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Design of astaxanthin cold application gel using hydroxy propyl methyl cellulose with superior release and antioxidant properties

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ABSTRACT

Design of astaxanthin with high antioxidant property has tremendous value for application. Herein, astaxanthin cold application gel with made by using carbomer-940 and hydroxy propyl methyl cellulose (HPMC), and the most important component contributed to HPMC. Since the gel matrix carbomer-940 and HPMC could change the drug release pattern and improve the in vitro release of the drug, in vitro release of astaxanthin can be improved and the antioxidant property of astaxanthin turned out to be significantly high due to the gel matrix. The optimal prescription of astaxanthin cold application gel was obtained by screening the types and dosages of carbomer-940 and HPMC through in vitro release, antioxidant experiment and viscosity experiment and the final dosage of HPMC-K4M was 0.2 g and carbomer-940 was 0.1 g. Therefore, it can be known that astaxanthin cold application gel is an effective strategy to enhance astaxanthin properties.

1. Introduction

Aging is a gradual, cumulative and natural phenomenon [1]. The essence of aging is the gradual and natural degradation of cells, tissues and organs of living organisms under the stimulation of many internal and external factors, which occurs with the increasing age [2]. In modern medical research, the prevention and control of aging is still a difficult issue and many scientists have made a lot of efforts for this purpose. Scientists have found that the mechanisms of aging mainly include the free radical theory, cross-linking theory, mitochondrial DNA damage theory, biofilm damage theory, chromosome mutation theory, genetic program theory, error theory, immune theory and endocrine theory, etc. At present, the results of studies on free radical damage to cellular macromolecules DNA, proteins and lipids, as well as information from energy metabolism tests and transgenic animal tests support the idea that oxidative damage is a direct cause of the aging process. Therefore, the study of antioxidants is of great importance for the prevention of aging. Antioxidants include anti-aging drugs for their ability to scavenge free radicals and prevent biofilm damage by free radicals [3]. Currently, commonly used antioxidants include vitamins, trace elements, complexes and enzymatic antioxidants [4–6].

Studies have shown that astaxanthin is by far the better antioxidant found in nature [7]. Astaxanthin, also known as astaxanthin and lobster shell pigment, is a red natural carotenoid, a major carotenoid present in marine organisms, which is widely used in biological applications, especially in shrimp, salmon, yeast and algal bodies. The chemical name of astaxanthin is 3, 3′-dihydroxy-4, 4′-diketonyl-β, β'-carotene, with the molecular formula $C_{40}H_{52}O_4$ and relative molecular mass of 596 [8]. The molecular structure of astaxanthin has a long chain of conjugated double bonds with unsaturated ketone groups and hydroxyl groups at the end of the conjugated double bond chain and the ketone groups and hydroxyl groups form α-hydroxy ketones [9,10]. All these structures have a more active electronic effect and can attract free radicals or provide electrons to free radicals for the purpose of scavenging free radicals [11,12]. Astaxanthin has the ability to scavenge free radicals produced by UV irradiation and to reduce photochemical damage to organisms, acting as a deterrent to photoaging of the skin [13]. However, the unstable nature of astaxanthin, its poor solubility in water, low in vitro release and susceptibility to oxidation make astaxanthin extremely limited in its application and it is particularly important to select a suitable formulation technology to broaden the application of astaxanthin.

Therefore, in order to solve the problems of astaxanthin's susceptibility to oxidation and low in vitro release, we need to find drug carriers

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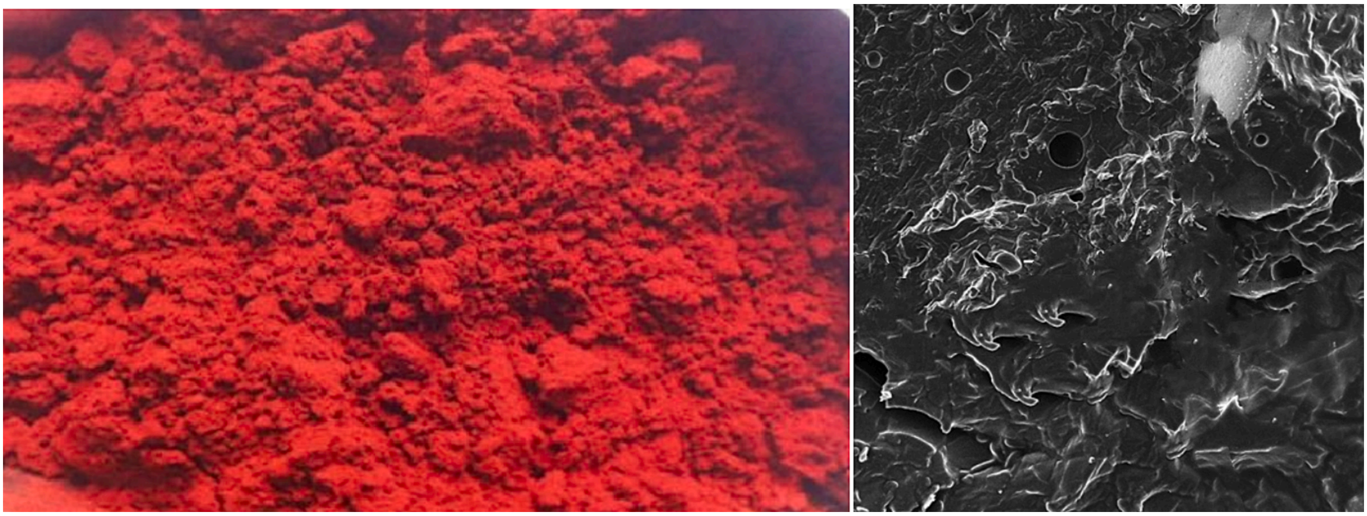

Fig. 1. A, astaxanthin powder; B, astaxanthin cold application gel was imaged under 10 × 50 times biological microscope.

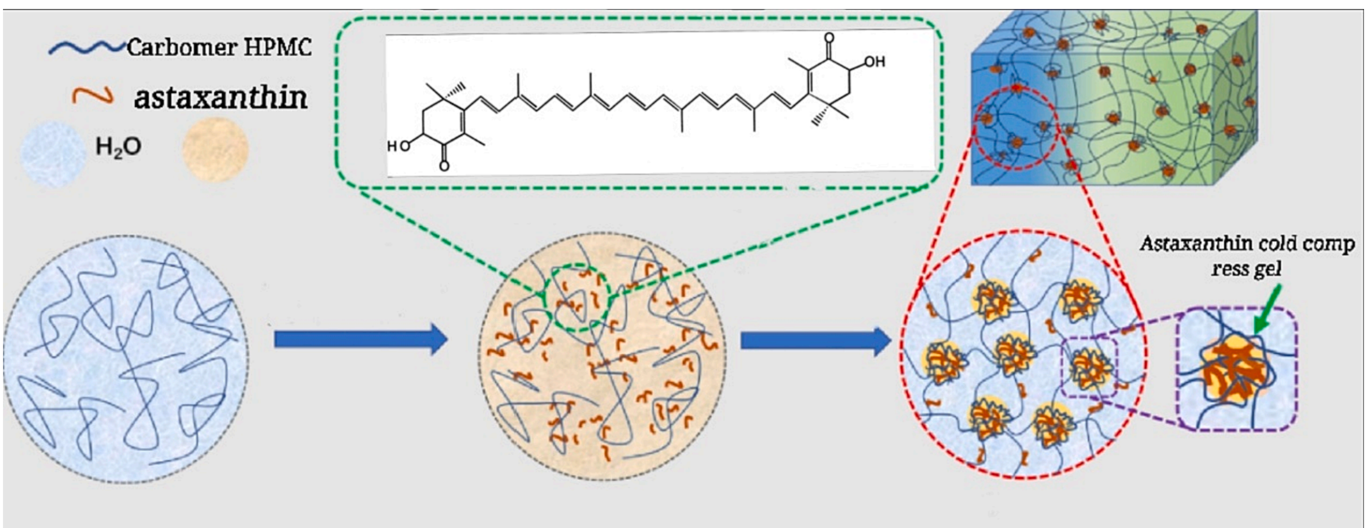

Fig. 2. The formation process of astaxanthin cold application gel.

to solve these problems. Gel is a new type of hospital formulation developed in recent years to meet clinical needs, which has the effect of increasing the local drug concentration and prolonging the release or diffusion process of the drug. It has the characteristics of higher bioavailability, better stability and less adverse reactions than other dosage forms [14]. We selected carbomer as main gel matrix because carbomer was water-soluble matrix and the used astaxanthin (purchased as modified astaxanthin) belonged to water-soluble. Carbomer-940 as a gel matrix for formulations is compatible with many other drugs used as excipients and is a good pharmaceutical excipient [15]. Carbomer-940 as a water-soluble gel matrix has the advantages of good permeability, fast onset of action, long duration of action, non-greasy feeling, non-irritation, easy to apply and good skin coupling [16]. HPMC has the advantages of cold water solubility, chemical inertness, stability, viscosity adjustability, metabolic inertness and safety [17,18,33]. It can be used as film coating material and film-forming material, as binder and disintegrant, suspending aid, blocking agent, slow and controlled release agent, porogenic agent, thickening agent and protective gel for colloids, capsule material, bio adhesive agent, as gel for topical use and as precipitation inhibitor for self-microemulsifying systems. Herein, HPMC was added as matrix to regulate drug release owing to its ability to impact viscosity of system.

Through the screening of carbomer-940 and HPMC, we can know that different types and dosages of HPMC change the drug release patterns of carbomer gel matrix and have an effect on drug release behavior faster release rate and higher release. Anhydrous ethanol is a volatile liquid and according to physics, the evaporation of liquid will take away heat and the vaporization of water and natural ingredients contained in the polymer gel will also take away heat. The effect of peppermint oil on the stimulation of cold sensory receptors of the skin and the constriction of capillaries can achieve local cooling and the effect of cold application [19]. In this study, astaxanthin was made into cold application gel to increase the in vitro release of the drug as well as to improve the antioxidant capacity of the drug as the focus of the study so that the drug can work more effectively [20]. Through the examination of in vitro release test, antioxidant test and gel viscosity test, the cold application gel of astaxanthin with high in vitro release and good antioxidant property was prepared for the purpose of anti-aging.

2. Materials and methods

2.1. Materials

Astaxanthin was purchased from Kunming Baiou Microalgae

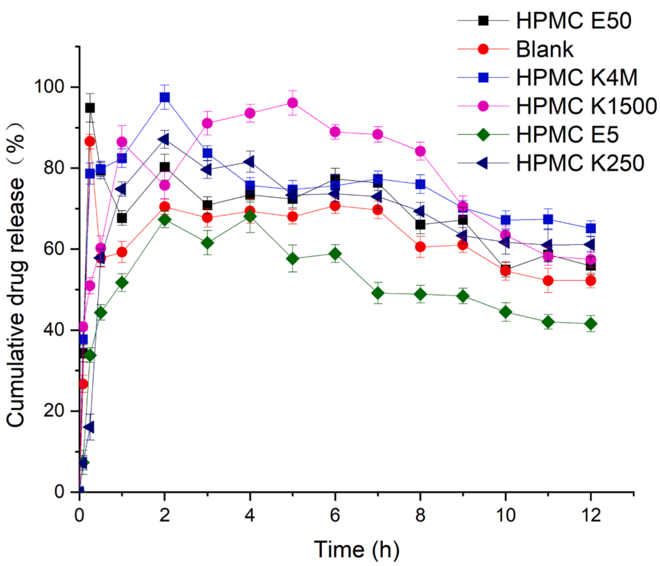

Fig. 3. Drug release curve of astaxanthin cold application gel with different types of HPMC.

Table 1
Viscosity of different types of HPMC in astaxanthin cold application gel.

Prescriptions	Viscosity (Pa.s)			Average Viscosity (Pa.s)
1	5.79	5.32	5.09	5.40
2	2.80	2.80	2.78	2.79
3	22.43	22.09	21.95	22.16
4	6.34	6.40	6.07	6.27
5	20.01	20.43	20.43	20.29
6	2.25	2.07	2.45	2.26

Technology Ltd (China). Carbomer-940, propanetriol, triethanolamine, butyl nipagin, menthol, tween- 80, anhydrous ethanol, DPPH (2, 2-biphenyl-1-bitter hydrazinyl), astaxanthin oil were bought from local companies in China. HPMC of different types HPMC-K1500 (295 kDa), HPMC-K250 (196 kDa), HPMC-K4M (500 kDa) and HPMC-E5 (3 kDa) were provided by Roche Reagent Company (China). Diverse molecular mass can be their main difference.

2.2. Methods

2.2.1. Preparation of astaxanthin cold application gel

Carbomer-940 was weighed and placed in a beaker, to which water was added and stirred thoroughly with a glass rod. HPMC and water were then added to the beaker and stirred thoroughly. It was allowed to stand overnight to swell sufficiently. 0.0045 g nipagin butyl ester, 0.09 g tween-80 and 2.00 g propanetriol was added to this beaker and stirred with a glass rod to allow it to dissolve. 0.045 g astaxanthin was added to the beaker, water was added, stirred with a glass rod and allowed to dissolve. Then 4 mL anhydrous ethanol and 0.04 g peppermint oil were added to the beaker, stirred thoroughly and water was added to bring the total mass to 15 g. The pH of the gel was adjusted to 5.5 ~ 6.5 with triethanolamine, stirred thoroughly and air bubbles were removed with ultrasound. The beaker was sealed and stored in the refrigerator for 24 h to obtain astaxanthin cold application gel.

2.2.2. In vitro release test

3 g of astaxanthin cold application gel with 100 mL of pH 7.4 phosphate buffer was loaded into a 100 mL flask and placed in a water bath with working conditions of temperature 37 °C and speed 100r/min at 5 min, 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 11 h, 12 h respectively with 5 mL of sample was aspirated by syringe (SYWF-50 Water Bath Thermostat Oscillator, Tianjin Letrai Instrument and Equipment Co, China). The samples were sampled and supplemented with equal amounts of pH 7.4 phosphate buffer solution and the absorbance of each sample was measured at 510 nm (UV-2600 Ultraviolet Spectrophotometer, Shimadzu Instruments Co, China) and the dissolution curves were plotted to calculate the cumulative in vitro release rate.

2.2.3. Viscosity measurement

The experimental setup was as shown in Fig. 6 using a 10 mL measuring cylinder with inner diameter D = 1.15 cm, l = 6 cm and H was the height of 8 cm liquid column. Astaxanthin cold application gels of different HPMC types were injected into the measuring cylinder with the liquid surface about 10 mm above the upper scale L_1 and the small steel ball sphere was gently placed on the liquid surface to record the time used between L_1 and L_2 in the sinking process of the steel ball and the viscosity was calculated according to the formula. (ρ' was the density

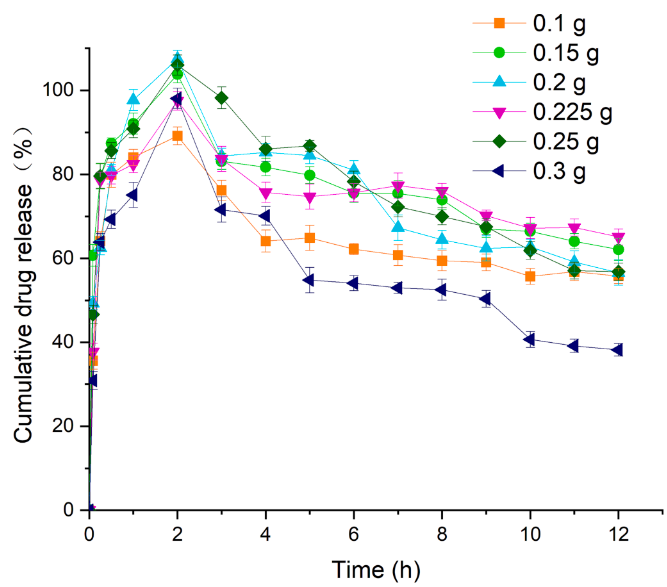

Fig. 4. Drug release curve of astaxanthin cold application gel with different dosages of HPMC-K4M.

Table 3
Viscosity of different dosages of HPMC-K4M in astaxanthin cold application gel.

Prescriptions	Viscosity (Pa.s)			Average Viscosity (Pa.s)
7	16.45	15.78	16.98	16.40
8	22.65	23.56	21.45	22.56
9	30.42	30.78	30.89	30.70
10	40.56	42.54	41.68	41.60
11	55.89	54.30	58.35	56.18
12	72.65	74.86	73.10	73.54

Table 2
Antioxidant properties of different types of HPMC in astaxanthin cold application gel.

Prescriptions	1	2	3	4	5	6
Inhibition rate	47.32 %	65.98 %	48.59 %	40.07 %	55.56 %	38.34 %

Table 4
Antioxidant properties of different dosages of HPMC-K4M in astaxanthin cold application gel.

Prescriptions	7	8	9	10	11	12
Inhibition rate	54.92 %	58.72 %	88.55 %	44.91 %	67.88 %	41.34 %

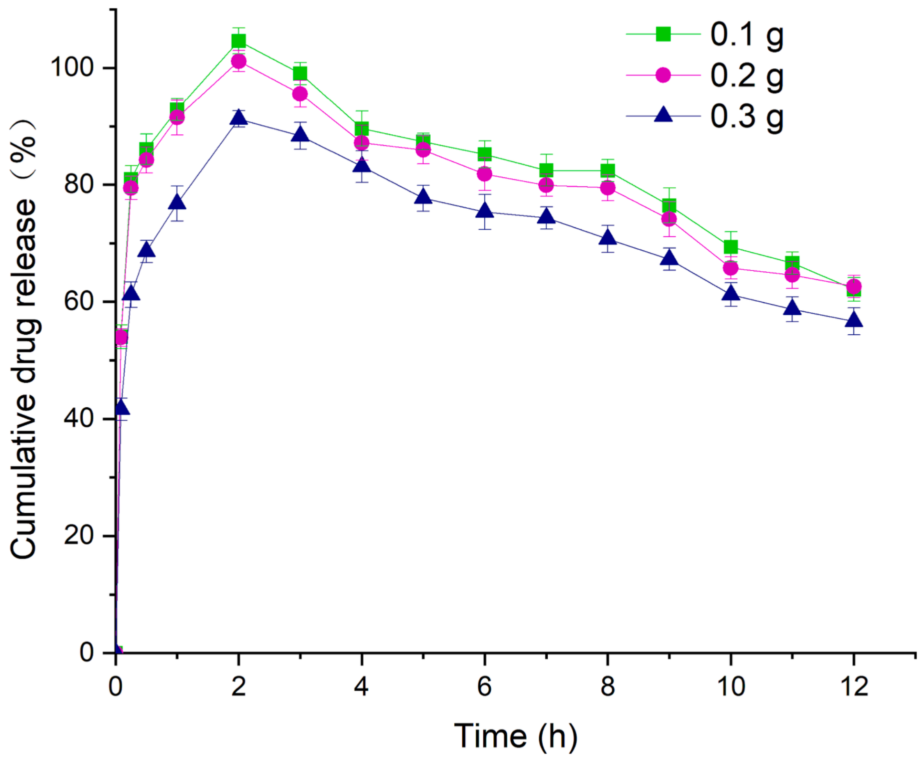

Fig. 5. Drug release curve of astaxanthin cold application gel with different dosages of Carbomer-940.

of the steel ball (kg/m^3), ρ was the density of the gel (kg/m^3), d was the diameter of the steel ball (m), D was the radius of the cylinder (m), t was the falling time (s), l was the length of the test section (m), g was the acceleration of gravity 9.8, η was the viscosity (Pa. s))

$$\eta = \frac{(\rho' - \rho)gd^2t}{18l} \times \frac{1}{\left(1 + 2.4\frac{d}{D}\right) + \left(1 + 1.6\frac{d}{H}\right)}$$

2.2.4. Anti-oxidation experiment

0.004 g of DPPH powder was weighed and fixed in a 100 mL brown volumetric flask with anhydrous ethanol, which could yield 0.1 mmol/L of DPPH solution and the above solution was kept in a dark place and set aside. 0.2 mL of astaxanthin cold application gel was added to 2.8 mL of DPPH reagent, shaken well, placed for 30 min (room temperature) and the absorbance value Ai of the above solution was measured at 517 nm; the absorbance value Ac of the mixture of 2.8 mL of anhydrous ethanol was added to 2.8 mL of DPPH reagent was also measured and then the absorbance value Aj of the mixture of 0.2 mL of astaxanthin cold application gel and 2.8 mL of anhydrous ethanol was measured[21,22]. To compare anti-oxidation ability of astaxanthin cold application gel with other published astaxanthin gels, and the obtained results were shown in supporting information.

DPPH inhibition rate was expressed as follows:

Inhibition rate = [1-(Ai-Aj)/Ac] × 100 %

3. Results and discussion

3.1. Formation of astaxanthin cold application gel

As shown in Fig. 1, 10x50 microscopic image of the cold application gel was observed by electron microscopy and the gel showed a honeycomb shape (B302 Biological Microscope, Chongqing Aote Optical Instrument Co, China). As shown in Fig. 2, the gel matrix was added to water, to which astaxanthin was added afterwards and finally the astaxanthin cold application gel was formed. As shown in Fig. 7, the astaxanthin cold application gel showed a red color and was applied to the skin without residue, irritation and easy application.

3.2. Screening of different HPMC types

In vitro release test as seen in Fig. 3, the release at 2 h of prescription 3 was significantly higher than the release of prescription 4(96.77 %), prescription 1(70.43 %), prescription 5(75.75 %), prescription 2(67.28 %) and prescription 6(80.24 %)[23]. In the anti-oxidation experiment as seen in Table 2, the antioxidant property order from strong to weak was: prescription 2(65.98 %) > prescription 5(55.56 %) > prescription 3 (48.59 %) > prescription 1(47.32 %) > prescription 4(40.07 %) > prescription 6(38.34 %)[24]. In the viscosity measurement as seen in Table 1, through a comprehensive examination of the gel viscosity of different types of HPMC, the viscosity of prescription 3(22.16 Pa.s) was greater than the viscosity of prescription 5(20.29 Pa.s), prescription 4 (6.27 Pa.s), prescription 1(5.40 Pa.s), prescription 2(2.79 Pa.s) and prescription 6(2.26 Pa.s). Due to the different HPMC types, it can be learned that in screening the HPMC types, the higher the viscosity, the

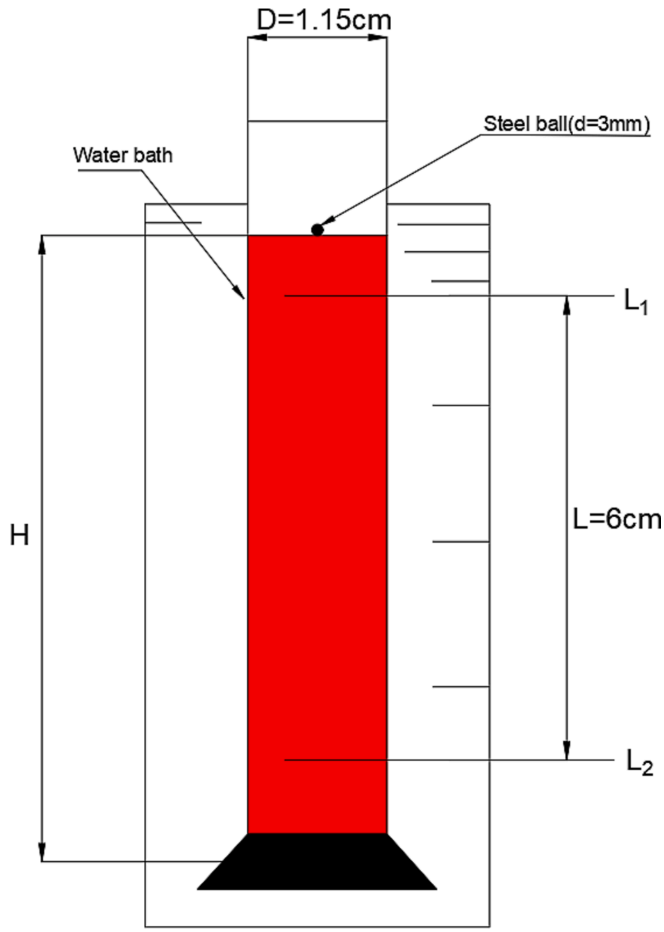

Fig. 6. Diagram of experimental device for measuring viscosity.

relatively higher the in vitro release at 2 h [25]. Therefore, from the above experiments, it can be seen that in screening of HPMC types of astaxanthin cold application gel, the antioxidant property of prescription 3 was lower than prescription 2 and prescription 5 but in vitro release and viscosity of prescription 3 within 2 h was significantly higher than prescription 2 and prescription 5. Therefore, HPMC-K4M was selected as the best excipient in screening of HPMC types of astaxanthin cold application gel. By comparing different types of HPMC and astaxanthin cold application gel without HPMC, it was known that HPMC influenced the drug release behavior and increased the drug release. When gel matrices HPMC-E5, HPMC-E50 and HPMC-K250 were used, they had a lower effect on drug release within 2 h than HPMC-K4M and poor subsequent release stability. In addition, although HPMC-K1500 has high release in astaxanthin cold application gel, its maximum release time was too long for practical application. For these reasons, the gel matrix HPMC-K4M was selected as the best gel matrix for astaxanthin cold application gel.

3.3. Screening of different HPMC dosages

In vitro release test as seen in Fig. 4, in vitro release at 2 h of astaxanthin cold application gel prescription 9 was 107.50 %, which was significantly higher than the in vitro release rate of 89.17 % for prescription 7, 103.80 % for prescription 8, 97.49 % for prescription 10, 106.01 % for prescription 11 and 98.09 % for prescription 12[26]. The gel matrix HPMC affected the release of astaxanthin cold application gel by screening different amounts of HPMC-K4M. The highest in vitro release at 2 h and stable subsequent release were observed when the amount of assisted gel matrix HPMC-K4M was 0.2 g. In the anti-oxidation experiment as seen in Table 4, the anti-oxidant property of prescription 9 was 88.55 %, which was significantly higher than the anti-oxidant property of 67.88 % for prescription 11, 58.72 % for prescription 8, 54.92 % for prescription 7, 44.91 % for prescription 10, 41.34 % for prescription 12. In summary, prescription 9 with HPMC-K4M dosage of 0.2 g, had the best antioxidant property. In the viscosity experiment as seen in Table 3, the viscosity order was prescription 7 (16.40 Pa.s) < prescription 8(22.56 Pa.s) < prescription 9(30.70 Pa.s) < prescription 10(41.60 Pa.s) < prescription 11(56.18 Pa.s) < prescription 12(73.54 Pa.s). Through the screening of different dosages of HPMC-K4M, it can be learned that the viscosity was relatively small, the in vitro release at 2 h was relatively high, the viscosity was small and the retention time was less, which was beneficial to the practical application [27]. Therefore, in the above series of experiments for screening the dosage of HPMC-K4M in astaxanthin cold application gel, the astaxanthin cold application gel of prescription 9 had highest antioxidant and in vitro release properties, and it also possessed moderate viscosity, easy

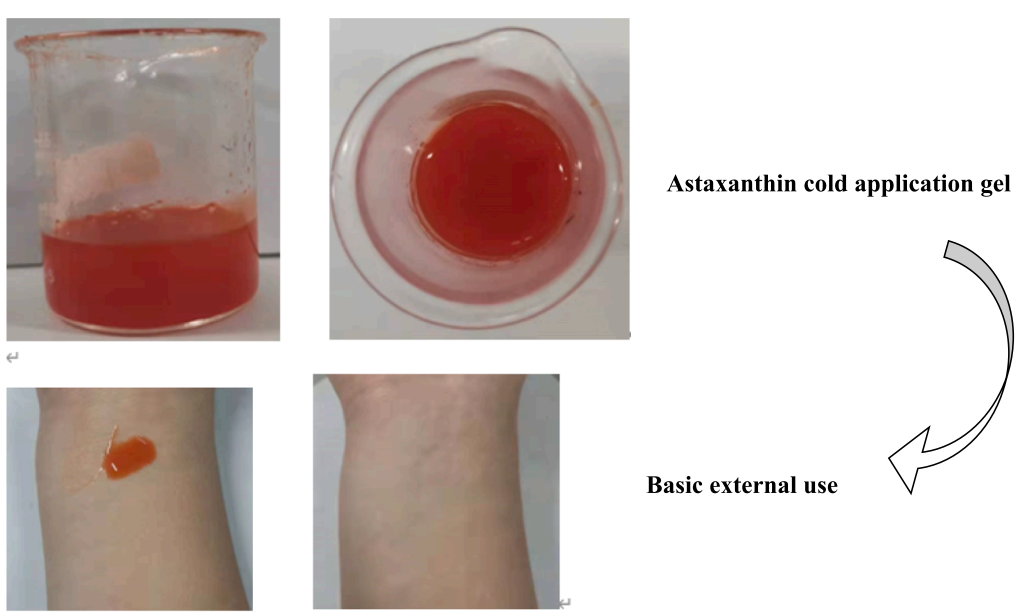

Fig. 7. Astaxanthin cold application gel and basic external use.

Table 5
Prescription of different dosages of carbomer-940 in astaxanthin cold application gel.

Prescriptions	HPMC-K4M (g)	Astaxanthin (g)	Carbomer-940 (g)	Glycerol (g)	Tween-80 (g)	Butyl nipagin (g)	Peppermint oil (g)	Ethanol (mL)
13	0.2	0.045	0.1	2	0.09	0.0045	0.04	4
14	0.2	0.045	0.2	2	0.09	0.0045	0.04	4
15	0.2	0.045	0.3	2	0.09	0.0045	0.04	4

Table 6
Viscosity of different dosages of carbomer-940 in astaxanthin cold application gel.

Prescriptions	Viscosity (Pa.s)			Average Viscosity (Pa.s)
13	5.98	5.69	5.98	5.89
14	15.48	16.32	13.97	15.26
15	22.98	23.05	25.69	23.91

Table 7
Antioxidant properties of different dosages of carbomer-940 in astaxanthin cold application gel.

Prescriptions	13	14	15
Inhibition rate	95.57 %	73.00 %	79.27 %

application and no color residue. Therefore, the dosage of HPMC-K4M was determined to be 0.2 g.

3.4. Screening of different carbomer-940 dosages

In vitro release text as seen in Fig. 5 and Table 5, the in vitro release of prescription 13 (104.63 %) was higher than the in vitro release of prescription 14 (101.17 %) and prescription 15 (91.22 %). By screening the amount of carbomer-940, the highest in vitro release at 2 h and smooth subsequent release were observed when the amount of carbomer-940 was set at 0.1 g[28]. In the antioxidant experiment as seen in Table 7, the highest antioxidant property of 95.57 % was obtained for the astaxanthin cold application gel of prescription 13, which was significantly higher than prescription 15 (79.27 %) and prescription 14 (73.00 %). It can be known that the best antioxidant property was obtained when the amount of carbomer-940 was 0.1 g[29]. In the viscosity experiment as seen in Table 6, the viscosity of prescription 13 (5.89 Pa.s) was lower than the viscosity of prescription 14(15.26 Pa.s) and prescription 15(23.91 Pa.s). It was clear from the above experiments that the lower the viscosity, the lower the in vitro release. Therefore, the optimal amount of carbomer-940 was a low dosage of 0.1 g. As seen in Table 7, in the above mentioned experiments for screening the amount of carbomer-940 in astaxanthin cold application gel, it can be concluded that the amount of astaxanthin cold application gel with carbomer-940 of 0.1 g had better antioxidant properties and in vitro release. As seen in Table 8 and Table 9, the antioxidant properties of water-soluble astaxanthin cold application gel and oil-soluble astaxanthin cold application gel were tested and the antioxidant property of prescription 16 (95.57 %) turned out to be greater than the antioxidant property of prescription 17(52.10 %). The antioxidant properties of water soluble astaxanthin cold application gel were superior to oil-soluble astaxanthin cold application gel. From the above, it can be seen that the matrix of astaxanthin cold application gel could change the drug release behavior, increase the drug release and improve the antioxidant property of astaxanthin.

3.5. The advantage of presented astaxanthin cold application gel

To study the advantage of presented astaxanthin cold application gel compared to reported astaxanthin gel, antioxidant experiment was conducted. Herein, published astaxanthin gel 1[30], published astaxanthin gel 2 [31] and published astaxanthin film [32] were prepared according to each report. The results revealed that the optimized astaxanthin cold application gel possessed highest antioxidant ability, which turned out to be its obvious advantage for anti-aging application.

4. Conclusion

The results came from in vitro release test, antioxidant test and viscosity test on astaxanthin cold application gel showed that the application of HPMC-K4M with dosage of 0.2 g and carbomer-940 with dosage of 0.1 g can be the optimial gel matrix for astaxanthin cold application gel with the best in vitro release and highest antioxidant properties. The gel matrix carbomer-940 and HPMC improved the in vitro release and antioxidant household properties of astaxanthin cold application gel. It solved the current problems of low in vitro release and relatively poor antioxidant properties of astaxanthin and provided partial data support for the anti-aging process of astaxanthin, which has tremendous value for the development of newly designed astaxanthin products.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Table 9
Antioxidant properties of water-soluble astaxanthin cold application gel and oil-soluble astaxanthin cold application gel.

Prescriptions	16	17
Inhibition rate	95.57 %	52.10 %

Table 8
Prescription of water-soluble astaxanthin cold application gel and oil-soluble in astaxanthin cold application gel.

Prescriptions	Astaxanthin types	Astaxanthin (g)	HPMC-K4M (g)	Astaxanthin (g)	Carbomer −940 (g)	Glycerol (g)	Tween-80 (g)	Butyl nipagin (g)	Peppermint oil (g)	Ethanol (mL)
16	Water-soluble	0.045	0.2	0.045	0.1	2	0.09	0.0045	0.04	4
17	Oil-soluble	0.045	0.2	0.045	0.1	2	0.09	0.0045	0.04	4

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mseb.2023.116982.

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