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Preparation and in Vitro Drug Release Studies of Iodine Thermosensitive in Situ Gel

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Abstrac: To investigate the preparation, dissolution and in vitro release behaviors of iodine thermosensitive in situ gel. Orthogonal test method was used to screen the best prescription. Using the formula of $Q=(W_1-W_t)/(W_1-W_0)\times 100\%$, the gel accumulative dissolution rate Q was calculated by a non-membrane model. The accumulative release rate was calculated by the standard curve. The dissolution rate and the release rate of the gel increased over time significantly. Thermosensitive in situ gel of iodine has a good sustained release effect.

Keywords: Iodine; thermosensitive in situ gel; Dissolution; Release in vitro

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1. Introduction

Periodontal diseases are chronic infectious diseases that results in the inflammation of specialized tissues that both surround and support the teeth. It can lead to a progressive loss of connective tissue attachment and alveolar bone [1]. It can cause other body tissues or organs lesions, such as cardiovascular disease, diabetes, chronic gastritis, gastric ulcer, stroke, hepatitis, nephritis, pregnancy complications, etc [2-8]. Nowadays, the narrow spectrum antimicrobial agents are used more and drug resistance is more seriously in the treatment of periodontal diseases. The iodine has a wide sterilization spectrum with strong and persistent antimicrobial activity, which can directly kill several kinds of gram positive and negative bacteria, spores and fungi [9]. Therefore, iodine agents are commonly used in local treatment of dental clinical. In situ gels refer to polymer solutions that can be administrated as liquid, and undergo a phase transition to semisolid gel upon exposure to physiological environment. Poloxamer, a non-toxic poly (ethylene oxide) /poly (propylene oxide) /poly (ethylene oxide) (PEO-PPO-PEO) triblock copolymers, plays an important role in situ gelling systems [10]. Poloxamer 407 and Poloxamer 188 were used as thermosensitive compounds in the preparing of in situ iodine gel. The thermosensitive in situ iodine gel was prepared in the People's Liberation Army 401 Hospital，and was compared with other antibiotics kinds of treating periodontitis drugs that can be sustained releasing drugs in 72h and improve the compliance of patients.

2. Methods

2.1 Material and Reagents

Poloxamer 407 and Poloxamer 188 were purchased from German BASF Company (German). The average molecular weight of Cabomer was 940, which was bought from Qingdao Tian Li Yuan Biotechnology Technology Co., Ltd. (Qingdao, China). Sodium hydroxide (purity > 96%) was provided by Shanghai Epiphanius Chemicals Limited Company (Shanghai, China).

Sodium thiosulfate standard titration solution (0.1 $mol\cdot L^{-1}$) was prepared (No. 401 Hospital of PLA, Qingdao, China). Anhydrous ether (purity > 99.7%) was provided by Sinopharm Group Chemicals Limited Company (Shanghai, China). Iodine (purity > 99.8%) was provided by Beijing Chemical Works (Beijing, China). Distilled water was used in all the experiments. All other reagents were of analytical grade.

2.2 Apparatus

FA1604 type electronic analytical balance (Shanghai Hengping Instrument and Meter Plant Co., Ltd); ZD-2A type automatic potentiometric titration (Shanghai Jinmai Instrument Co., Ltd); Digital constant temperature water bath pot (Shanghai Mei Xiang Instrument Co., Ltd).

2.3 Prescription Screening to Determine Factors and Levels

Experiments were arranged according to the L9 (34) orthogonal test table, in which Carbomer (A), Poloxamer 407 (B) and Poloxamer 188 (C) were as examine factors, and each factors arrange has three levels (Table 1). According to the design of orthogonal table, gel samples were in airtight tubes, kept in dark place, and placed in a 37 ±1℃ constant temperature water bath for 48h. The appearance, viscosity, degree of

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release and temperature of gels were observed as examining index. All items for 10 points, the rest is satisfied with 0 ~ 10 points. The range of R determines the primary and secondary factors and optimal levels.

Table1 Factors and levels of L9 (3^4) orthogonal test

Levels	Factors		
	Carbomer-940 A/%	Poloxamer 407 B/%	Poloaxmer 188 C/%
1	0.5	22	2
2	1.0	24	3
3	1.5	26	4

2.4 Preparation of in Situ Thermosensitive Iodine Gel

Poloxamer 407 and poloxamer 188 were applied adequately and dispersed in water by magnetic stirring. These poloxamers were fully swelling in 4℃ refrigerator for 48h. The iodine poloxamer solution was prepared by dissolving 0.2g iodine in anhydrous diethyl ether and then adding it into poloxamer solution with a 35℃ water bath to make anhydrous diethyl ether evaporated. Carbomer and NaOH were mixed in distilled water with the proportion of 1:0.4 as a carbomer blank gel. Poloxamer solution of iodine was added in carbomer blank gel by stirring to obtain the thermosensitive in situ gel of iodine.

2.5 The Determination of Dissolution Rate

The weight of the tube is recorded as W0, and the weight of tube which has 0.5g situ gel is recorded as W1. After precision weighing, 1ml physiological saline was slowly added in the tube with a 37±1℃ constant temperature water-bath and then separately dumped out of the upper solution in 2h, 4h, 8h, 12h, 36h, 24h and 48h. The tube was wiped with filter paper and weighed (Wt). 1ml physiological saline was rejoined in the tube and then the tube was placed in the constant temperature water bath pot. Gel dissolution rate Q was calculated by the following formula:

$$Q = (W_1 - W_t)/(W_1 - W_0) \times 100\%$$

Table 2 Orthogonal test and results

Test number	A	B	C	The comprehensive score
1	1	1	1	5.5
2	1	2	2	6.5
3	1	3	3	8.0
4	2	1	2	9.5
5	2	2	3	8.5
6	2	3	1	7.5
7	3	1	3	6.5
8	3	2	1	8.0
9	3	3	2	5.0
K1	20	21.5	21	
K2	25.5	23	21	
K3	19.5	20.5	23	
K1(average)	6.7	7.2	7	
K2(average)	8.5	7.7	7	
K3(average)	6.5	7.8	7.7	
R	2.0	0.4	0.7	

2.6 Determine the Accumulated Release Rate

Samples dissolved at different time points and were filtrated with microporous membrane filtration and abandon filtrate. Using potentiometric titration method for determination, sodium thiosulfate titrant ($0.1\ mol \cdot L^{-1}$) for titration and consumption volume was recorded. Each 1 ml sodium thiosulfate standard solution ($0.1\ mol \cdot L^{-1}$) is equivalent to 12.69mg of the I. Accumulation release percentage (ARP) was calculated as the following formula:

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ARP = (concentration of iodine released / concentration of iodine given) × 100%

3. Results

3.1 The Orthogonal Experiment Results

The range analysis showed that the contribution of factors that impact on the prescription matrix sequence was A factor> C factor> B factor (RA > RC > RB). The best formula is poloxame 407 24%, poloxamer 188 2%, carbomer-940 1% which is determined by K average (Table 2).

3.2 The Dissolution Rate of Drug Release Curve

In vitro dissolution curves of thermosensitive in situ gel of iodine was shown in Figure 1. Accumulation dissolution percentage (ADP) is as ordinate, and the time T as abscissa. The results showed that the corrosion rate of gel increased significantly with the time increasing and the release of drug was completely at the same time. It shows that the release of drug in situ gel mainly through dissolution.

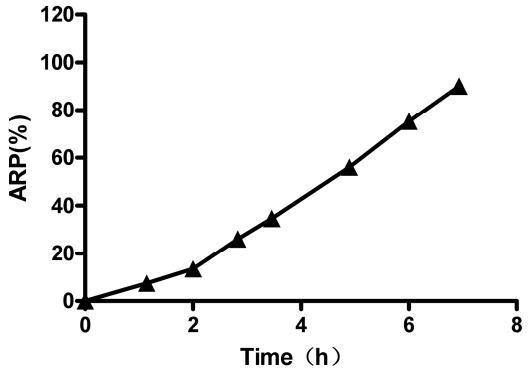

Figure 1. In vitro dissolution curves of thermosensitive in situ gel of iodine.

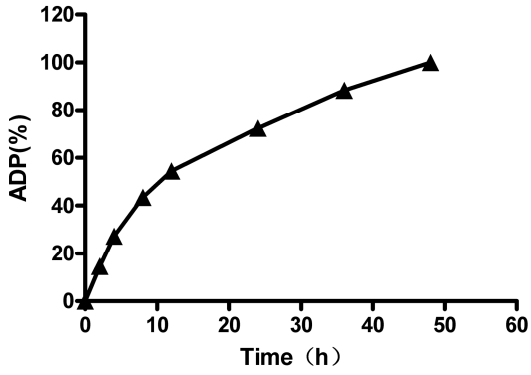

Figure 2. In vitro release curves of thermosensitive in situ gel of iodine.

3.3 The Cumulative Drug Release Curve

The cumulative release dosage was calculated at each time point, and the in vitro release curves of thermosensitive in situ gel of iodine was shown Figure 2. ARP is as the ordinate, and the time T as the abscissa. Higuchi equation of linear regression was determined: $Y = 13.628T^{1/2} - 7.8422$, $r = 0.991$, and the straight slope is the drug release rate.

4. Conclusion

Iodine does not dissolve in water, but is soluble in ether, chloroform, ethanol and other organic solvents. Ether are volatile and the boiling point is 34.6℃ which below the formation of the situ gel temperature (37℃), so ether was chose as solvent to dissolve the iodine. It was said that iodine can completely admixed with poloxamer solution [11]. The complex nature and the function are similar to povidone-iodine, and the concentration of free iodine in the poloxamer is significantly greater than povidone-iodine. In order to simulate the initial release of drug in the body, a non-membrane model [12] was adopted in this experiment. The experiment results shows: The release of situ gel mainly released by way of dissolution, the main reason is that poloxamer is the thermosensitive gel matrix, and carbomer is used for water-based gel matrix. Their surface is easy to corrosion and degradation in aqueous medium susceptible [13]. The situ gel mainly release through the dissolution way, in which drug releasing can avoid sudden release effect that may cause a sudden change of drug concentration. Studies [14] have reported that the thermosensitive in situ gel drugs release following the Higuchi equation, and the addition of carbomer can increase the viscosity of the gel which should not be corrosion, thus the thermosensitive in situ gel can reduce the drug release rate and achieve the goal of slow release.

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