Preparation of the Diclofenac Sodium pH Sensitive Gel for Eyes

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Abstract: Objective: To prepare the diclofenac sodium pH sensitive gel for eyes (DS-pH sensitive gel). Methods: It’s used for the index that viscosity under non-physiological conditions and physiological conditions were less than 1100mPa·s and more than 2500mPa·s respectively, the dosage ranges of Carbopol 980 and HPMC were screened. The formula of DS-pH sensitive gel was optimized by orthogonal test. Results: The best formula contained Carbopol 980 0.35g, HPMC 1.0g, ethylparaben 0.01g, mannitol 5g, diclofenac sodium 100mg, and water for injection 100mL. Conclusion: The DS-pH sensitive gel was prepared successfully.

Keywords: Diclofenac Sodium; pH sensitive in situ gel; formula; orthogonal test

1. Introduction

Diclofenac sodium (DS) is a non-steroidal anti-inflammatory drug, with anti-inflammatory, analgesic and antipyretic effects[1]. It can be used for the treatment of acute pain and ophthalmic non-infection inflammation of the anti-infection treatment[2]. In situ gel was divided into temperature-sensitive, pH-sensitive and ion-sensitive[4]. In situ gel eye drops has longer retention time in the eyes compared with eye drops, and is easier to control the dosage compared with gels for eyes[3-5]. The Arthurs considered to prepare DS-pH sensitive gel,
which can reduce numbers of administration, and improve patient compliance.

2. Materials and methods

2.1 Materials

NDJ-1E Rotational Viscometer, pH Analyzer, Precision Analytical Balance, Diclofenac sodium, Cabopol 980, HPMC, Ethylparaben, Mannitol

2.2 Single factor screen of Carbopol 980 and HPMC dosage range

According to the results of the preliminary experiment, Carbopol 980 was weighed by 0.1 g, 0.2 g, 0.3 g, 0.4 g, 0.5 g, 0.6 g, 0.7 g, 0.8 g in the beaker for 5 hours to completely swell. The swelling Carbopol 980 will be configured for a series of Carbopol 980 solutions with a concentration of 0.1% to 0.8%. The pH of Carbopol 980 solution was adjusted to 5.0 and 7.4 with phosphate buffer. The viscosity values under both pH values were measured by NDJ-1E rotational viscometer.

The HPMC was weighed by 0.3g, 0.4g, 0.5g, 0.6g, 0.7g, 0.8g, 0.9g, 1.0g adding to the beaker with the distilled of water at 80°C and let them sit for 24 h. The Carbopol 980 was weighed with 0.35g in beaker and adding the appropriate amount of water for injection and putting it aside for 5h. The swollen Carbopol 980 was added to HPMC and formulated into a series of HPMC solution with a concentration of 0.3% to 1.0%. The pH of HPMC was adjusted to 5.0 and 7.4 with phosphate buffer. The viscosity values under both pH values were measured by NDJ-1E rotational viscometer.

2.3 Effects of Diclofenac sodium and other additives on pH-sensitive gel viscosity

The solutions that obtained by adding diclofenac sodium, 5% mannitol and 0.01% ethylparaben to the solution of Carbopol 980 / HPMC prepared by the method above-mentioned respectively. The viscosity of these solutions and its gel were measured.

2.4 Orthogonal test

According to the above results, it was confirmed that the concentration of Carbopol 980 and the concentration of HPMC had an effect on pH in situ gel. The concentration of Carbopol 980 ranged from 0.3% to 0.4%, and the concentration of HPMC ranged from 0.5% to 1.0%. The orthogonal table with 4 factors and 3 levels was selected. The viscosity was less than 1100 mPa s under non-physiological condition, the viscosity was more than 2500 mPa s under physiological condition and the retention time of gel in the eye that was the index, and the three indexes were integrated into one result.
3. Results and discussion

3.1 Results of Single factor screen for Carbopol 980 and HPMC dosage range

The effects of Carbopol 980 and HPMC on viscosity of DS-pH sensitive gel were shown in Fig.1 and Fig.2.

![Figure 1](image1.png)

**Figure 1.** The fluidity and gelling ability of different concentrations of Carbopol 980 aqueous solution.

![Figure 2](image2.png)

**Figure 2.** The fluidity and gelling ability of different concentrations of HPMC aqueous solution.

It can be concluded from Fig.1. that the fluidity and gelling capacity are more suitable when the concentration of Carbopol 980 is between 0.3% and 0.4%. But because of its large number of carboxyl groups in the molecule. It is stronger Neutralization and lead to stimulate the role of the eye tissue. It is generally not alone. So add the HPMC into a mixture to form a gel. Fig.2. shows that the concentration of HPMC ranged from 0.5% to 1.0% and combined with Carbopol 980 and its gelling capacity is appropriate.

3.2 Effects of Diclofenac sodium and Other additives on viscosity of pH-sensitive gel

The effects of Diclofenac sodium and Other additives on viscosity of pH-sensitive gel were shown in Tab.1.
Table 1. Effects of Diclofenac sodium and other additives on viscosity.

| Compositions of pH-sensitive gel | Viscosity under non-physiological condition (mPa·s) | Viscosity under physiological condition (mPa·s) |
|--------------------------------|-----------------------------------------------|-----------------------------------------------|
| Carbopol 980/HPMC              | 890                                           | 2600                                          |
| Carbopol 980/HPMC/DS           | 895                                           | 2650                                          |
| Carbopol 980/HPMC/DS/Mannitol  | 890                                           | 2600                                          |
| Carbopol 980/HPMC/DS/Mannitol/Ethylparaben | 891 | 2610 |

According to Tab.1, it can be seen that the viscosity of the blank matrix with the other additives—less than 1100 mPa s in the non-physiological condition and the viscosity is more than 2500 mPa s in the physiological condition—is closed to the viscosity of the blank matrix. Therefore, it can be concluded that other additives have less influence on the viscosity of the pH sensitive eye gel and can be ignored.

3.3 Results of orthogonal test

The results of orthogonal test were shown in Tab.2.

Table 2. Results of orthogonal test.

| Number | Factors | Content of Carbopol 980 (%) | Content of HPMC (%) | Result |
|--------|---------|----------------------------|---------------------|--------|
| 1      | 0.3     | 0.5                        | 43                  |
| 2      | 0.3     | 0.75                       | 39                  |
| 3      | 0.3     | 1.0                        | 55                  |
| 4      | 0.35    | 0.5                        | 61                  |
| 5      | 0.35    | 0.75                       | 66                  |
| 6      | 0.35    | 1.0                        | 76                  |
| 7      | 0.4     | 0.5                        | 76                  |
| 8      | 0.4     | 0.75                       | 44                  |
| 9      | 0.4     | 1.0                        | 75                  |

Mean value1 | 45.667 | 60.000
Mean value2 | 67.667 | 49.667
Mean value3 | 65.000 | 68.667
Range        | 22.000 | 19.000

According to Tab.2, it can be concluded that the range of Carbopol 980 is more than that of HPMC, so the amount of Carbopol 980 has a greater influence on the viscosity of the gel. According to mean 1, mean 2 and mean 3 can be obtained the dosage of Carbopol 980 is 0.35g and the dosage of HPMC is 1.0g. The best formula of contained Carbopol 980 0.35g, HPMC 1.0g, ethylparaben 0.01 g, mannitol 5g, diclofenac sodium 100mg, and water for injection was added to 100mL.
3.4 Discussion

Carbopol 980 is the most used pH sensitive polymer materials. It is a polyacrylic polymers. Because of the presence of a large number of carboxyl (56% ~ 58%), it can be dispersed and dissolved in water to form transparent liquid. The inorganic base or organic base can dissociate the carboxyl group to the negative charge so that the repulsive interaction on between the negative charge, resulting in the expansion and swelling of the molecular chain to form gel. The main models are Carbopol 941, Carbopol 940 and Carbopol 980. The higher concentration of the Carbopol 980 alone is too acidic to stimulate the eye and causing discomfort. Therefore, it can be used in combination with other substrates to reduce the use of Carbopol 980, and HPMC is generally used.

Cabopol 980 is not only the pH value of the gel matrix but also affects the properties of Carbopol 980. The ion strength of the medium can change the sensitivity of the Carbopol 980 gel to the pH value. When the ion intensity is large, Carbopol 980 is easy to release the proton and its pKa value decreases. At lower pH value, the solution is dissolved and the viscosity is reduced. Sodium chloride wasn’t used, because it is an ion isotonic regulator, but mannitol can be used as an isotonic modulator for DS-pH sensitive gel.

4. Conclusion

The best formula of contained Carbopol 980 0.35g, HPMC 1.0g, ethylparaben 0.01 g, mannitol 5g, diclofenac sodium 100mg, and water for injection was added to 100mL.

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