratio on Tg and emulsion properties of aminoalkyl methacrylate copolymer

On the premise that the DM quality remains unchanged, the effect of monomer mass ratio on Tg and emulsion properties of aminoalkyl methacrylate copolymer was investigated. And the results were shown in Fig.1 and Table.1.

**Table 1.** Effect of monomer mass ratio on emulsion properties of aminoalkyl methacrylate copolymer

| Monomer ratio m\(_{\text{DM}}/m_{\text{MMA}}/m_{\text{MBA}}\) | Tg/\(^{\circ}\)C | Viscosity/mPa.s | Filtrate/% |
|---------------------------------------------|-------------|----------------|---------|
| 6/6/0                                       | 68.37       | 274            | 0.8     |
| 6/5/1                                       | 62.15       | 222            | 0.6     |
| 6/3/3                                       | 35.20       | 151            | 0.1     |
| 6/1/5                                       | 15.40       | 293            | 0.4     |
| 6/0/6                                       | 7.12        | 703            | —       |

As shown in Table 1, when the amount of DM is constant, the Tg of the copolymer gradually increases with the increasing of amount of MMA. When mDM/mMMA/mMBA is 6/1/5 and 6/0/6, the Tg of the copolymer is 21.22\(^{\circ}\)C and 17.21\(^{\circ}\)C, respectively. Thus the products are easy to adhere to each other during storage, because the Tg is lower than room temperature When used for coating materials. While mDM/mMMA/mMBA is 6/5/1 and 6/6/0, the Tg of the copolymer is 56.01\(^{\circ}\)C and 72.95\(^{\circ}\)C, respectively. The formed film is brittle and easy to crack due to the high content of MMA in the copolymer. Thus, the plasticizer was needed to improve the flexibility and promote the spreading and mutual bonding of the copolymer emulsion on the surface of the substrate when used as coating materials,
which is favorable for the formation of the complete film. Moreover, the emulsion viscosity and product filtrate reflect the stability of emulsion properties. In Table 1, the viscosity and filtrate of the monomer ratio of mDM/mMMA/mMBA of 6/3/3 were much smaller than other ratios, and the performance stability of the copolymer emulsion was good. In summary, the monomer ratio of 6/3/3 was the appropriate proportion.

3.3. Effect of emulsifier content on emulsion properties of aminoalkyl methacrylate copolymer

After a large number of experiments, the OP-10/CTAB/EFS-4070 of mass ratio of 1/3/2.4 composite emulsification system was selected. The viscosity and filtrate of the emulsion were less when the dosage was 4.5% of the monomer. And the polymerization stability is poor when the amount is less than 4.5% of the monomer with the occurrence of demulsification, and more filtrate is produced. While more than 4.5%, the system is easier to get into agglomerate and the viscosity increased. This reson was that the emulsifier dosage is too large, and easy to produce a bridging gel effect with the water-soluble DM homopolymer, which makes the polymer particles agglomerate and destabilize. Thus the emulsion performance is stable when amount of the composite emulsion system is 4.5%.

3.4. Application test of stomach aminoalkyl methacrylate copolymer emulsions

30g of stomach aminoalkyl methacrylate copolymer emulsion and 2g of citric acid were adding into 1/2 distilled water, and stirring uniformly. Then 12g t alc powder, 4g titanium dioxide and the remaining distilled water were added into the system. The coating liquid of content of 18% was obtained after stirring uniformly and filtration. The core of the tablet is coated by a coating pan with weight gaining 4–5mg/mm². Then the sprayed tablet is dried in a drying box for 24 hours to remove the moisture. Six batches of samples were randomly selected to determine the degree of disintegration in water and artificial gastric juice, and the moisture absorption and weight gain rate of the bare film exposed to air for 60 days was also investigated.

Table 2. Application test of stomach aminoalkyl methacrylate copolymer emulsions

| sample | Disintegration | moisture resistance |
|--------|---------------|---------------------|
|        | Water/min     | artificial gastric juice/min | moisture/% | moisture after 60 days/% |
| 1      | >60           | 21                  | 5.1        | 5.5                     |
| 2      | >60           | 22                  | 5.0        | 5.2                     |
| 3      | >60           | 19                  | 5.3        | 5.4                     |
| 4      | >60           | 18                  | 5.1        | 5.4                     |
| 5      | >60           | 20                  | 5.3        | 5.5                     |
| 6      | >60           | 20                  | 5.5        | 5.7                     |

As shown in Table 2, a pharmaceutical tablet coated with a stomach aminoalkyl methacrylate copolymer has a good disintegration effect in artificial gastric juice. While the water absorption of tablets exposed to the air in the form of bare sheets increased little. Which indicate that the coating material has good moisture resistance and performance stability.

4. Conclusion

The stomach aminoalkyl methacrylate copolymer emulsion was successfully prepared Through the emulsion polymerization process, with he mass ratio of DM, MMA and BMA of 6/3/3, and OP-10/CTAB/EFS-4070 composite emulsification system of 1/3/2.4. The coating materials can be directly used for pharmaceutical preparations which has good film forming property, moisture resistance and effectively prevents the drug from being exposed to moisture and deteriorates in the air. It spend 20 minutesis to dissolved completely in artificial gastric juice, which meets the requirements of stomach polymers.
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