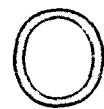

A review of pharmaceutical polymeric controlled-release membranes

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Pharmaceutical polymeric controlled-release membranes have caught many researchers' attention because of the rapid development of controlled-release preparations. Several researchers investigated the controlled-release polymeric membranes from various points of view. The present article reviews the progress in the studies of membrane-forming materials, methods of preparation and mechanical properties of the controlled-release membranes. The main purpose of this review is to provide foundations for drug release mechanism investigation and formulation design of membrane controlled-release formulations.



ONE of the purposes for the development of controlled-release (CR) preparations is to find a way to obtain ideal blood drug concentration. Many pharmaceutical researchers have done excellently in this domain. Nowadays a lot of CR products, such as matrix tablets, osmotic pumps, transdermal drug delivery systems and so on, have been developed and appeared on the market. Among all these preparations controlled-release membrane preparations (CRMP), whose drug release rate are controlled mainly by membranes coating the solid cores outside, are regarded as an excellent CR dosage form. Coated granules, coated pellets and coated tablets can all be classified into this division. During the past decade CRMP developed rapidly and has become more and more important. Along with the increasing importance of CRMP, pharmaceutical polymeric CR membranes have caught many researchers' attention. Several efforts have been launched to investigate the novel properties of pharmaceutical CR membranes. The present article reviews various techniques for preparing CR membranes, different membrane-forming materials and investigation methods for the physico-chemical properties of CR membranes.

Membrane-forming materials

The drug release rates of CRMP are mainly controlled by the polymeric membranes coating the solid cores outside. Therefore, the structure and properties of the polymer, which forms the CR membrane, directly affect the drug release rate of the preparation. Although several polymers have been widely used to produce CR membranes for a long time, many new polymers are put into use in this field.

Ethylcellulose (EC) perhaps is the earliest polymer used in the development of CRMP¹. It is prepared by reacting alkali cellulose (obtained by treating crude cellulose with an alkaline solution) with ethyl chloride and actually is a cellulose ether compound. The EC which is used as membrane-forming material has an ethoxyl content of 48.2 ~49.5 and can be graded according to its viscosity². Organic solvents are usually used in the coating process for EC, however, because of the toxicity and expensiveness of solvent EC aqueous latex has been employed in coating process for many years. Aquacoat[®] and Surelease[®] are the two popular aqueous latex systems that are widely used in CRMP^{3,4}.

Another polymer used in marking CRMP is cellulose acetate (CA). According to its acetyl content, CA can be divided into several groups. The water permeability of CA is decreased dramatically along with increasing acetyl content. With the excellent film-forming ability in organic solvents such as dichloro methane and dimethyl acetone, CA is widely used in chemical industry. To prepare osmotic pumps is the main application of CA in pharmaceuticals⁵⁻¹⁰. By adjusting the ratio between CA and other film-forming materials, various CR membranes with different permeability can be obtained. Although many difficulties are encountered in preparing water-permeable membranes from CA latex, it still has found extensive application in the development of CRMP^{11,12}.

Acrylate resin can also be a film-forming material for CRMP¹³⁻¹⁶. Actually, acrylate resin is a mixture consisting of methacrylate, acrylate and methacrylic acid. In accordance with their different solubility acrylate resin may be divided into three groups, the gastric-soluble, the enteric-soluble and the osmotic permeable. So it can be used to prepare CRMP with various purposes. The fact that osmotic pumps coated with acrylate/methacrylate copolymer latex been reported demonstrates the excellent application of acrylate latex in CRMP^{17,18}.

In addition to the three main polymers mentioned above, cellulose hydrogen phthalate and ethylene vinyl acetate have also been tried to make CRMP^{19,20}.

Membrane-coating solvents

Because of the polymers' special physico-chemical properties and uncommon technology requirements of CRMP organic solvents are required in membrane coating process. However, the toxicity and high cost curtail the application of the organic solvents in coating process. More than a decade ago, aqueous latex coating emerged and arose the interest of many pharmaceutical researchers^{21,22}. Many reports dealing with the latex coating have been published and two membrane-forming mechanism were established by Bindschaedler et al.²³ and Guo et al.²⁴ respectively.

Aqueous coating technique found extensive application in CRMP for abandoning organic solvents. CA, EC and acrylate resin aqueous latex have been used in preparing osmotic pumps, controlled-release pellets and other

MCRP^{25,26}. But some unavoidable problems still remain in latex coating techniques such as the weak mechanical property of latex membrane, drug release rate influenced by additives in aqueous polymer latex and so on. Several workers investigated these problems deeply and pursued the solution^{27,28}. The appearance of osmotic pump coated with acrylate resin latex is the mark of success in solving the mechanical strength problem of aqueous latex¹⁸, since osmotic pump requires the outer membrane be strong enough to stand high osmotic pressure inside the membrane. But it is too early to say that we can make the aqueous latex coating perfectly suitable for developing CRMP.

The study of physico-chemical properties of CR membranes

The physico-chemical properties of the CR membranes affect the drug release rate from CRMP and the drug release mechanism directly. Therefore the research work in this field is the core of the total study of CR membrane.

1. The preparation of model membranes

Model membranes are the membranes that simulate the CR membranes coated outside the drug granules, pellets or tablets. The model membrane and the actual CR membrane should be produced from the same polymer or polymers. Casting method, which appeared in 1960s, is an old method for preparing model membranes. This method is still used in making model membranes for the research purpose²⁹. Lindstedt et al.³⁰ reported that polymer solution could be sprayed onto the rotating disk to make model membrane. In order to get the most comparable model membrane, sodium chloride tablets with a radius of 10 to 20 mm were prepared. The tablets were placed in a coating pan and coated with film-forming polymer solution following the actual coating process. Then the membranes coating outside the tablets could be stripped off. This method conformed to the real coating process but specific techniques are required in studying the mechanical properties of such small membranes.

2. Permeability of CR membranes

Permeability of CR membrane is described as the membrane penetration coefficient of certain drugs in water. Drug release rate of CRMP is objectively controlled by the

permeability of CR membrane. Horizontal diffusion cells are employed to detect the permeability of CR membrane so that gravity effect can be excluded¹³. During experiment, drugs are introduced into one cell and samples are taken from the other cell at certain time points. According to the Fick's law, the penetration coefficient of the drug to the membrane can be obtained.

3. Factors influencing the permeability of CR membranes

Film-forming materials, plasticizers, pore-forming reagents, dissolution media and coating solvent can all affect the permeability of the CR membranes to a certain extent respectively.

Film-forming materials play an important role in CRMP. Under the same film-forming conditions, EC has lower permeability than CA. Lindstedt et al.³⁰ reported that the water permeability of EC was only 1/10 of that of CA under the same condition. The reason for the dramatically small permeability was attributed to the specific structure and physico-chemical properties of each polymer. Additionally, it is well known that the solubility of acrylate resin is dependent on the pH of the environment.

Plasticizers exert magnificent influence on the permeability of CR membranes^{4,32}. The permeability may vary with the plasticizer type and different amount of the plasticizer. Saettone et al.³³ reported that the permeability of EC decreased with the increment of the amount of plasticizer added into the CR membrane. They prepared theophylline pellets coated with EC plasticized by acetylated monoglycerides, diethyl phthalate, dibutyl phthalate and dibutyl sebacate. The amount of plasticizer varied from 8 to 30%. The results showed that the presence of plasticizer decreased the permeability of the CR membrane. But the tendency to decrease became ambiguous when the amount of the plasticizer reached a certain level. Hutchings and Sakr²⁶ indicated that the permeability of the CR membrane coated with EC, which is plasticized with dibutyl adipate, showed no significant increase in 0.1 M hydrochloride solution while the level of plasticizer increased from 30 to 35%. This phenomenon also occurred when diacetyl hexate was used as a plasticizer. Perhaps the effect of plasticizer on permeability is saturated.

The permeability of CA membrane also associates with the amount of plasticizer. Guo studied the permeability of CA CR membrane plasticized by triacetin glycerin and three polyvinylalcohols with different molecular weight³⁴. He reported that the water permeability of CA CR membrane decreased with increasing plasticizer content, however, the relationship would not hold well if the amount of plasticizer reached a certain level. This would be attributed to the antiplasticization effect of the plasticizer at lower level. The mobility of polymer would be more active under the lower level of plasticizer. When the environment temperature reached the glass transition temperature (T_g) of the polymer, the antiplasticization effect disappeared.

Pore-forming materials are usually added into the coating solution in order to increase the permeability of the CR membrane. These substances include small molecular weight substance, such as urea, sorbitol and glycerin, or water-soluble polymer, such as hydroxypropyl methyl cellulose (HPMC), so drug release rate can be regulated significantly by adding pore-forming material to the CR membranes^{1,17}. However, we should pay attention to the study of Gunder et al.³⁵ who investigated the permeability of EC CR membrane containing HPMC. He indicated that when temperature fell below the minimum membrane-forming temperature, HPMC had the tendency to form membrane again and drug release rate could be reduced by the film-forming tendency. The character of CR membrane formed by more than one polymer is rather complex and further research is necessary to understand.

During the dissolution test of CRMP the dissolution media can affect the drug release rate. The change of osmotic pressure of dissolution media result in the alteration of the drug release rate of osmotic pumps, whose release rate mainly depend on the osmotic pressure difference between the dissolution media and inner membrane solution. As for as pH-dependent soluble polymer-acrylate resin is concerned, it is easy to understand that the permeability of CR membranes formed by acrylate resin will alter along with the change of the pH value of dissolution media. Hutchings and Sakr²⁶ reported that the rate of drug release from CR membrane in phosphorous buffer solution was greater than that in 0.1 M hydrochloride solution. the effect of plasticizer for CR membrane is curtailed by using phosphorous buffer solution as the dissolution media.

The composition of coating solution determines the membrane-forming mechanism of CR membrane. For

example, the presence of water will greatly change the process of dissolution of EC in ethanol when alcohol-water-EC triphase coating solutions are employed in preparing the CRMP. Since the evaporation rate of water is different from that of alcohol, phase separation will happen in polymer solution and pores will be formed due to the presence of water. The pore-forming rate will decrease with the increase of the amount of alcohol^{26,36-38}.

4. The mechanical property of CR membranes

In this section the mechanical properties of polymer such as tensile strength, work of failure, elastic modulus, viscoelastic property, glass transition temperature (Tg) and expansion coefficient of the polymer are discussed. Nowadays the study of mechanical properties of CR membrane mainly focuses on the detection of the hardness, film flexibility, elastic modulus and Tg of CR membrane and investigates how these parameters affect the drug permeability of the CR membrane. Thermomechanical analysis (TMA) has been widely used in the determination of mechanical properties of polymeric CR membranes since Masilungan reported the novel method³⁹. Many advanced research methods such as differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and X-ray diffraction have been used to study the CR membrane⁴⁰.

Hjartstam et al.⁴¹ detected the effect of stress on the permeability of EC membrane. They indicated that the permeability of potassium chloride for the membrane increased significantly under the action of stress because the stress could result in a change of CR membrane. When the stress was smaller than the fracture force, the change was reversible. Parikh et al.²⁹ reported the calculation of hardness and elastic module of EC membrane by using load-time curve. Guo^{28,34} investigated the Tg of CA CR membrane by thermoanalysis machine and discussed how these parameters change the drug release rate of CRMP.

The effect of CR membranes on drug release mechanism of CRMP

In addition to the properties of individual drug, the composition of the CR membrane is one of the main factors that regulate the drug release rate of CRMP. The CR membranes together with the pellets, tablets and granules coated with the membrane determine the mechanism of drug release from CRMP.

Water-soluble substance are contained in many CR membranes. When the CRMP are placed in an aqueous environment, water-soluble substance are dissolved and leached out. Drugs are released through the pores formed by the leaching out of the these substances. Shinji et al.³⁸ studied the process of phenylhydrochloride permeating EC membrane with different porosity and the effect of osmotic pressure of different release media. The results showed that phenyl-hydrochloride obeys the mechanism of osmotic release mechanism and the osmotic pressure difference was the release drive. Jana et al.¹⁷ confirmed the conclusion that the release of soluble drugs across microporous membrane obeyed the osmotic release mechanism by studying the release of potassium chloride from CRMP coated with acrylate. But the diffusion process of the drug across the CR membrane always exists. When the pore-forming reagent reached a certain level, the drug diffusion rate will not be neglected. Lindstedt et al.³⁰ studied the release process of potassium chloride through EC and HPMC membrane and reached a conclusion that the drug would be released by osmotic mechanism when the amount of HPMC was lower than 24%. IF the amount of HPMC were greater than 24%. the diffusion process would become the release method of drug combing with the osmotic release process.

In conclusion, more attention has been paid to the study polymeric CR membrane and the investigation will be broadened and deepened. The achievements obtained in this field are bound to provide vigorous tools for the development of CRMP.

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