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Master'sthesis

on the topic:

PREPARATION AND PROPERTIES OF ORAL ADHESIVE PLASTER CONTAINING PERIPLANETA EXTRACT

Completed: student of the group MPhch-20
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Summary

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This research is devoted to the development of a new type of oral adhesive tablet that combines polymer materials and natural biological extracts (Periplaneta americana). It has good adhesion, long adhesion time and high material quality. The medicine uses the natural extract of Periplaneta americana and uses its unique membrane repair effect. The material adopts high tensile strength, strong adhesion carbomer 941 and hydroxypropyl methyl cellulose polymer materials.

MTT assay was used to determine the toxicity of drug-loaded adhesion layer matrix on Hela cells. The results show that ulcer patch had good biocompatibility. Finally, the drug release behavior from the ulcer patch was studied by an amino acids analysis in the release medium using amino acid analyzer. The results show that the active components of amino acids can be effectively released from the matrix of ulcer patch, which laid a foundation for the therapeutic effect. The slow-release effect of the film provides a more efficient way to treat oral ulcers. The key production process of the product in industrial production is introduced, and the corresponding suggestions are put forward.

Key words:Oral ulcer patch, Periplaneta extract, Bioadhesion, Drug release

List of abbreviations

BDDS- Bioadhesive drug delivery system

CB-Carbomer

CB941-Carbomer 941

CLSM- Confocal laser scanning microscope

CMC-Carboxymethyl cellulose

CMCNa- Carboxymethyl cellulose

EC- Ethyl cellulose

GI-Gastrointestinal tract

HPMC- Hydroxypropylmethylcellulose

CONTENTS

INTRODUCTION

Bioadhesive materials can adhere to the gel layer or mucosal surface and load the drug through specific adhesive materials, which can accurately reach the lesion location in the body and serve the drug, even promote the release of drugs, improve the therapeutic effect and the body size of the treatment, and even reach the whole body. Although many bioadhesive agents have achieved good results in vivo and in vitro, and have developed rapidly. However, when it is applied to the human physiological system, the actual effect is quite different from the experimental effect. This is because no matter the simulation of animal models, in vivo and in vitro experiments can not truly show the migration, release and adhesion behavior of adhesive materials in human body. With the discovery of various biological adhesion materials with various properties, the adhesion properties will be continuously innovated and optimized. At the same time, traditional Chinese medicine preparations have a better development direction with the development of adhesive materials.

Periplaneta americana, commonly known as cockroach, is widely distributed in tropical and subtropical areas. This product was first published in ***Shennong Herbal Classic***and listed as middle grade. It is also recorded in the ***Compendium Of Materia*** Medica that it can dissipate blood stasis, soften hardness, dissipate cold and expel heat, conduct Qi and benefit pulse. Modern pharmacological studies show that Periplaneta americana has the effects of antiliver fibrosis, enhancing immunity, anti-tumor, promoting wound healing and tissue repair, and improving microcirculation. The drugs with Periplaneta americana extract as raw material can strengthen local blood circulation, improve the shedding of necrotic tissue on the wound surface, and accelerate the wound repair. They are commonly used in the repair of skin trauma and digestive tract ulcer. Oral ulcer is a common ulcerative injury disease occurring in oral mucosa.

It has severe pain and obvious local burning pain. In severe cases, it will also affect diet and communication, causing great inconvenience to daily life. Glucocorticoid drugs such as dexamethasone acetate adhesive tablets are often used in clinical treatment, but these drugs mainly use their anti-inflammatory effect to alleviate discomfort and have no obvious direct effect on ulcer repair. At present, drugs are also taken clinically to promote the repair of oral ulcer, but when administered in this way, the drug has a short residence time on the traumatic surface and is easily affected by saliva dilution, so its anti oral ulcer effect is limited.

Based on this, we use high molecular materials to make an oral adhesive, and use the oral drug delivery system, so that the drug has the characteristics of accurate dose, long blood concentration maintenance time and high bioavailability, which can avoid the first pass effect of liver, effectively prolong the administration time and reduce the administration times. Therefore, Periplaneta americana oral adhesive is made by combining Periplaneta americana and polymer oral film. On the basis of the efficacy of Periplaneta americana, the use of polymer biological adhesive material to carry drugs to treat oral ulcer in the way of direct contact, adhesion and sustained effect can prolong the drug action time to the greatest extent and enhance the drug efficacy, which has high clinical significance.

Firstly, the prescription of oral adhesive film was determined through experiments, including the prescription of non adhesive layer materials and the prescription of adhesive layer materials. Using Carbomer, HPMC and other polymer materials, a double-layer oral adhesive was manufactured by internal mixing method and tape casting method. Analyze and observe the morphology and adhesion properties (adhesion force, adhesion duration, etc.) of oral adhesive tapes with different prescriptions, and determine the prescription and preparation process of adhesive layer and non-adhesive layer. The adhesion, swelling degree and other properties of the material were characterized.

Secondly, on the basis of optimizing the prescription and technology, the extract of American catfish was loaded to prepare the drug loaded adhesive film. To study the effect of drug loading on the membrane performance, study the drug release performance of drug loaded adhesive membrane, and determine the best drug loading method and drug loading amount.

Finally, the drug analysis method of the extract was established to evaluate the quality standard of drug loaded adhesive film.

At present, there is little research on the film of Periplaneta americana in the treatment of oral ulcer. The preparation of oral film has high economic value and clinical significance. However, the patch has the disadvantage of less drug loading. In the future, research will be carried out from the aspects of screening the effective components of Periplaneta americana extract and enhancing the drug loading performance of film-forming materials, so as to develop an anti ulcer patch of Periplaneta americana with more drug loading and significant effect, so as to reduce the times of administration and improve the efficiency of treatment and rehabilitation.

Section 1(*Theoretical)*

MECHANISM OF BIOLOGICAL ADHESION

Biological adhesion refers to the ability of natural or synthetic polymers to adhere to the surface of mucus or epithelial cells and physiological tissues. Based on the systematic study of the mechanism of biological adhesion, the commonly used biological adhesion materials and their classification, the structure and properties of adhesion materials, the adhesion mechanism, the factors affecting biological adhesion properties, the introduction of typical biological adhesion materials and the experimental research methods for determining biological adhesion properties are reviewed.

1.1 Theoretical foundations of the mechanism of biological adhesion

- ***Electron transfer theory***

Due to the great difference between the structure of adhesion material particles and mucosal epithelial cells, when two surfaces with different structures and compositions are in contact with each other, electron migration will occur, resulting in the double-layer phenomenon at the contact interface. This adhesion is mainly due to the electrostatic attraction brought by electron transfer. For example, polyglucosamine, in which the positive charge is considered to be the most important factor to produce biological adhesion effect.[1]

- ***Adsorption theory***

According to this theory, the adhesion in bioadhesive polymers is mainly realized by other chemical forces. For example, through hydrogen bonding, van der Waals force or hydrophilic hydrophobic interaction. For example, polycarbonate has strong hydrogen bonding force because it contains carboxyl and hydroxyl groups. According to the adsorption theory, hydrogen bond is the main reason affecting its adhesion.

- ***Wetting theory***

The wetting theory requires that the bioadhesive polymer should have close contact with the mucus surface. It is considered that the adhesive polymer must

have sufficient water solubility and be able to wet and diffuse to the mucus layer.Based on this, we can study the bioadhesive properties of bioadhesive polymers by analyzing the changes of surface tension and free energy when the adhesion solution contacts the target tissue.[2]

- ***Diffusion interpenetration theory***

According to this theory, we believe that the adhesion between the adhesive polymer and the target tissue is caused by the mutual diffusion, penetration and entanglement of multiple molecular chain segments.When the mutual penetration between molecular chains reaches a certain degree, the interaction between chains will produce strong adhesion.[3] The adhesion rate depends on the diffusion coefficient of the interacting bioadhesive polymer, which depends on the molecular weight, degree of crosslinking, mobility of molecular segments and flexibility of molecular chains.

- ***Fracture theory***

This theory is the most widely used theory to explore the study of bioadhesion in vitro.In order to evaluate the bioadhesive properties of bioadhesive polymers, the method adopted is to measure the force required to separate the two interacting surfaces by using the adhesion of bioadhesive materials to make them contact with the target tissue under a certain external force, which can directly show the bioadhesive properties of polymers.

- ***Cell adhesion theory***

This theory is applicable to specific adhesion. For specific biological adhesion materials, the specific interaction between adhesion materials and epithelial cell surface is realized through the affinity between receptors and ligands, so this biological adhesion material has certain specificity and targeting. Typical bioadhesive materials and their classification. If an ideal bioadhesive material is described, it should have the characteristics of firm adhesion, safety, no irritation, multi-function and specific targeting.But in fact, it is difficult to obtain fully qualified bioadhesive materials. At present, the commonly used adhesive materials aregelatin, hydroxypropyl methylcellulose, sodium

carboxymethylcellulose, Carbomer, plant lectin and so on.If they are classified, they also belong to different categories according to different classification forms.[4]

Potential bioadhesive forces

Type of forces	**Examples of polymers**
Receptor-ligand affinity	Lectin ; antibody ; fimbrial protein
Covalent bond	Cyanoacrylate
Hydrogen bond	Carbopol; polycarbophil
Electrostatic interaction	Chitosan
Van De Waals force	All bioadhesive polymers
Mechanical interaction	All bioadhesive polymers

1.2 Typical biological adhesion materials and their classification

In terms of solubility, bioadhesive materials can be divided into water-soluble and non-water-soluble. Water soluble materials mostly exist in linear or random polymers, such as polyvinylpyrrolidone. However, non-water-soluble materials mostly exist in soluble but incompletely soluble network polymers, which are formed by stable chemical bond crosslinking.[5] For example, crosslinked sodium carboxymethyl cellulose.

- ***According to the structural characteristics of polymer***

According to the structure of adhesive materials, they can be divided into polyacrylic acid, cellulose (such as HPMC) and chitosan.Because its structure contains carboxyl, hydroxyl or amino groups, adhesive materials with different structures may have different charges, which can be positive, negative or neutral. According to park [6] et al., anionic polymers, especially carboxyl compounds, have the best adhesion, followed by neutral compounds, and cations have the lowest adhesion.

- ***According to sources of bioadhesive materials***

It can be divided into natural adhesive materials, semi synthetic adhesive materials and synthetic adhesive materials.Such as natural adhesive materials: gelatin, starch, plant lectin, etc., but its characteristics are limited by the source and specification. Semi synthetic adhesive material: it has a wide range of sources, low price and biological inertia.For example, cellulose derivatives. Synthetic adhesive material has low cost, the same quality standard and mature process. Common are carbomer 940, Carbomer 941, etc.

- ***Specific bioadhesive polymers***

Bioadhesive materials with specific functions can adhere to specific target cells by virtue of the affinity between receptors and ligands.

In recent years, bioadhesive materials have been used in bioadhesive delivery system. When the system is used in human body, the drug loaded

adhesive material can reach the calibrated target in vivo. Using the characteristics of bioadhesive materials, the residence time of drugs at the target can be prolonged and the therapeutic effect can be improved. [7]

According to the classification and summary, the bioadhesive polymers used in drug delivery systems should have the following characteristics: (1) bioadhesiveness is not only reflected in the solution, but also maintains good bioadhesiveness in a variety of environments and is suitable for systems in a variety of environments as much as possible;(2) It is suitable for drug delivery system and should coexist well with drugs with different dissolution properties;(3) Strong function, such as: promoting the release of loaded drugs (4) targeting, better targeting the absorption site and improving the therapeutic effect (5) safe, non-toxic and non-irritating.

- ***Hydroxypropyl methylcellulose HPMC***

Hydroxypropyl methylcellulose is a semi synthetic, inactive, adhesive, non-ionic cellulose mixed ether polymer. It is often used as a lubricant in Ophthalmology, or as an excipient or excipient in oral drugs.[8] When HPMC is used as adhesive layer, there is hydrogen bond force in mucin, which shows good biological adhesion. Secondly, HPMC surface activity can effectively improve the dissolution of insoluble drugs and improve the quality of tablets.[9] HPMC has good film-forming property. After film-forming, the film has good transparency and high tenacity, and will not adhere to each other in production. When using drugs that are susceptible to moisture, water absorption and unstable drugs, using HPMC as isolation layer can greatly improve the stability of drugs.[10]

- ***Carbomer***

Carbomer (CB) is a high molecular polymer crosslinked with pentaerythritol and acrylic acid.It contains a large number of carboxyl groups (56% - 66%).It is also a pH dependent polymer, maintaining its solution form under acidic pH, but forming a low viscosity gel under alkaline pH.Compared with other adhesive materials (HPMC, etc.), Carbomer has the advantage of better mucosal adhesion.Secondly, it is usually used to control the dissolution rate of

essential drugs.[11] If used with other adhesive materials: first, high concentration carbomer can play a protective role to prevent drugs from entering cells.2、Due to the strong adhesion of Carbomer, it is possible to damage the mucosal surface. Therefore, when carbomer is mixed with other materials, adjusting the amount of carbomer can better grasp the adhesion strength of the material.[12]

- ***Sodium carboxymethyl cellulose (CMCNa)***

Carboxymethyl cellulose (CMC) is a cellulose ether obtained from ordinary cellulose through modification technology (etherification).However, CMC is insoluble in water due to its acid structure. In order to better apply CMC more widely, it is generally made into sodium salt to improve its water solubility.The solution properties of CMC depend on its average chain length and degree of polymerization.[13] When it is used as film-forming agent, the adhesion and drug release rate are increased, which is conducive to increase the adhesion performance of the adhesive sustained-release agent, prolong the residence time of the preparation at the target position and significantly improve the drug efficacy.

- ***Chitosan***

Chitosan is the product of polysaccharide chitin after deacetylation. If we look at the molecular structure of chitin, chitosan and cellulose, we can find a regular and obvious phenomenon - C2 position, cellulose is hydroxyl at C2 position, chitin is acetylamino group and chitosan is amino group.Characteristics of chitosan: biodegradability, cell affinity and biological effect.For chitosan, chitosan containing free amino group is the only alkaline polysaccharide in nature.Secondly, the amino group in the molecular structure of chitosan is more active than the acetylamino group in chitin, which makes chitosan have more excellent biological functions and can carry out chemical modification reactions.Therefore, chitosan is considered as a functional biomaterial with greater potential and more utilization value than cellulose.[14] In terms of biological adhesion function, due to its positive charge, it shows the interaction

with the negatively charged ions of mucus sialic acid residues. Therefore, it has very good biological adhesion characteristics and can be used for film-forming materials and preparation of oral adhesive films.[15] Because the structure of chitosan is a linear polymer, it provides greater flexibility of polymer chain. Using this, people have synthesized chitosan derivatives with excellent biological adhesion.

1.3 Factors affecting the bioadhesive properties of polymers

- ***Molecular weight and chain length***

For linear polymers, the length of molecular chain increases with the increase of molecular weight, which is conducive to their mutual penetration and entanglement with mucin molecules.Under suitable conditions, the bioadhesive properties of the polymer are proportional to the molecular weight.Taking polyethylene glycol as an example, when its molecular weight is 20 kDa, the biological adhesion is almost 0;However, when the molecular weight increased to 4000 kDa, it showed good bioadhesion.As another example, CMCNa can show sufficient bioadhesive properties only when the molecular weight is large enough.[16]

- ***Charged ions and dissociation***

When evaluating the properties of bioadhesive polymers, anionic polymers are the best for charged ions if bioadhesive properties are taken as the standard.In anionic polymers, polymers with carboxyl groups are better than those with sulfonic groups.For the degree of dissociation of polymer, when the carboxyl group of polyacrylic acid is in the non-dissociated state, it is conducive to the formation of hydrogen bond with mucin, which is conducive to the generation of bioadhesive effect.[16] Therefore, for this adhesive polymer such as polyacrylic acid, its bioadhesive properties can be maximized by controlling the degree of dissociation of the polymer.

- ***Hydrophilicity and swelling***

Generally speaking, hydrogen bonds in bioadhesive polymers affect the properties of polymers, which means that excellent bioadhesive polymers should have a considerable number of hydrophilic groups to promote the formation of hydrogen bonds.When the polymer surface is in contact with the surface of mucus, water absorption dehydrates the mucus part and improves the stability of mucus adhesion.The water absorption process is affected by many aspects, including pH,

hydrophilic groups, ion strength and so on.If the water absorption rate is fast, the faster the chain diffusion and hydrogen bond formation, the faster the effect of biological adhesion.On the other hand, the swelling phenomenon of polymers in the environment is also very important to the performance and quality of biological adhesion.[17] Excessive swelling may reduce the adhesion and adhesion effect.

- ***Polymer concentration***

The concentration of bioadhesive polymer is related to adhesion. The concentration affects the adhesion performance. When the concentration is too low, the interaction force is not strong enough.When the concentration is too high, the crimp degree of polymer molecular chain increases and even dehydrates.[18]The activity and transferability of molecular chains are reduced, which greatly reduces the number of polymer molecular chains in the adhesive layer and weakens the adhesion of the adhesive layer.

- ***Effect of external force***

The adhesion properties of bioadhesive polymers are affected by the degree of swelling and the type and number of polymer molecular chains in the adhesion layer, and the most obvious factors are the contact time between the adhesion layer and the polymer and the external force.[19]Under appropriate conditions, the adhesion performance of polymer will be directly proportional to the contact time of adhesive layer and the external force.

- ***Ion strength***

The strength of ions will also affect the swelling and spatial structure of polymers, thus affecting the distribution of polar functional groups and the mobility of molecular segments.With the increase of ionic strength, the swelling property of the polymer decreases, and even has the trend of dehydration. Its spatial conformation is not conducive to the formation of adhesion.

- ***pH value of administration part***

The pH value of the environment in which the polymer is located will also affect the adhesion properties of the polymer.Firstly, pH value will affect the dissociation of functional groups contained in polymers, the formation of hydrogen bonds, the force between charges and the migration of molecular chains.Taking polycarbonate as an example, when the pH value in the environment exceeds about 5.0, its bioadhesive performance decreases.This is because the bioadhesion of polycarbofe is maintained by the hydrogen bond interaction between carboxyl and mucin molecules.[20] On the other hand, when the pH in the environment is higher, the negative charge will be carried between polycarbonate and mucin, which will produce electrostatic repulsion, which will have the opposite effect on the adhesion and weaken the adhesion performance.

Thus, oral adhesive tablets need good adhesion to increase the residence time in the oral cavity. After the prescription of the adhesive material is determined, the key to whether the adhesive material can produce better adhesion is swelling. Only when the adhesive material swells better only in this way can the high molecular polymer be stretched better, and the mucosal tissues can penetrate fully to produce strong adhesion. After the adhesive sheet is in contact with the oral mucosa, the adhesive material and the mucosal surface will have a certain binding effect, that is, the adhesive material interacts with the glycoprotein of the oral mucosa, and then hydrogen bonds with the sugar residues to form a mucus gel network structure, so that the tablet has adhesion. From the experimental results, it can be found that as the external pressure increases and the pressure time increases, the greater the bonding effect produced by the adhesive material, the adhesion force will also increase, because as the pressure and time increase, the tablet and the If the mucosa is in full contact, the tablet can swell better. It does not mean that the larger the swelling rate of the tablet, the better. When the bioadhesive material swells too much, a large amount of water will enter the macromolecular chain of the adhesive material, which will weaken the interaction between the adhesive material and the mucous membrane and decrease the adhesion force. Therefore, the oral adhesive tablet should have a suitable swelling rate, so that the

oral adhesive tablet has good adhesion, and it can also increase the adhesion time of the drug on the oral mucosa and increase the effective concentration of the drug.

1.4 Experimental methods for bioadhesive properties

The experimental methods for determining the adhesion of bioadhesive materials are divided into in vitro experiment and in vivo experiment.For in vitro experiments: first, because they are suitable and conducive to the study of molecular penetration, drug release, compatibility and physical stability, the surface interaction between preparation and mucosa, and the strength of biological adhesion.Through these tests, the environment of bioadhesive polymers in drug delivery system can be simulated.Secondly, most of the experimental data of biological adhesion come from in vitro experiments [21]. It can be used for the preliminary screening of materials, and then through the comparison of experiments, the biological adhesion materials used in further in vivo experiments can be determined, and the mechanism of biological adhesion can be clarified more clearly.Finally, the final evaluation of bioadhesive materials must be completed through in vivo tests.

In vitro experiment

- ***Measurement of tensile strength and separation force***

The adhesion test of bioadhesive materials is a common in vitro experimental method.

Firstly, the tested bioadhesive material and target tissue are fixed on the scaffold respectively, and a balance is connected to the scaffold of the adhesive material, so that the adhesive material can contact with the target tissue under the condition of certain external force and maintain it for a certain time to make it adhere.

Secondly, an external force is applied, which is large enough to separate the adhesive material and the target tissue from the contact surface. At this time, the separation force is recorded as an important parameter to evaluate the adhesion performance.The method has the advantages of easy equipment and operation, short experimental time and low experimental cost. It can be widely used to evaluate various bioadhesive agents.

However, the problem of this experiment is also obvious. First, the simplicity of the instrument will lead to low precision.If you want to obtain repeated results, the test conditions and target tissue must be the same, and the objective conditions cannot be guaranteed to be completely the same.In addition, for materials with strong biological adhesion, the fracture usually does not occur only at the interface between the adhesive material and biological tissue, but also in other places.From reality, in the drug delivery system in normal human body, except for the oral mucosa and vaginal mucosa, it is difficult for other drug delivery positions in the body to give external force to promote the close contact between the material and the target tissue.[22] Therefore, the results obtained by this method reflect the adhesion characteristics of the dosage form in vivo。

- ***Pouring technology***

Circulation Taoism.It measures the speed of the adhesive particles moving on the surface of the adhesive layer under the action of external force by taking pictures with a camera.The adhesion performance of particles can be intuitively displayed by moving speed.

Falling liquid membrane method.That is, the target tissue piece is fixed on an inclined plane at a certain angle, and on this basis, a suspension of adhesion material particles is added to the surface of the target tissue.Kurt current method or other suitable methods are used to measure the number of adhesive particles in the liquid flowing out of the inclined plane, and the number of particles transferred to the tissue surface through adhesion within a certain period of time.[23]

The focus of perfusion experiment is that the prepared target tissue (target tissue) is repeatable. When evaluating the adhesion of an adhesive material, the amount of mucus that can be retained on the tissue surface and the repeatability and reliability of experimental results are very key indicators.

- ***Colloidal gold staining***

The interaction of mucin gold conjugate with hydrogel surface produces red phenomenon.It can be used to quantitatively compare the adhesive properties of various hydrogels.The technology uses red colloidal gold particles - stable adsorbed mucin molecules (mucin gold conjugate). After the interaction, mucin Au conjugates can make the surface of the mucin hydrogel surface appear red. By measuring the red intensity, we can quantitatively compare the mucin properties of the gels and the gold binding of the gels. The pH dependent stability of the mucin Au conjugates is investigated, and the best condition of the mucin Au staining is determined.[24]

- Rheological method

This method is to study the rheological properties (elasticity, plasticity, viscosity and strength) of adhesive polymer and mucus before and after mixing, mainly viscosity, and evaluate the adhesion effect between them.Theoretically, the viscosity of adhesive polymer and mucin is directly proportional to the adhesion of polymer.[25] However, if the adhesion effect of polymer and mucin in homogeneous mixture cannot explain the adhesion performance of polymer and mucin in heterogeneous environment.

- ***Confocal laser scanning microscope (CLSM) method***

Confocal laser scanning microscope (CLSM or LSCM) is a technology to obtain depth selective high-resolution optical images.The main feature of confocal microscopy scanning is that the focused image can be obtained from the selected depth, which is called optical slice.CLSM combines laser scanning with three-dimensional detection of fluorescent labeled biological objects, and uses fluorescent markers to measure the mucosal adhesion strength of liposomes.[26]

In vivo experiment

- ***γ -Scintillation scanning***

Gamma scintigraphy. The isotope (adhesive polymer) is recorded by means of a gamma camera at various time points in vivo under normal

physiological conditions after the use of radioisotope to label the polymer Position and movement process in the body, and observe the important time node of the polymer in the body.

For this method, the advantages:

1. It is not harmful to the body and the safety performance is high.

2. The movement track of the adhesive material in the whole-body range can be observed, in turn, it is possible to study with high precision the effect that the drug and the developing target site, or even the lesion area, have on the adhesion properties of the polymer.

Disadvantages:

1. Equipment is expensive and costly.

2. Gamma camera scanning is indeed an indirect imaging technique. [27] This leads to the suggestion that the location of radionuclide retention observed in the experiments is perhaps not directly due to the effect of adherent material.

- ***X-ray, radioactive and fluorescent labeling tracing method***

GI (gastrointestinal tract) transport time can be measured by using one of many radiopaque markers, such as barium sulfate coated on bioadhesive dosage forms.For example, in vivo mucosal adhesion was measured with barium sulfate tablets. Two healthy rabbits were selected and orally administered with tablets. X-rays were taken at different time intervals to evaluate GI (gastrointestinal tract) transport by X-ray examination.[28]

Radioactive or fluorescent labeled adhesive materials were injected into experimental animals by surgery or other methods.After injection for a period of time, the experimental animals are treated, the animal organs or target tissues to be observed are extracted and divided into different areas. The fluorescence and radioactivity intensity in different hair divided areas are measured by scintillation counting or CLSM in each area. The results can be used to evaluate the bioadhesive performance of the polymer or the dosage form.At present, this

method is basically applicable to various dosage forms, and is very suitable for investigating the overall movement of dosage forms in the gastrointestinal tract.[29]

- ***Enema isolation method***

The experimental animals were divided into a small segment of small intestine.The adhesive polymer material to be measured is made into a medicament or otherwise through the section of the small intestine to determine the amount of polymer successfully adhered to the section of the small intestine within a certain time, so as to evaluate the bioadhesion of the polymer.The divided small intestine can maintain blood circulation. Further, we can select different divided areas to investigate whether the adhesive materials will produce different adhesion on specific parts.[30] advantages: the area can be controlled, the experiment is flexible and easy to control.Disadvantages: it involves animal medicine, and the actual operation is complex. Some operations will also stimulate the production and secretion of other mucus in animals, which will lead to errors in the experimental results and affect the accuracy and authenticity of the experiment.

1.5Research progress of oral adhesive preparations containing cockroach extract.

(Overview)

- *Research progress of Periplaneta americana*

Periplaneta americana, commonly known as cockroach, is widely distributed in tropical and subtropical areas. This product was first published in ***Shennong Herbal Classic*** and listed as middle grade. It is also recorded in the ***Compendium of Materia Medica*** that it can dissipate blood stasis, soften hardness, dissipate cold and expel heat, conduct Qi and benefit pulse. Modern pharmacological studies show that Periplaneta americana has the effects of anti liver fibrosis, enhancing immunity, anti-tumor, promoting wound healing and tissue repair, and improving microcirculation. The drugs with Periplaneta americana extract as raw material can strengthen local blood circulation, improve the shedding of necrotic tissue on the wound surface, and accelerate the wound repair. They are commonly used in the repair of skin trauma and digestive tract ulcer.

Periplaneta americana contains proteins, polysaccharides, flavonoids, lipids, classifications and other substances, and also contains 8 trace elements required by the human body, essential amino acids such as valine and leucine, and more than 20 non-essential amino acids, etc. [31]

Periplaneta americana, dried and used as medicine, has high medicinal value and has more than 200 important ingredients to match it. As a traditional Chinese medicine, it is cold in nature, salty in taste, and slightly toxic. It can enter the three meridians, remove blood stasis, break blood, connect bones and renew tendons, reduce swelling and relieve pain, and treat low back pain, bruises, arthritis and other diseases. Modern medicine has proved that American cockroach can also have a therapeutic effect on leukemia, and can inhibit the spread of tumors, and has a certain therapeutic effect on certain cancers [32]

In the 1970s, in China, "" Kangfuxin Liquid "" has been developed based on Periplaneta americana, which is mainly used to treat gunshot wounds in the army, and is now widespread. However, from the literature of numerous studies on Periplaneta americana, the current study in China is focused on the aspects of population survey, distribution, growth pattern and degree of infestation of various Blattaria species, control and resistance of Periplaneta major, growth propagation and situation report, comparison of the killing efficiency of various killing agents with respect to the mechanism of killing, gene expression and sensitization Research; research on medicinal value development, etc.

In international, mainly for the study of the morphological structure of Periplaneta americana, and in medical, mainly for the research of digestive tract and nerve impulse of Periplaneta americana, etc.

- ***Overview of oral ulceration***

Oral ulceration is clinically one of the most common oral mucosal diseases, mainly occurring on the lips, tongue and oral mucosa, its external shape is round or ovoid, its size and size ranges from rice grain to yellow bean size, the duration of the lesions is generally one to two weeks can recover by itself, but it also has the characteristics of recurrent attacks, with burning sensation during attacks, irritating food can trigger a series Intense burning sensation and pain. The etiology of oral ulcers is intricate and may be caused by local trauma, infection with viruses and bacteria, digestive system dysfunction, endocrine changes, and psychoneurological factors, among others. Ancient physicians have many insights into the lesion mechanism and etiology of oral ulcers, most of which are due to fire heat, cold evil, temper stagnation, kidney deficiency Qi deficiency, and deficiency of up and Down syndrome Facial cause. The existing drugs for the treatment of oral ulcers are mainly anti-inflammatory, analgesic, corrosive, hormonal drugs, which have some efficacy but also show some problems: long-term application of hormone containing drug formulations, may produce dependence, and immunity degradation

adverse effects; the vast majority of topical formulations can reduce pain but accelerate healing and so on Suboptimal efficacy.[33]

- ***Overview of Bioadhesive drug delivery system***

Bioadhesive drug delivery system (BDDS) is a new branch of modern drug delivery system.Bioadhesive preparation is a kind of drug preparation which takes bioadhesive material as drug carrier and adheres to mucosa for a long time.[34] Compared with other dosage forms, bioadhesive agents have the following main advantages: ①carriers are mostly composed of bioadhesive materials, which have different degrees of adhesion to mucosa, which can prolong the release time and improve the absorption of drugs;② The action site is the human tissue mucosa, and the drug directly enters the whole body blood system through mucosal transport, which avoids the first pass effect of the liver and improves the bioavailability of the drug.③It has targeting function. For local diseases, it can greatly increase the local drug concentration and avoid the disadvantage that it is difficult for oral drugs to reach the effective concentration at the focus.According to the different parts of the preparation acting on human tissues, it can be divided into oral adhesive preparation, nasal adhesive preparation, gastrointestinal oral adhesive preparation, eye adhesive preparation, uterine and vaginal adhesive preparation, rectal adhesive preparation and other dosage forms.

1.6 Development of oral adhesive preparations

Due to the abundant blood vessels in oral mucosa, local treatment and administration of oral diseases, cardiovascular drugs, anti-inflammatory analgesics and local anesthetics can achieve the purpose of systemic treatment through the absorption of oral mucosa [35].Oral adhesive preparation has become the fastest developing oral preparation in recent years, especially in traditional Chinese medicine preparation.According to the structure and morphology of the preparation, oral adhesive preparations are divided into three types:

- ***Adhesive ointment***

Tanaka [36] et al. Used gelatin: CMCNaamylopectin (1:1:1) dispersed in 30% Plastibaseto prepare ointment that can adhere to the oral cavity, resulting in continuous adhesion in the oral mucosa, prolonging the residence time of the drug and improving the bioavailability.But its taste is not good. Due to the continuous secretion of saliva and frequent activities in the mouth, the residence time is not long enough.

- ***Oral patch***

Patel VM [37] and others used chitosan and PVP K-30 to prepare propranolol hydrochloride oral patch, which can be continuously released in the oral cavity for 7 hours. Liu Guoqin [38] and others developed dexamethasone acetate and Carbopol into double-layer patches of soluble adhesive polymer materials and insoluble polymer materials.The drug containing adhesive layer composed of soluble polymer has good adhesive performance and high drug concentration. Sticking to the sore surface can make the local hormone concentration higher and longer, with good absorption effect, low dose and light side effects. The drug-free protective layer made of insoluble polymer material can delay the dissolution of the drug layer in the oral cavity, reduce the bitterness, prevent discomfort, increase the action time and improve the curative effect. Zhou Yinqi [30] and others developed Tinidazole with Carbopol 934p and HPMC K4M as adhesive materials

Oral adhesive tablet can make the drug adhere to the oral cavity for a long time and play a quick and long-term role, so as to improve the clinical efficacy of the drug.Wu Qiongzhu [39] and others developed felodipine oral adhesive tablets with hydroxypropyl methylcellulose (HPMC) and carbomer as biological adhesive materials, and confirmed that the oral administration of Felodipine is feasible.Zhou Dongxin [40] developed oral mucosa adhesion sustained-release tablets using biological adhesion technology, which can adhere drugs to oral ulcer wounds, not only prolong the action time of drugs on the wounds, but also protect the wounds.

- ***Oral film***

Fu Zhijun [41] and others developed compound KuiNing into a mucosal adhesion sustained-release film, and determined the film made of polyvinyl alcohol (model 1750), sodium carboxymethylcellulose and polycarboxyethylene in the ratio of 3 ： 6 ： 1 as the best prescription, so as to prolong the retention time in the oral cavity and the release rate of drugs in the preparation, so as to improve the efficacy.Zhou Dongxin [42] made Qingkui compound traditional Chinese medicine into oral mucosa adhesion sustained-release drug film, which increased the adhesion of the film, delayed the dissolution (disintegration) time of the film material, and prolonged the release rate of drugs in the drug film.Du Xia et al. [43] used PVA: CMC Na as 1:1 membrane material to prepare iced tea oral ulcer composite membrane for the treatment of oral ulcer. It has faster curative effect. Compared with powder and single-layer membrane, it has the advantages of single-sided absorption, prolonging the efficacy, avoiding easy movement and falling off of normal mucosa due to adhesion to the drug membrane.Shen Yanxiang et al. [44] used CMC Na as membrane material and developed the compound double-layer ulcer film of traditional Chinese and Western medicine for the symptoms of recurrent aphthous ulcer. It has the characteristics of accurate content, stable performance, good adhesion, complete absorption and rapid effect.

Therefore, Periplaneta americana oral patch is made by combining Periplaneta americana and oral patch. Using Bioadhesive drug delivery system

(BDDS) for better delivery of drugs. On the basis of retaining the efficacy of the original dosage form, it can treat oral ulcer by direct contact, adhesion and effective administration, which can prolong the drug action time and enhance the drug efficacy to the greatest extent, and has high clinical significance. Periplaneta americana oral patch was prepared by combining freeze-dried powder of Periplaneta americana extract with film-forming materials to achieve long-term local treatment of oral ulcer wounds. The drug is a natural drug preparation with no irritation. The adhesive administration directly acts on the lesion of oral ulcer. After administration, the wound feels cool and is easy to be accepted by patients.

Summary of this chapter

At present, bioadhesive materials can adhere to the gel layer or mucosal surface, and load the drug through specific adhesive materials. It can not only accurately reach the lesion location in the body, but also promote the release of drugs, improve the therapeutic effect and the body size of the treatment, and even reach the whole body. Thus, the therapeutic ability of some systemic diseases is greatly improved. Although many bioadhesive agents have achieved good results in vivo and in vitro, and have developed rapidly. However, when it is applied to the human physiological system, the actual effect is quite different from the experimental effect. This is because no matter the simulation of animal models, in vivo and in vitro experiments can not truly show the migration, release and adhesion behavior of adhesive materials in human body. With the discovery of various biological adhesion materials with various properties, the adhesion properties will be continuously innovated and optimized. At the same time, traditional Chinese medicine preparations have a better development direction with the development of adhesive materials

With the invention of various bioadhesive materials, the development of various science and technology and the proposal of new mechanism theories, ideal bioadhesive materials have the advantages of strong adhesion, safety and harmlessness, promoting drug release, specific adhesion, good biocompatibility and low cost. At present, it is still necessary, potential and broaddevelopment prospect to study better bioadhesive materials in pharmacy.

Section 2(Predstadnytsko-analitichny)

RESEARCH ON THE ADHESIVE PROPERTIES OF ADHESIVE MATERIALS

Oral adhesions with the help of adhesions produced by the contact of polymer polymers with oral mucosa, prolonging the retention time of drugs in the oral cavity, controlling the release rate of drugs, which can improve the bioavailability of drugs and better exert local or systemic therapeutic effects. Oral adhesive sheet preparation the most critical is for the selection of bioadhesive materials, which are mainly divided into two main categories: natural polymers and synthetic polymers. Natural polymers mainly include: cellulose derivatives (e.g.: HPMC, HPC, MC, CMCNa, etc.), chitosan, hyaluronic acid, starch. Synthetic polymers mainly include: polyacrylic acids (e.g.: polycarbophil, Carbomer), polymers.

In this paper, the prescription of oral adhesive membrane, including the prescription of nonadherent layer materials and the prescription of adhesive layer materials, were determined by pre-experiments. Using carbomer 941, HPMC (hydroxypropyl methylcellulose), through the machining and casting methods, double layered oral adhesions were fabricated. The morphology and adhesion properties (adhesion, adhesion duration, etc.) of oral adhesions with different prescriptions were analyzed and observed to determine the prescription and preparation process of adherent and nonadherent layers. Later characterization experiments were performed on the adhesiveness and other properties of the materials. Secondly, based on the optimization of the prescription and process, the loading of extracts from Blattella Americana was performed to prepare drug loaded adhesive film. The effect of drug loading on membrane performance was investigated. Drug release performance study of

drug loaded adhesive film to determine the optimal drug loading method and drug loading content, drug analysis method of extract of Blattella Americana was established to carry out drug loaded adhesive film quality standard study.

2.1 Prescription determination and preparation of polymer adhesion layers

Instruments and materials

Main drugs or reagents

Table 2.1

Name of drug and reagent	Manufacturer	Specifications
Ethyl cellulose	Shanghai McLean Biochemical Technology Co., Ltd	200cps
Carbomer941	Shanghai McLean Biochemical Technology Co., Ltd	AR
castor oil	Shanghai McLean Biochemical Technology Co., Ltd	AR
Triethyl citrate	Shanghai McLean Biochemical Technology Co., Ltd	AR
titania	Shanghai McLean Biochemical Technology Co., Ltd	99.8% metals basis, 5-10nm, anatase
Hydroxypropyl methyl cellulose	Shanghai McLean Biochemical Technology Co., Ltd	Usp2910,2% viscosity: 15MPa. S
Absolute ethanol	Shanghai McLean Biochemical Technology Co., Ltd	AR
American larch extract	Xi'an ruierli Bioengineering Co., Ltd	10:1

Note: all chemicals are of analytical grade and can be used without further purification.

Main instruments involved in the experiment and relevant information

Table 2.2

Name of experimental instrument	Model	Manufacturer
Ultrasonic cleaner	Kq5200 type	Kunshan Ultrasonic Instrument Co., Ltd
Intelligent magnetic stirrer	ZNCL-BS140*140	GongyiYuhua Instrument Co., Ltd
Electronic balance	TE124S	Saidoris scientific instrument (Beijing) Co., Ltd

Electric blast drying oven	101type	Beijing Yongguangming Medical Instrument Co., Ltd
Glass instrument airflow drying oven	nothing	Henan Yuhua Instrument Co., Ltd
PH meter	PHS-3E	Shanghai LeiciChuangyi Instrument Co., Ltd
Ultraviolet visible spectrophotometer	UV-6000H	Shanghai Yuanxi Instrument Co., Ltd
Booster electric agitator	Jb50-d type	Made by Shanghai specimen model factory
Electric centrifuge	800type	Jiangsu Jintan Jiangnan Instrument Factory
Interfacial Shear Rheometer	OCA25	Beijing odrino Instrument Co., Ltd
Scanning electron microscope	BA210	Mcdio Industrial Group Co., Ltd
Nano particle size meter	Winner802	Jinan Weina particle instrument Co., Ltd

Preliminary experiment of non-adhesive layer

Table 2.3

Non adhesive layer prescription	Ethyl cellulose (200cps) (g)	Absolute ethanol	Castor oil (g)	Effect
Content	4.0	40g	0	Slightly sparse
	5.0	40g	0	moderate
	4.0	40ml	1.2	Too thin
	3.0	40ml	0	moderate

Determine the non-adhesive layer prescription as No. 2 for experiment.

According to the results of the preliminary experiment in Table 2.3, accurately weigh 5.0 g of ethyl cellulose (200 CPS) and place it in 40 g of absolute ethanol. Stir magnetically until the ethyl cellulose is completely dissolved in the absolute ethanol. Observe the dissolved solution. It is

transparent and viscous, with a moderate viscosity, and should not be too thin or too thick, as shown in Figure 2.1.

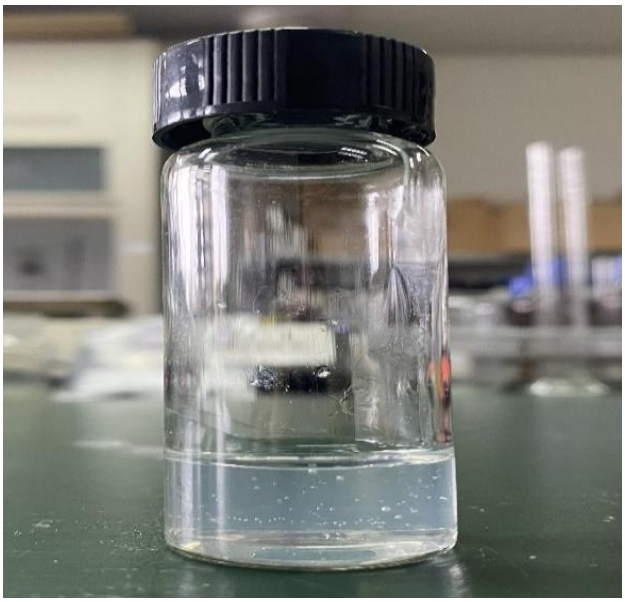


Figure 2.1- Ethyl cellulose ethanol solution

The operation is as follows: Take an appropriate amount of the above solution, paste multiple layers of tape around the dry glass plate, control the thickness of the film to be about 0.025mm, and spread it evenly on the transparent and clean glass plate to form a transparent liquid film, (Figure 2.2, 2.3) Put it in a blast drying oven, set the temperature to 55 degrees Celsius, and dry for 2 hours to obtain a dry, transparent, non-adhesive film.

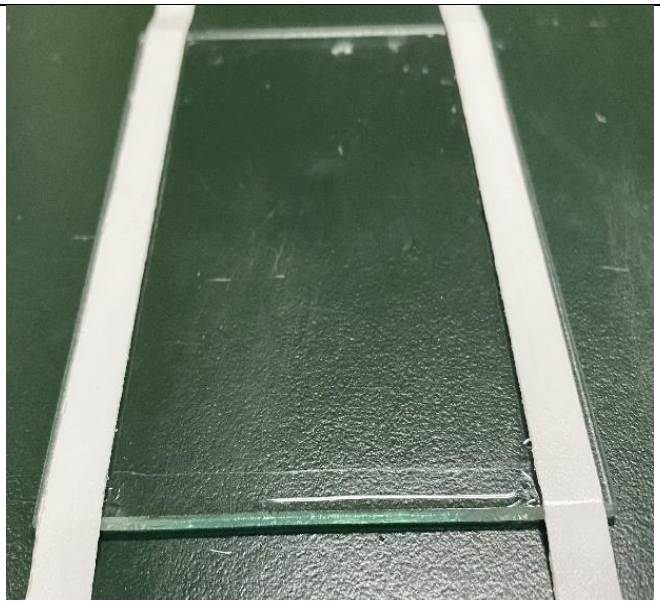


Figure 2.2 – Spread evenly on a transparent and clean glass plate to form a transparent liquid film

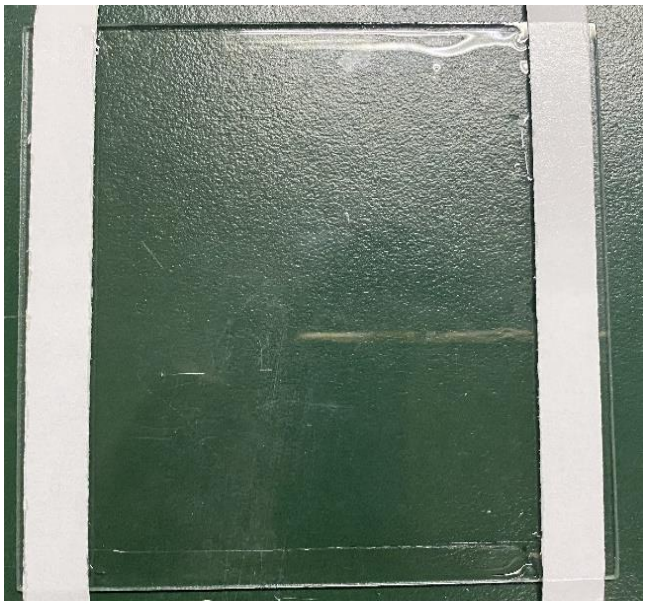


Figure 2.3–Spread evenly on a transparent and clean glass plate to form a transparent liquid film

Preparation of the adhesion layer

According to the preliminary experimental results in Table 2.4 and Table 2.5, the adhesion layer of the tablet was prepared. (Titania 0.1g)

Pre experiments on choice of excipients

Table 2.4

Pre experiment optimization record of adhesive layer prescription											
Component	Number	Ethyl cellulose	Hydroxypropyl methylcellulose	Castor oil	Triethyl citrate	Carbomer 941	Carbomer 940	Polycarbophil	Carbomer 934p	Water (g)	Absolute ethanol (g)
content	1	0.3	0.6	0	1	2.5				0	35
Unit g	2	0.5	1.25	0	1	2.5				0	35
	3	0.5	1.25	1	0	2.5				5.0	35
	4	0.5	1.25		1		2.5			10.0	25
	5	0.5	1.25	1	0		2.5			5.0	35
	6	0.5	1.25	1	0		2.5			0	35
	7	0.5	1.25	1	0			2.5		5.0	35
	8	0.5	1.25	0	1			2.5		0	35
	9	0.5	1.25	0	1			2.5		0	25
	11	0.5	1.25	0	1				2.5	5.0	35
	12	0.5	1.25	1	0				2.5	5.0	35
	13	0.5	1.25	0.5	0.5				2.5	5.0	35
	14	0.5	1.25	0.6	0	2.5				5.0	35
	15	0.5	1.25	0.5	0.5	2.5				5.0	35

Effect of excipient combinations

Table 2.5

Number	Preliminary effect
1	The surface of cast film is uniform and the adhesion is slightly low
2	The casting film has uniform surface and good adhesion
3	The casting film has uniform surface and good adhesion
4	The viscosity is too high, casting is difficult, the surface is uneven, but the adhesion is not good
5	High viscosity, difficult casting, uneven surface and poor adhesion
6	Uneven casting and good adhesion
7	The casting is uniform, but there are holes or cracks in the film
8	The casting is very uniform. After increasing the thickness of the adhesive layer, the small holes become less and the adhesive force is weak
9	The casting uniformity is not good, it is difficult to form film, and the adhesion is weak.
11	The casting uniformity is general, the effect is less than that of polycarbonate and cb941, and the effect is greater than that of cb940.Better adhesion than cb941.
12	The casting uniformity is general, and the effect is less than that of cb934 containing triethyl citrate and polycarbophil. Adhesion greater than cb941
13	Average casting uniformity.
14	Uniform casting and good adhesion.
15	Good casting uniformity and adhesion.

Finally, prescription 15 was determined as the adhesive layer prescription for experiment.

Multiple prescriptions with different ratios of carbomer and HPMC with different drug loading contents were formulated simultaneously for comparative experiments.

Various prescriptions with different ratios of carbomer and HPMC and different drug content.

Table 2.6

Prescription number	HPMC : CB941	Drug content g	castor oil g	Triethyl citrate g	titania g
P1	1:1	0	0.5	1.0	0.1
P2	1:1	0.1	0.5	1.0	0.1
P3	1:1	0.3	0.5	1.0	0.1
P4	1:2	0	0.5	1.0	0.1
P5	1:2	0.1	0.5	1.0	0.1
P6	1:2	0.3	0.5	1.0	0.1

The experimental operation is as follows:

① Accurately weigh 0.50 g of ethyl cellulose (EC) and dissolve it in 30.0 g of absolute ethanol, add 1.0 g of triethyl citrate and 0.50 g of castor oil in sequence, and mark it as solution A.

② Accurately weigh 0.1g of titanium dioxide, dissolve it in 5.0g, and vibrate with ultrasonic until it is completely dissolved, and mark it as solution B.

③ Mix solution A and solution B for 2 hours and fully fuse to form solution C.

④ Precisely weigh 1,25g of hydroxypropyl methylcellulose (HPMC), add it to solution C, and stir magnetically for 3 hours.

⑤ Accurately weigh 2.50g of Carbomer 941, place it in the sealed bag, and add solution C.

⑥ Fully mix until uniform and without agglomeration.

⑦ High-speed centrifugation to remove air bubbles.

⑧ Take out the non-adhesive layer after casting, take an appropriate amount of the adhesive layer and evenly cast it on top of the non-adhesive layer, use the tape around the glass plate to control the thickness, and put it in a blast drying oven at 50 degrees Celsius and dry for 24 hours.

⑨ Take out, separate the glass plate, and cut the appropriate size (6cm×6cm) to obtain an unloaded double-layer adhesive patch. As shown in Figure 2-4.

Figure 2.4- Un-drug-loaded adhesion layer

2.2 Preparation of Adhesive Tablets Loaded with Periplaneta Extract

① Accurately weigh 0.50g of ethyl cellulose (EC), dissolve it in 20g of absolute ethanol, add 0.50g of castor oil and 1,0g of triethyl citrate while magnetic stirring.

② Accurately weigh 0.1g of the American cockroach extract, dissolve it in 15g of absolute ethanol, stir magnetically until it is completely dissolved, and the solution is light yellow.

③ Mix the two parts of ① and ② with magnetic stirring, add 0.1g of titanium dioxide, and continue to stir for 2 hours.

④ Add 1.250g of hydroxypropyl methylcellulose (HPMC) to the above solution and continue to stir for 3 hours.

⑤ Accurately weigh 2.5g of Carbomer 941 into a sealed bag.

⑥ Add the solution in ④ into the sealed bag, and mix thoroughly.

⑦ High-speed centrifugation to remove bubbles, use the non-adhesive layer completed by casting, take an appropriate amount of the drug-loaded adhesive layer and evenly cast on the non-adhesive layer, use the tape around the glass plate to control the thickness, and put it in a blast drying oven at 50 degrees Celsius for 24 hours.

⑧ Take out, separate the glass plate, and cut the appropriate size (6cm×6cm) to obtain a double-layer adhesive patch containing the extract of Periplaneta americana. As shown in Figure 2-5.

Figure 2.5- Drug loaded adhesion layers

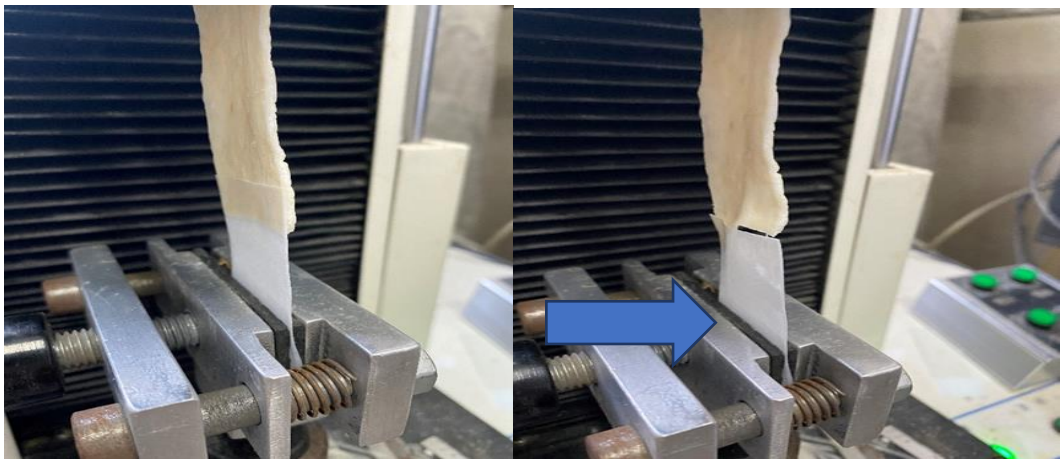
At this point the adhesion layer is basically fabricated, and for its performance, a series of experiments will be performed.

2.3 Performance test of oral adhesive tablets

Determination of adhesion and influencing factors

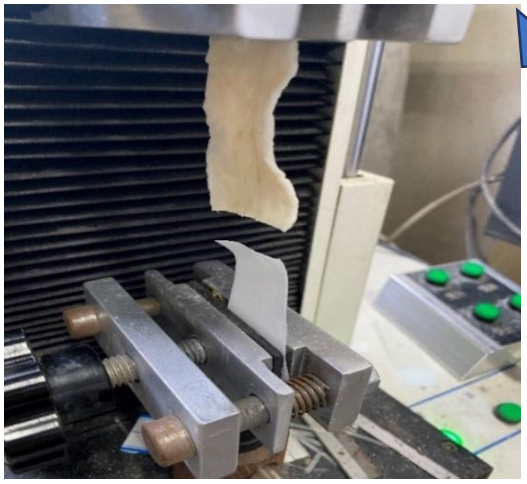
- ***Determination of adhesion***

Prepare each square oral adhesive tablet, use an interface rheometer, take a fresh pig large intestine, overlap a part of the pig large intestine with the adhesive tablet, and fix the overlap area to 30mm×30mm. Take a 200g weight to press the overlap site for 30s to adhere the pig large intestine to the oral cavity. The two sides of the film are fixed on the two clamps of the interface rheometer, and the clamps are moved up and down to pull the porcine large intestine and the oral adhesive sheet until the two are separated from the joint. At this time, when the two are separated, the interface rheometer applies the size of the force is the size of the adhesive force of this prescription oral adhesive tablet. The experimental process is shown in Figure 2.6, and the results are shown in Figure 2.7. Take prescriptions P4 and P6 to determine the relationship between the displacement and adhesion of the clip of the interface rheometer and the relationship between stress and strain. The difference between the two prescriptions is one of them is loaded with drugs, and the other is not loaded with drugs. The results are shown in Figure 2.8 and Figure 2.9.



The two interfaces overlap and start to stick

Apply force at both ends until separation occurs



Until the two materials are completely

Figure 2.6 Determination of adhesion size of buccal adhesive patches using an interfacial rheometer.

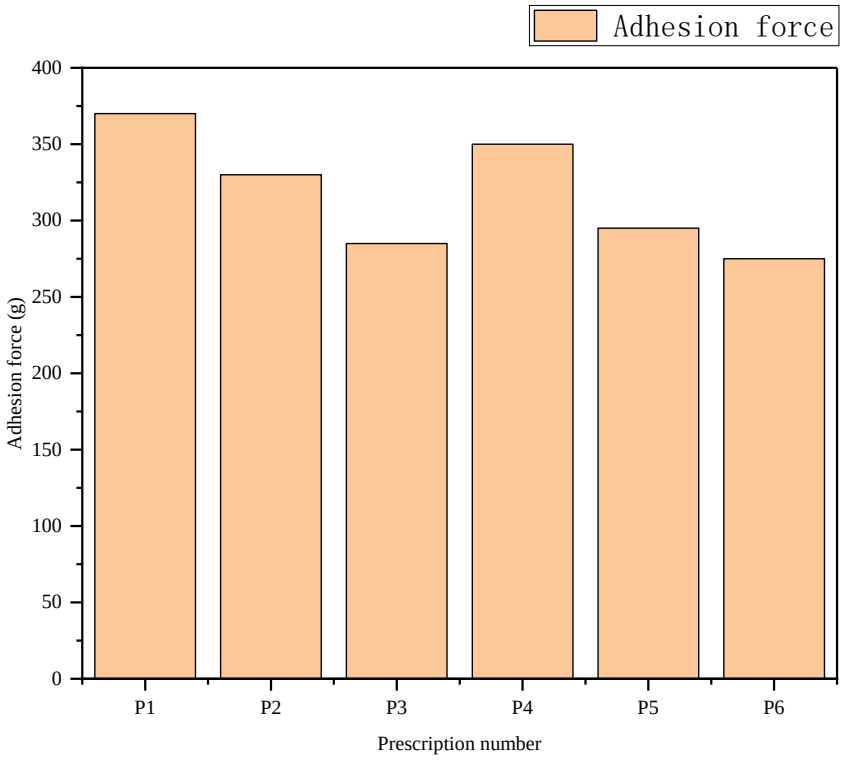


Fig. 2.7 - Adhesive force values of each prescription

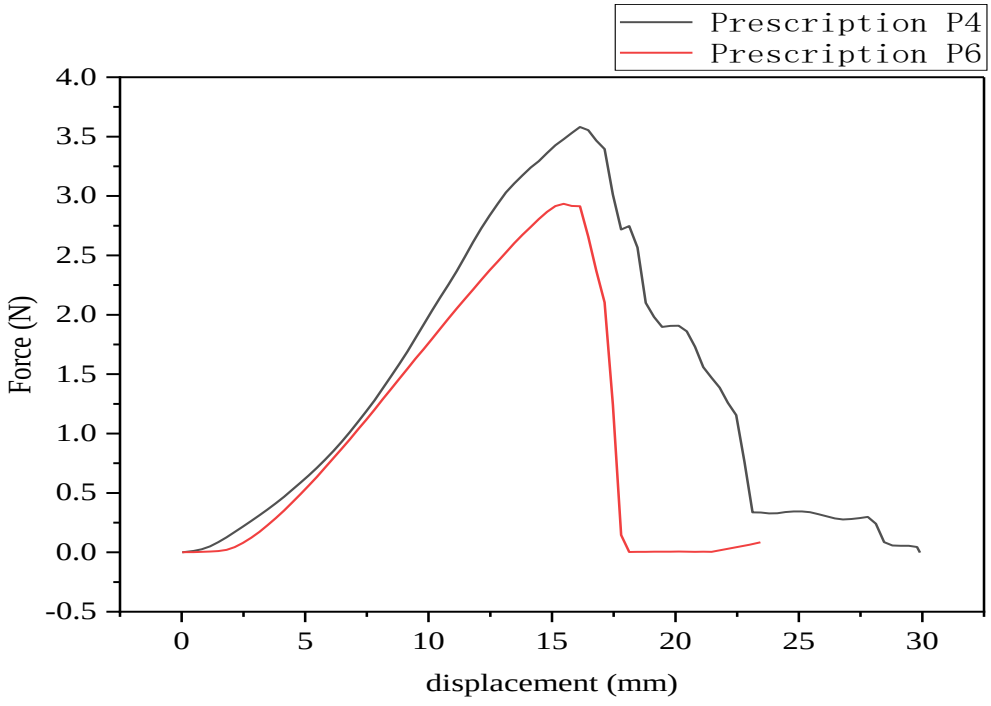


Fig. 2.8 - The relationship between the force and displacement of the two prescriptions

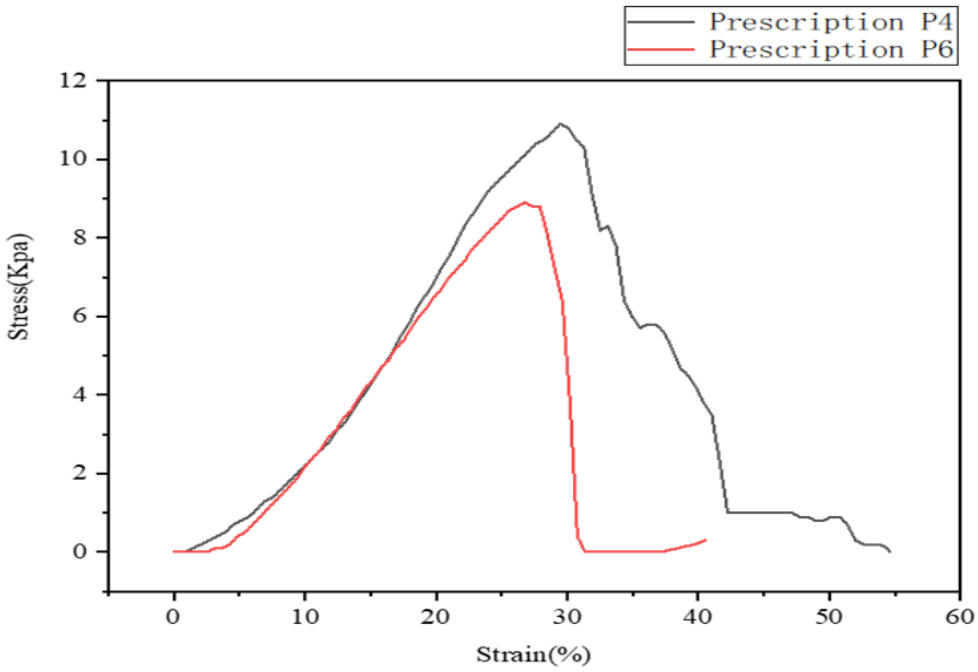


Fig. 2.9 - The relationship between stress and strain of the two formulations

From the above two figures, it can be seen preliminarily that the adhesion force of the tablets prescribed by group A was overall greater than that of the tablets prescribed by group B, and the adhesion force of the tablets of both groups showed a decreasing trend with the increase of drug content.

The non-drug loaded adherent tablets gave more force compared to the non drug loaded tablets in displacing the same distance, likewise, more stress was required to produce the same strain after drug loading by the adherent materials.

- ***Influence of pressure intensity***

Prepare blank oral adhesive tablets of prescription P1. Use 20, 50, 100, 200, 300, 400g weights to compress the contact area between the adhesive tablet and the pig's large intestine, which is 30mm×30mm, and the time is 30s. Determine the adhesiveness of the tablet. Attached force, the result is shown in Figure

2.10

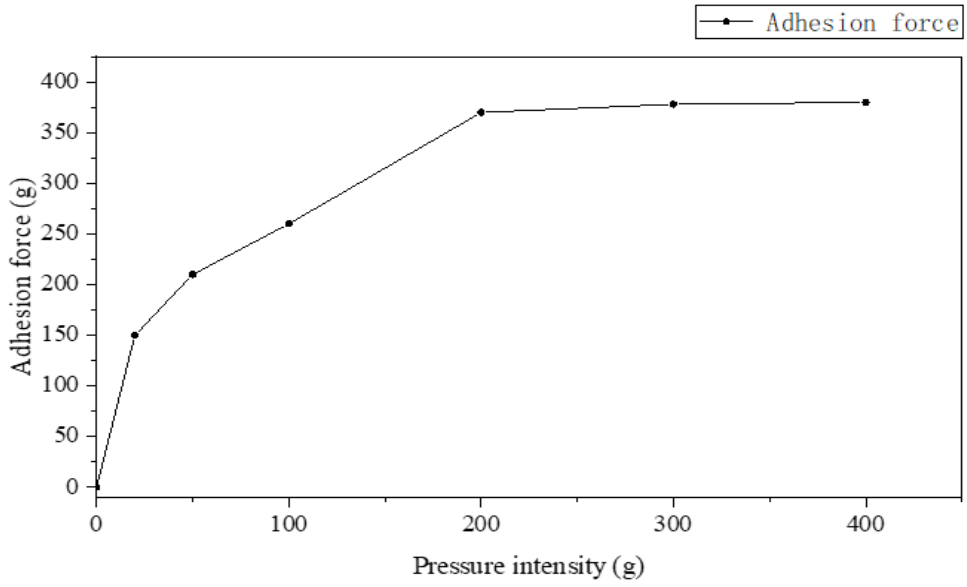


Fig.2.10 - Effect of preload on adhesive force of buccal adhesive tablets

From Figure 2.10, it can be concluded that under the same other conditions, external pressure (gravity generated by weights of different masses) is applied to the adhesion area. As the applied external pressure increases, the oral adhesive sheet and pig The adhesive force of the large intestine material gradually increases. When the applied pressure reaches a certain level (weight of 200g weight), the adhesive force of the tablet no longer increases significantly and tends to be stable.

- ***The effect of pressure time***

Prepare the blank oral adhesive tablets of prescription P1, keep the variables unique, and compress them with 200g weights for 0.5, 1, 1.5, 2, 3, and 5 minutes, and measure the pressure produced by the tablets receiving different

time pressures. Adhesion, there sults are shown Fig.2.11

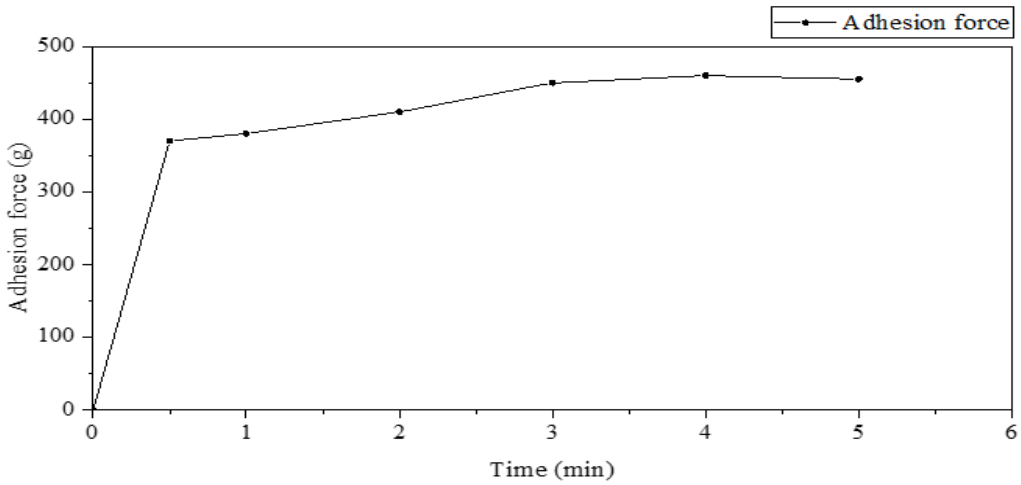


Fig. 2.11- Effect of preload time on adhesive force of buccal adhesive tablets

It can be seen from Figure 2.11 that when the pressure received by the adhesive sheet is constant (gravity generated by a 200g weight), as the pressure duration increases, the adhesive force of the tablet will increase with the pressure duration. Large, when the pressure duration reaches 3min, the adhesive force of the adhesive sheet tends to be stable and no longer increases with time.

- ***The effect of drug content on adhesion***

Select prescriptions P1, P2, and P3 to mark them as group A, and select prescriptions P4, P5, and P6 to mark them as group B. The tablets in each group consisted of an adhesive sheet with a blank drug and two adhesive sheets loaded with different contents of Periplaneta extract. Fresh pig intestine was taken from the inner wall of the large intestine, and a 200g weight was used to use its gravity to compress a 30mm×30mm In the area where the materials overlap, the duration of the external force is 30s. The adhesive force of the

adhesive sheet when it is peeled from the pig's large intestine is measured by the interface rheometer. The results are shown in Figures 2.12 and 2.13

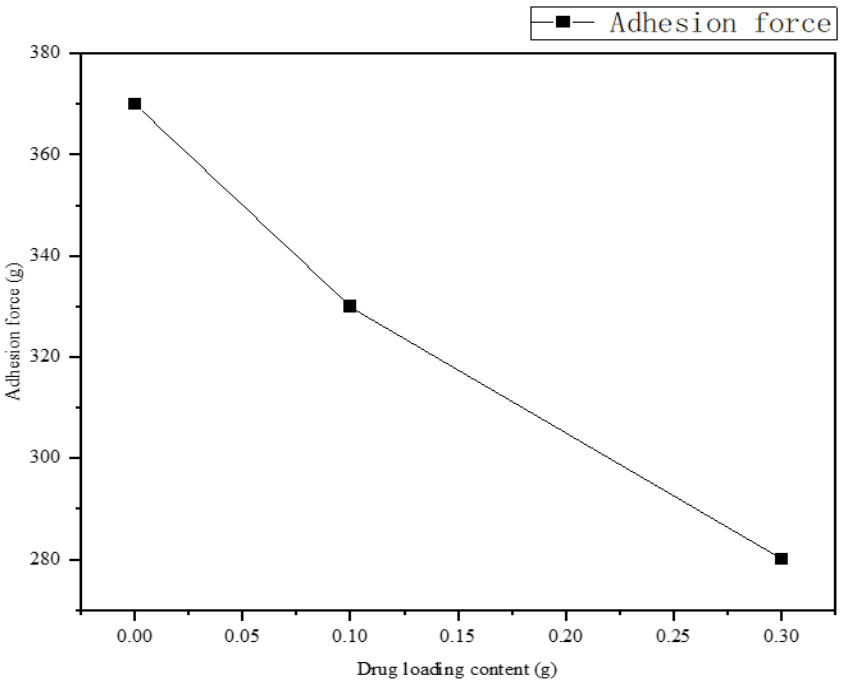


Fig. 2.12 Group A Effect of different content of drug loading on tablets

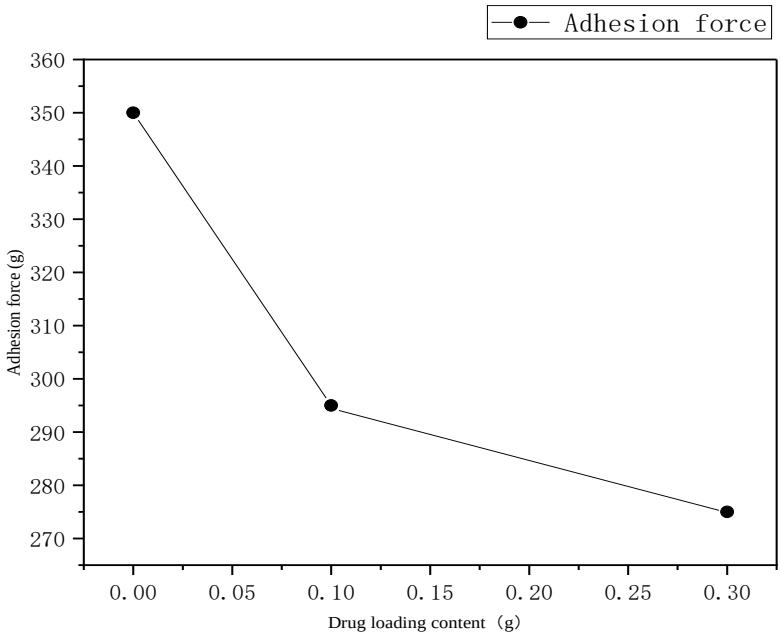


Fig. 2.13 - Group B Effect of different content of drug loading on tablets

It can be seen from Figure 2.12 and Figure 2.13 that when other conditions are kept the same, the pressure given to the material joint is constant (200g weight weight), and the continuous compression time is also constant (30s).

In group A: With the increase in the content of the cockroach extract in the prescription tablets, the adhesive force of the tablets shows a downward trend. Compared with group A, the overall trend of group B is also showing an increase in drug concentration and a decrease in adhesion, but the trend is different, which is caused by other factors.

- ***Influence of the ratio of CB941 to HPMC***

If in order to find out whether the change in the ratio of CB941 and HPMC content will affect the adhesion of the adhesive sheet. From the prescription ingredients of the adhesion layer, we can know that the content ratio of HPMC: CB 941 in group A is 1:1, and the content ratio of HPMC: CB 941 in group B is 1:2. The two groups of different ratios of HPMC: CB 941 We can get preliminary results by comparing the adhesive force produced by the adhesive sheet on the same coordinate axis. As shown in Figure 2.14

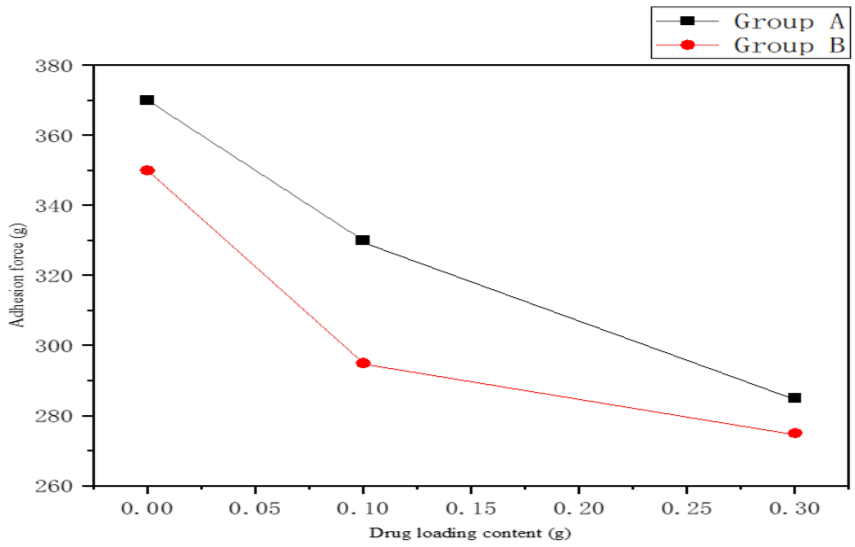


Fig. 2.14 -The adhesion forces of two groups at different ratios were compared

In the adhesive tablets, when the same content of S. chinensis extract is loaded, the external force is compressed for a certain time and the magnitude of the external force is constant, the overall trend of the tablet adhesion of the A group in the figure is higher than that of the B group. Agent adhesion. In the formulation of the adhesion layer, we used the content of carbomer as the benchmark to increase the content of HPMC to the content of carbomer 941, reaching a ratio of 1:1, so we passed the control line chart. We can know that increasing the content of HPMC in the tablet prescription can improve the adhesion of the tablet

2.4 *In vivo* and *in vitro* adhesion time of oral adhesive tablets

- In vivo adhesion time determination

6 healthy volunteers (aged 20-40 years old) are recruited. Volunteer subjects use dry fingers to place the oral adhesive sheets on the left and right sides of the cheeks of the mouth, and gently press for a few seconds to make them adhere to the cheeks of the mouth On the mucous membrane, the subject can talk and drink normally but cannot eat during the whole process. Record the start time and the time when the oral adhesive sheet falls off the oral cavity. Results are shown in figures 2-15.

- Determination of in vitro adhesion time

A number of fresh porcine large intestine that had been decontaminated and relatively flat were selected. The porcine large intestine was cut neatly and flat. The prescriptions of each test number were pasted separately on the porcine large intestinal intima with the only control variable (pressure 200 g, contact area 30 mm × 30 mm, pressure duration 30 s) were neatly mounted in a constant temperature water bath at 37 ° C, pH 6.2. The time taken for each prescription patch to fall off the porcine large intestine was observed and recorded. Results are shown in figures 2.15.

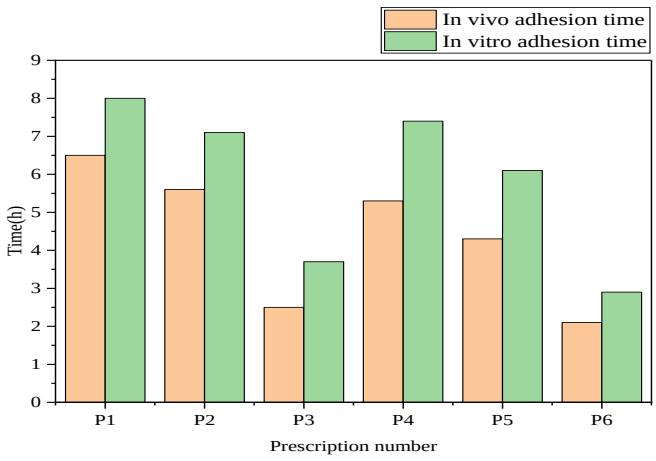


Fig. 2.15 - In vitro and in vivo adhesion time of each prescription tablet

It can be seen from Figure 2.15 that, from the overall trend, regardless of the surrounding extract load, the overall trend of in vivo adhesion time is smaller than the overall trend of in vitro adhesion time. In terms of individual trends, as the content increases, the load of surrounding extracts, in vivo adhesion time and in vitro adhesion time will all decrease. Judging from the ratio of CB941 to HPMC in group A and group B, if the content of HPMC increases, the adhesion time of the adhesive sheet will increase. Therefore, these factors are important factors that affect the adhesive force of the adhesive tablet in actual adhesion.

DISCUSSION

After the adhesive sheet is in contact with the oral mucosa, the adhesive material and the mucosal surface will have a certain binding effect, that is, the adhesive material interacts with the glycoprotein of the oral mucosa, and then hydrogen bonds with the sugar residues on the glycoprotein oligochain, so as to form a mucus gel network structure, so that the tablet has adhesion. From the experimental results, it can be found that with the increase of external pressure and the extension of pressure duration, the content of adhesion material increases. The stronger the bonding effect produced by the adhesive material, the adhesive force will also increase, because with the increase of pressure and time, the tablet fully contacts the mucosa and the adhesive force increases, but after the drug is loaded, the adhesive force decreases.

At present, there is no unified method and standard for the evaluation of oral mucosal adhesion. This article refers to related literature and improves the self-made adhesion measuring device to determine the adhesion of various prescriptions. The test method and operation are simple. During the test, we found that the adhesive material will hydrate after it comes into contact with the mucous membrane. The more severe the hydration, the lower the adhesion.

First, it is known through experiments that the polymer materials with the combination of carbomer 941 and HPMC have strong adhesion and material strength. But the properties of adherent tablets after drug loading appeared to change, and the non drug loaded adherent tablets were required to give more force when displaced the same distance compared with the non drug loaded tablets, similarly, the adherent material after drug loading required more stress. All else being equal, an external pressure was applied to the adhesion area, and as the applied external pressure increased, the adhesion force of the oral adhesive sheet to porcine large intestine materials gradually increased, and when the applied pressure reached a certain point, the adhesion force of the tablets no longer increased significantly, and leveled off. When the pressure received by the

adherent pieces was certain, the adhesion force of the tablets will increase with the duration of pressure and increase with the duration of compression, when the duration of reaching pressure reaches a certain time, the adhesion force of the adherent pieces tends to plateau and no longer increases with the duration of time. When the drug concentration increases, the adhesion force produces a decreasing trend. When increasing the content of HPMC in the prescription of tablets, it can play the role of improving the adhesion force of tablets.

Bioadhesion refers to the phenomenon of adhesion between high molecular polymer materials with certain bioadhesive properties and biological mucosa [45]. Bioadhesive can prolong the local residence time of the drug, increase the local drug concentration of the drug in a specific part of the organism, and further improve the bioavailability of the drug. The adhesive properties of bioadhesive materials mainly depend on the properties and polymerization properties of high molecular weight polymer materials, such as the relative molecular weight, viscosity, hygroscopicity, and specific binding ability of bioadhesive materials. Affect the adhesion of bioadhesive materials.

For Carbomer, it is an acrylic polymer cross-linked with synthetic acrylic acid and allyl sucrose or allyl pentaerythritol. It is a white loose powder at room temperature with a slight odor and strong hygroscopicity. Therefore, it should be sealed and stored during the test or storage process to avoid moisture absorption and agglomeration affecting the performance of the auxiliary material. As an excipient, it is often used in semi-solid preparations such as gels and tablets. Secondly, it has good adhesion properties, which can prolong the local action time of the drug and improve the efficacy of the drug. Carbomer is stable in nature and has no irritation or allergic reaction to the oral mucosa.

Hydroxypropyl methyl cellulose (HPMC) is a semi-synthetic material made by the polymerization of part of cellulose methyl and part of polyhydroxy propyl ether. HPMC is white, milky white granular or fibrous powder with good fluidity. HPMC can be dissolved in water to form a white to transparent colloidal solution with a certain viscosity.

Hydroxypropylmethylcellulose is one of the most widely used pharmaceutical excipients in the industry, and it has many characteristics that other excipients do not have Stability: relatively stable to acid and alkali, long-term storage does not affect the viscosity, very stable; chemically inert: because it is a non-ionic cellulose ether, it will not react with other excipients during use as an excipient; Cold water solubility; metabolic inertia: the human body neither metabolizes nor absorbs in the body; viscosity adjustability: according to the different proportions of different rubber materials, its viscosity also has a certain linear relationship; HPMC is a safe, non-toxic, and non-irritating to the human body Sexual substance.

In the preparation process of oral adhesive tablets, a combination of two or more adhesive materials is often used. For example, the combination of carbomer and hydroxypropyl methyl cellulose has good adhesion. In this experiment, carbomer and hydroxypropyl methyl cellulose are used as adhesive materials, and the different ratios of carbomer and hydroxypropyl methyl cellulose are 1:2, 1:1. The investigation of adhesion is oral adhesion. An important evaluation index for the attached sheet, only when the adhesive sheet reaches a certain adhesive force, can it maintain sufficient adhesion time on the oral mucosa, and the release of the drug can be completely. Adhesion between mucous membranes. The influencing factors of adhesion were measured, and it was confirmed that the external pressure intensity of the adhesion interface, the duration of external pressure, the influence of drug loading on the adhesion performance, and the influence of the ratio of adhesion materials on the adhesion performance. The oral adhesive tablet loaded with Periplaneta extract is prepared according to the optimal prescription, the preparation process is simple, the quality is controllable, and its performance can be further researched and developed.

Section3*(Design and recommendation)*

BASIC INTRODUCTION OF INDUSTRIAL PRODUCTION MATERIALS AND DRUGS

In industrial production, since oral adhesive tablets will directly affect the oral cavity, we should pay attention to the safety of the tablet materials and the drugs contained. This chapter will conduct Cytotoxicity tests on oral adhesive tablets containing Periplaneta americana extract, including Cytotoxicity of polymer adhesion materials and Periplaneta extracts. Secondly, this chapter will also test the ingredients of the cockroach extract in the tablet. By testing the content of specific amino acids, the dissolution effect of the drug can be reflected. The extraction process of Periplaneta extract involved in the industrial production of oral adhesive tablets, the key technology, equipment and process of banburying and casting of polymer film.

- ***Matrix and excipients***

Bioadhesion in the field of pharmacy mainly refers to the adhesion state of some high-molecular polymers in the body, and its main function is to act on the cell mucosa of the human oral cavity, eyes, nose, vagina and various digestive pathways [46]. Mucus is secreted by the mucous membrane, mainly composed of mucus proteins, carbohydrates, fats, inorganic salts, water and other substances. The role of mucus proteins can promote mucus gelation, aggregation and adhesion [47]. The surface of the tissue mucosa has better wetting conditions, which is also one of the best conditions for the swelling polymer material to be in close contact with it. Each molecular piece of the adhesive material is embedded in the intercellular space or with various sticky parts in the mucus. Interpenetrate. The polymer is produced by a variety of comprehensive reactions such as various mechanical mosaics, covalent bonds, electrostatic attraction, van der Waals forces,

hydrogen bonds, and water dispersion bonds. Preservation and maintenance of microbial adhesion. The bonding strength is related to the charge density, number of molecules, molecular space structure, swelling degree and concentration of polymer materials [48]. In addition, the surface chemical polarity of the polymer in the drug, the flexibility of the chain segment, the pH value of the treatment site, and the mucus content may have some adverse effects on it.

Bioadhesive can be summarized as all macromolecular compounds that can adhere to the mucosa of biological tissues, and their action phenomenon can be called bioadhesion [49]. In recent years, artificial bioadhesion has made the application of mucosal chemical adhesion technology develop rapidly. Adhesives are usually widely used in the mouth, eye sockets, vagina and even some specific areas of the gastrointestinal tract, and are transported by the epithelial cells of the human mucosa. Due to the particularity of its dosage form, it can improve the tightness and consistency of the drug in contact between the body and the mucous membrane, which is conducive to the absorption of the drug [50]. In addition, the use of mucosal adhesives is very easy to control the absorption rate of the drug and the number of absorbents. Many oral infections are caused by microorganisms directly eroding the epithelial cells of the oral cavity and gastrointestinal tract. They are all a typical microbial adhesion. We can use bioadhesive as raw materials to make mucosal adhesives, so that the drugs can be better absorbed by the mucosa, so that we can truly achieve the main purpose of preventing diseases. In this study, the proportion of HPMC in the prescription was set up in different experimental groups, and the results showed that the adhesion properties are also different, which is closely related to the bioadhesive properties of HPMC. The adhesion of polymer auxiliary materials needs to go through two stages: contact processing and joint. After the film contacts the oral mucosa, a series of physical and chemical reactions will occur, and then connect with the oral mucosa to prolong the adhesion period of the mucosa. In a humid oral environment, the film has begun to swell and form an adhesion layer. When

the dry film containing the oral liquid is over water, the adhesion will decrease. Therefore, the dissolution rate of the film and its swelling degree have a very significant impact on its adhesion and drug release characteristics.

3.1Periplaneta americana extract

Periplaneta has been used as medicine for a long time and has a long history of medical culture and pharmacy. It was first seen in the "*Shen Nong's Materia Medica*" and listed as a Chinese herbal medicine. It is used for medical and medicinal purposes by modern medicine. Known as the largest insect in domestic cockroaches, other common species include Australian cockroaches, Japanese cockroaches, German cockroaches, and variegated cockroaches [51]. Periplaneta americana contains active ingredients such as polysaccharides, peptides, and alkaloids. Modern pharmacologists and researchers have found that it has the effects of resistance to oxidation in the body, resistance to liver fibrosis, prevention of liver and treatment of malignant tumors [52]. Periplaneta is the "cockroach" in the mouth of ordinary people. It was first used as medicine to treat diseases such as silt removal and infertility.

Since the 1980, researchers have conducted large-scale studies on the content of amino acids in the extract of Periplaneta, and the results show that the content of amino acids in the extract is as high as 43.17%. Not only that, but also the proportion of amino acids with certain medicinal functions 55.43%. In addition, active substances such as polyols, organic acids, alkaloids, serotonin and isocoumarin have been found in the laboratory; modern pharmacological studies have shown that American cockroach has the function of promoting vascular proliferation and tissue repair; anti-oxidation; Anti-inflammatory and analgesic; antibacterial and antiviral; anti-tuberculosis; strong heart accelerates pressure and improves hourly microcirculation; resistant anti-tumor, enhances self-immunity and other pharmacological functions [53]. Periplaneta americana extract has been recognized for its clinical effects in repairing, strengthening heart function, hepatitis and liver fibrosis. For example, a large number of extract liquid

preparations have been widely used in drug trials and clinics, and they have shown good therapeutic effects in the treatment of gastric ulcers. Chinese patent medicines with Periplaneta americana as the main raw material, such as Kangfuxindrops, Jinke capsules and Xinmailong injection, have been widely used in clinical practice [54,55]. A large number of clinical studies have also fully shown that it improves the blood microcirculation on the surface of the wound by promoting the re-proliferation of local granulation connective tissue in the wound and the restoration of oral blood vessels, and accelerates the re-shedding of local necrotic granulation tissue to quickly Effectively repair local wounds that cause oral ulcers.

Chemical composition

①Protein, amino acid, peptide.

The main components of animal medicine are mostly protein and amino acids, and the amount is relatively high. Yang Fang et al. [56] used an automatic amino acid analyzer to determine the types and amounts of amino acids in Periplaneta americana. The results showed that the total amount of amino acids in Periplaneta americana was as high as 43.17%, and the amount of medicinal amino acids accounted for 55.43% of the total amino acids. Neuropeptides generally refer to a type of special information substance with low amount and high activity that exists in nerve tissue.

② Carbohydrates In recent years, polysaccharides, as one of the main active ingredients of Periplaneta americana, have attracted the attention of scientific researchers. Wang Yongyi et al. [57] studied the extraction and separation methods of polysaccharides in Periplaneta americana, and the results showed that alkaline extraction and protease extraction can obtain higher amounts of polysaccharides. Li Xiaoqing et al. [58] optimized the extraction and separation

process of Periplaneta americana polysaccharide by salt extraction method and dilute alkali method. The salt extraction method used 3 factors (salt concentration, extraction temperature, extraction time) and 3 levels of orthogonality. In the test, the dilute alkali method uses an orthogonal test with 3 factors (alkali concentration, extraction temperature, extraction time) and 3 levels.

The results showed that the main factor affecting the extraction of polysaccharides by salt extraction was salt concentration and it was positively correlated; the amount of polysaccharides extracted by dilute alkali method was positively correlated with alkali concentration and immersion time, but had little correlation with extraction temperature. Xiao Peiyun et al. [59] used the phenol-sulfuric acid method to determine the total sugars of Periplaneta americana from different breeding bases. The results showed that the total sugars of Periplaneta americana from different bases ranged from 15.56 to 45.65 mg/g, which was quite different. This may be related to factors such as feed, breeding cycle and production area processing during the cultivation of medicinal materials.

③Fatty acids In the past 10 years, GC-MS has been used to analyze the chemical components of American cockroaches, and it has been found that there are relatively high amounts of fatty acids and their esters. Meng Songnian et al. [60] studied the oleochemical components of Periplaneta americana and identified 19 compounds. The amount of fatty acids accounted for 36.77%. Among them, the unsaturated fatty acid is octadecenoic acid (13.86%) and octadecadienoic acid (8.23%); the saturated fatty acid is hexadecanoic acid (10.13%). Luo Jianrong et al. [61] determined the fat-soluble components of American cockroaches, and the results showed that the total amount of fatty acids and fatty acid esters accounted for 26.62%. Jiao Chunxiang et al. [62] determined the chemical composition of the alcohol-extracted water-soluble components of Periplaneta americana, and the

amount of fatty acids and fatty acid esters was 5.88%. Mei Ming et al. [63] detected 13, 27, and 42 compounds in the non-methylated extract of Periplaneta americana oil, the methylated extract of Periplaneta americana, and the base methylated extract of Periplaneta americana, respectively. They are alkanes, fatty acids and fatty acid ester compounds, of which fatty acid esters are mostly compounds with 12 carbons or more. Yu Xin et al. [64] analyzed the supercritical CO_2 (SFE-CO_2) extract of Periplaneta americana and detected 50 chemical components, most of which are unsaturated fatty acids and esters, with a content of 76.33%.

3.2 MTT method to measure the toxic effect of Periplaneta americana extract on HeLa cells

- Laboratory equipment and drugs

Experimental instrument

Table 3.1

Instrument	Model	Manufacturer
High speed freezing centrifuge	Neofuge 1600R	Shanghai Lishen Scientific Instrument Co., Ltd
Cell ultra clean workbench	ZHJH-C115B	Shanghai Zhicheng instrument analysis Manufacturing Co., Ltd
Ultra low temperature storage box	DW-86L728J	Haier biomedical Co., Ltd
Vortex mixer	Vortex-2	Shanghai Hushi Industrial Co., Ltd
Decolorization shaker	TS-1	Qilin bell Instrument Co., Ltd
Cell incubator	311	Thermo Fisher Technology Co., Ltd
Inverted optical microscope	DM IL LED	Leica BIOSYSTEMS
HH series digital display constant temperature water bath pot	XMTD203	Jiangsu Science and Technology Instrument Co., Ltd

List of experimental drugs

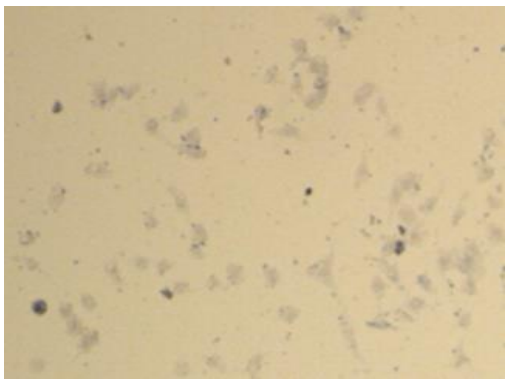
Table 3.2

Experimental drugs and reagents	Specifications	Manufacturer
Thiazole blue (MTT)	98%	Sigma-Aldrich
Lipopolysaccharide	biotechnology grade	ETA biology
Disodium hydrogen phosphate	Analytical purity	Sinopharm Chemical Reagent Co., Ltd
Potassium dihydrogen phosphate	Analytical purity	Sinopharm Chemical

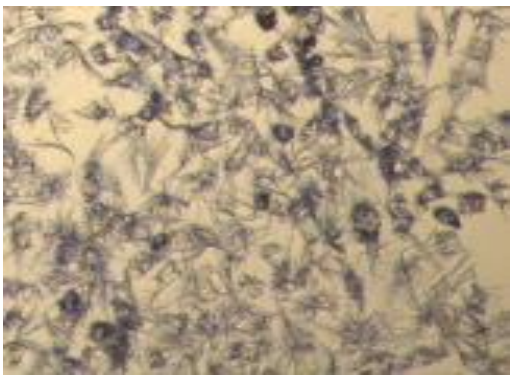
		Reagent Co., Ltd
Phosphate buffer (PBS)	biotechnology grade	Sangon Biotech
RPMI Medium Modified		HyClone
FETAL BOVINE SERUM		GEMINI
TRYPSIN 0.25%（1X）		HyClone

The duration of exposure of exponential growth cells to cytotoxic drugs usually depends on the time required to produce the maximum damage, but it is also affected by drug stability . After the drug is removed, the cells are allowed to proliferate for another 2 ~ 3 populations, doubling the time, so that the living cells that can proliferate can be distinguished from those that cannot proliferate [65]. Then the number of viable cells was determined by MTT dye reduction reaction. As long as the MTT methyl product is dissolved in a suitable solvent, it can be quantified by spectrophotometry

MTT can react with succinate dehydrogenase in mitochondria of living cells to produce blue purple crystalline substance methyl (as shown in Figure 3-1), which is insoluble in water and deposited in living cells [66]. After being dissolved by DMSO, the blue purple nail has a special absorption peak at 492 nm. When the number of collected cells is within a certain range, the number of living cells is directly proportional to the absorbance at 570 nm after methylphenidate dissolution.



A



B

Fig. 3.1- A shows the toxicity of the tested materials; B non toxicity of materials tested

Experimental steps

①HeLa cells were tiled in 96 well plates and diluted to 0.5 ~ 1 with DMEM + 10% FBS × 104 / well, overnight culture (37 °C, 5% CO2).

②After the cells completely adhere to the wall, add samples to stimulate the cells. Add 0.1, 0.2, 0.3, 0.4 and 0.5 respectively（μg/ml）The culture system of three kinds of cockroach extracts (0g, 0.1g, 0.3g) containing different contents (g / ml) was 100 μ L per hole; Three repeat wells were set in each group, and the rest were control wells (only cells and DMEM + 10% FBS medium were added). Add 100 to the holes around the outermost side respectively μL PBS solution. The experimental design is shown in Figure 3.2. The cells were cultured for 24 hours. Sample1 is an adhesive tablet containing 0g Periplaneta extract, sample 2 is an adhesive tablet containing 0.1g Periplaneta extract, and Sample3 is an adhesive tablet containing 0.3g Periplaneta extract.

③Remove the medium containing the sample, add an appropriate amount of PBS and wash it twice, and then add 100% to each well μ L medium containing 0.5% MTT (5 mg / ml) and continue to culture for 3-4 hours.

④Remove the medium containing MTT and buckle the 96 well plate upside down on clean paper for 3 times. Add 100 per hole μ L DMSO, shake away from light for 10 min, and measure the absorbance of cell lysate at 492 nm.

⑤ Cell viability is calculated according to the following formula:

cell viability% = Ax / A_0 × 100%； Ax is the absorbance of the experimental group and A_0 is the absorbance of the blank control.

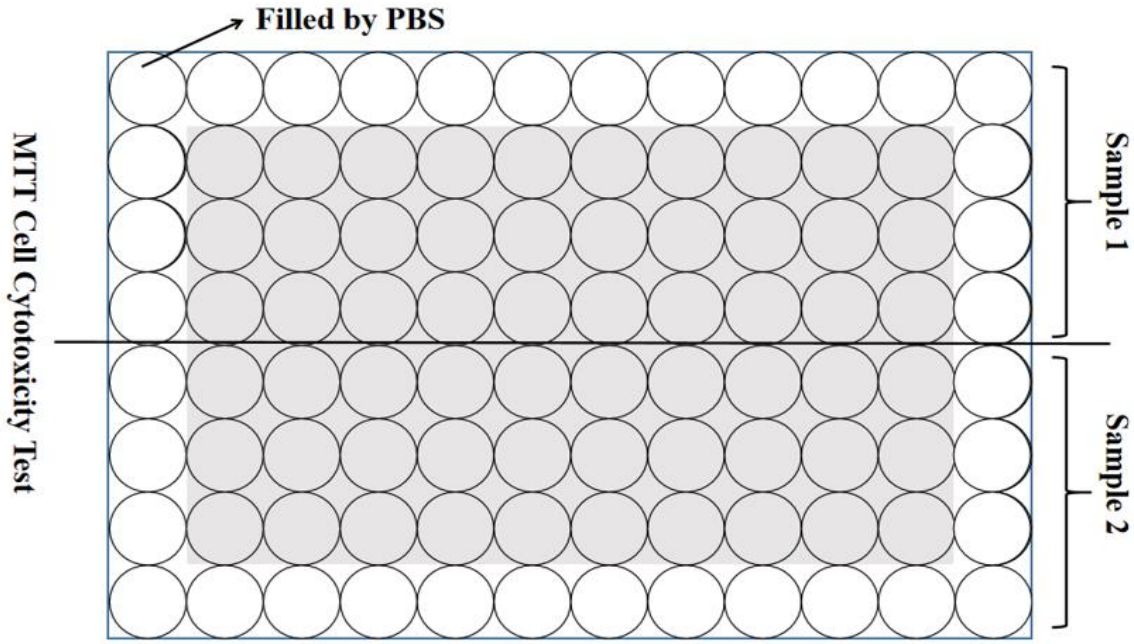


Fig.3.2 - Schematic diagram of cell experiment in 96-well plate

- ***Experimental principls:***

In order to detect whether Periplaneta extract has killing effect on HaiLa cells, MTT cytotoxicity test was used. HeLa cancer cells were stimulated with adhesive tablets containing different concentrations of Periplaneta extract. All experiments were repeated for 3 times, and the obtained data were analyzed by *GraphPad Prism* software. T-test was used for comparison between groups, * $P < 0.05$, * * $P < 0.01$, * * * $P < 0.001$.

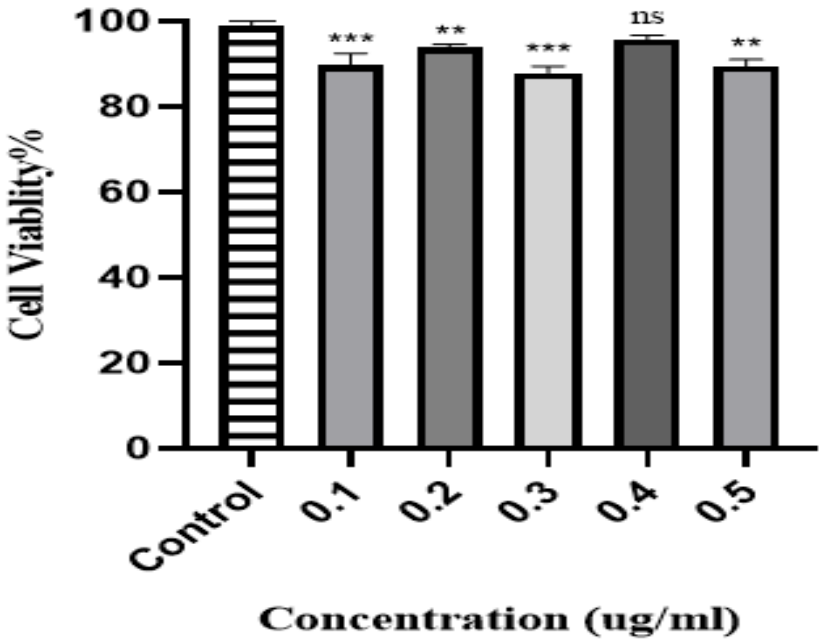


Fig.3.3- Sample1 Has high cell viability and the material is non-toxic

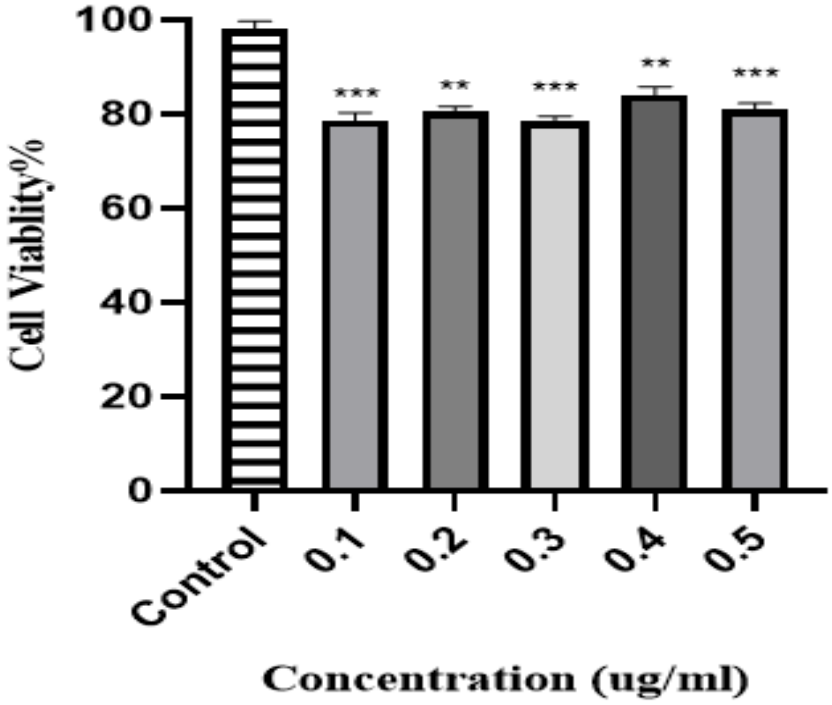


Fig.3.4- Sample 2 Has high cell viability and the material is non-toxic

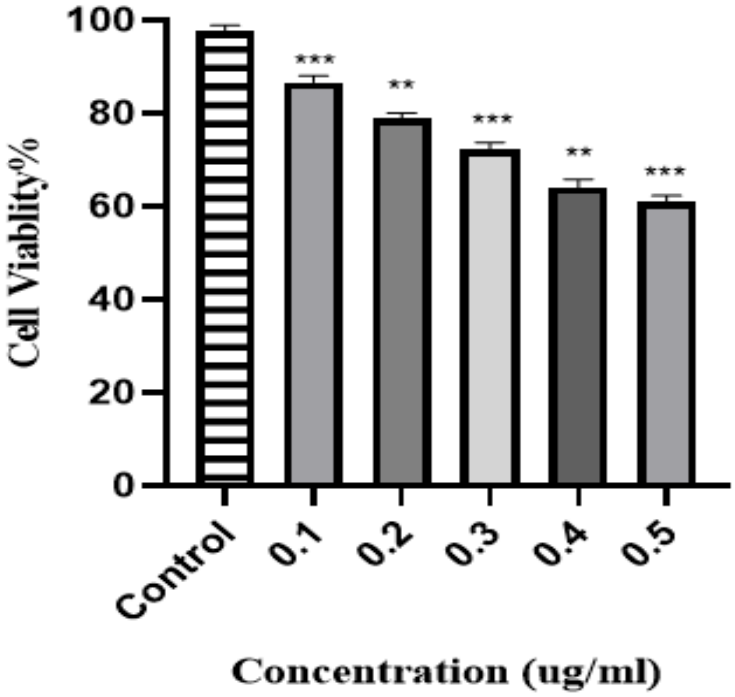


Fig.3.5- Sample 3 The decrease of cell concentration indicates that there is toxicity when the drug concentration is too high

Conclusion: the experimental results show that the adhesive layer made of polymer material itself has no toxicity. When the drug content was 0.1g, the cell concentration did not decrease with the increase of medium concentration, indicating that the drug was not toxic; When the drug content was 0.3g, the cell concentration decreased and toxicity appeared with the increase of medium concentration.

3.3 Identification of Periplaneta extract from oral ulcer membrane

The oral ulcer membrane containing Blattella major was dissolved in water, and the amino acid components were investigated by amino acid autoanalyzer, and the experimental results are shown in Fig.3.6 and Table 3.3. As can be seen, there were multiple components, among which the predominant amino acids included: alanine (peak 6), glycine (peak 5), and proline (peak 2). The main matrix of the oral ulcer membrane was an acrylic bioadhesive polymer, which might interact with the active components of amino acids and peptides from Blattella major extract to affect its release.

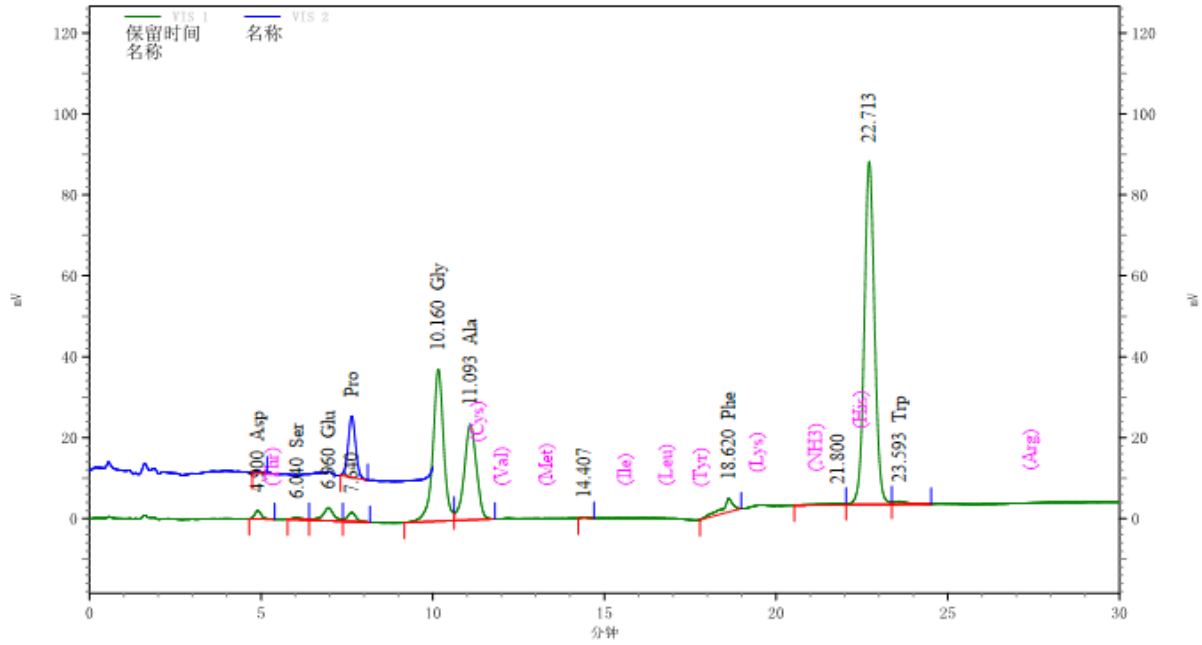


Fig.3.6-Amino acid analysis chromatogram of oral ulcer membrane solution containing Periplaneta extract

Amino acid analysis results

Table.3.3

VIS 1 result						
PK#	RT	Name	Height	Area	ESTD Conc/nmol	Conc/ng
1	4900	Asp	8185	111444	0.089	110785
		Thr			0.000BDL	0.000
2	6.04	Ser	1636	36979	0.028	2.929
3	6.96	Glu	12572	282707	0.222	32.706
5	10.16	Gly	150002	3269919	2.663	199.908
6	11.093	Ala	94488	2331670	2.126	189.369
		Cys			0.000BDL	0.000
		Val			0.000BDL	0.000
		Met			0.000BDL	0.000
		Ile			0.000BDL	0.000
		Leu			0.000BDL	0.000
		Tyr			0.000BDL	0.000
8	18.62	Phe	13324	305466	0.312	51.514
		Lys			0.000BDL	0.000
		NH3			0.000BDL	0.000
		His			0.000BDL	0.000
		Trp	3002	91564	0.065	13.233
		Arg			0.000BDL	0.000
Total			283209	6429749	5.504	
VIS 2 result						
PK#	RT	Name	Height	Area	ESTD Conc/nmol	Conc/ng
2	7.64	Pro	60557	917135	3.541	407.526
Total			60557	917135	3.541	407.526

The experimental results show that the active ingredients of amino acids can be effectively released from the ulcer membrane matrix, which lays the foundation for the therapeutic effect.

3.4 Industrial preparation of oral adhesive tablets

Significance of oral ulcer film preparation

What is the difference between oral ulcer film and traditional medicine? Compared with the two, the more effective method of traditional medicine is to choose spraying agent, spraying powdered medicine containing medicine on the affected area of oral ulcer to achieve the treatment of oral cavity The effect of ulcer, but this method is a little irritating, because it will directly stimulate the mouth ulcer, the pain is very strong, not only that, in the process of applying the medicine, a lot of powder will be wasted by spraying. In comparison, the oral ulcer film is more gentle and non-irritating, and it does not waste medicine.

The film agent is a film dosage form made by wrapping the drug into the cavity of the polymer film or dissolving it into the inside of the polymer film. The product can be used for oral or sublingual administration. It can also be applied to mucosa and oral cavity. This type of film-forming agent has the characteristics of small size, light weight, convenient carrying, simple production process, good system and locality and so on. According to different therapeutic film raw materials and the special application properties of various therapeutic film drugs, as well as the special requirements for the clinical therapeutic application of drugs, different therapeutic films can be prepared by selecting materials, such as various quick-acting therapeutic films or Various quantitative slow-acting therapeutic drugs [67]. The British Pharmacopoeia (BP1948) contains 4 kinds of membranes such as atropine based on gelatin. Mainland China has gradually started the independent research and development of such film formulations since the 1970s. In 1985, these new film formulations were included in the Chinese Pharmacopoeia for the first time.[68]

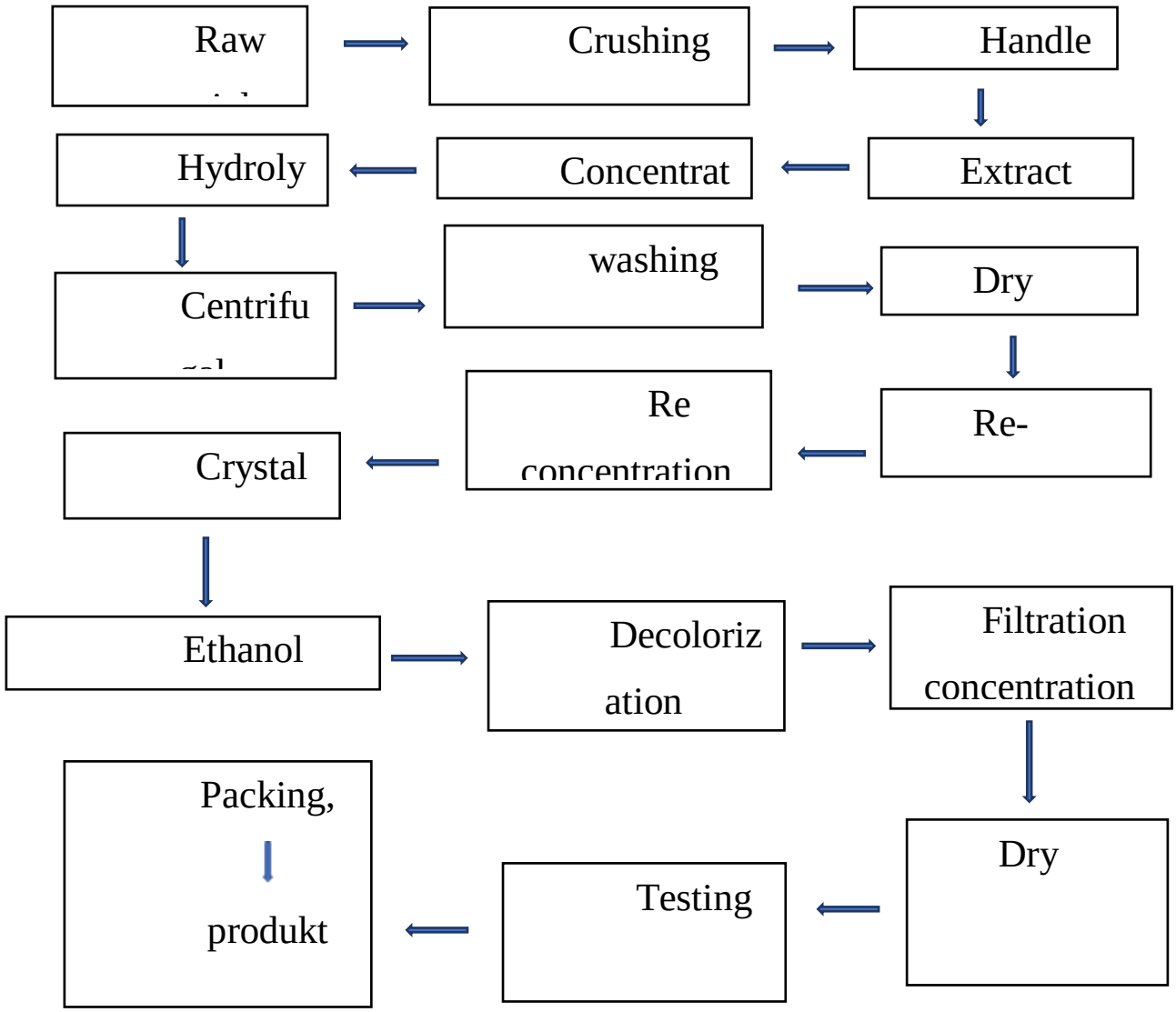
The oral ulcer film is different from the transparent film we imagined. The difference is that it is a tiny film containing drugs that can treat oral ulcers. Compared with traditional drugs for the treatment of oral ulcers, the film can be Put it directly on the area suffering from oral ulcers, so that the medicine can be fully applied to the affected area of oral ulcers. According to the different conditions of different patients, different types of medicated oral ulcer films can be selected. Although the ingredients are not the same, anesthetics and propolis are commonly added. In this way, it can not only moisturize the oral mucosa near the affected area, but also reduce oral ulcers. Pain and drug stimulation. This is the real prescription. Choosing to use oral ulcer film to treat oral ulcers is a good choice.

Extraction method and technology of Periplaneta extract in industry

The method used in the existing extraction process of American cockroach is the traditional pure extraction method. Separating a single active component from the American cockroach requires relatively high cost, and the required equipment is also relatively complicated, and the entire process takes a long time, and the loss of active component content is large, and the benefits obtained are difficult to measure. Existing studies have shown that the extract of Periplaneta americana has good effects in anti-tumor, promoting tissue repair, analgesia, anti-inflammatory and improving immunity. Compared with the separation process of effective components such as polysaccharides and peptides in Periplaneta americana, the preparation process of the extract of Periplaneta americana is relatively simple and has greater economic value. At present, there are methods for preparing American cockroach: ① Soak the killed living body of American cockroach with a certain concentration of ethanol, then decoct the worms in water several times, combine the decoction liquid, and vacuum concentrate to make an

extract; ②For America The cockroaches are inactivated by hot water, and the worms are soaked in a certain concentration of ethanol for a long time, and then heated and refluxed with ethanol and water for extraction. The extraction temperature exceeds 65°C, and then the extract is concentrated to obtain an extract. It can be seen from the above that the current preparation of Periplaneta americana extracts is processed by ethanol or higher temperature methods, but such processing methods will inactivate the active ingredients such as proteins, small molecular peptides and polysaccharides, thereby greatly reducing the activity. The medicinal value of the extract of Periplaneta americana; the extract prepared by the above preparation process has not undergone a certain purification treatment, and the concentrated extract contains more impurities, and the dried extract is easier to be dissolved in moisture. It is stored and used It is extremely inconvenient; and the above steps did not degrease the body of the American cockroach, and the body oil of the American cockroach interferes with the leaching of the active ingredients, and is partially dissolved in ethanol, and is made into an extract along with the extracted ingredients. , Which in turn affects the quality and use value of the extract. Therefore, the best choice now is to use low-temperature freeze-drying technology, which can produce American cockroach extract powder, improves the use value and storage convenience of American cockroach extract, and broadens the application range of American cockroach extract. The general process flow is shown in Figure.3.7.

Fig.3.7 General process flow chart of Periplaneta extract purification



Preparation and key technology of tablet adhesion layer

① Banburying：

Carbomer 941 and cellulose derivative aqueous solutions are typical non-Newtonian fluids with high viscosity, which brings great difficulties to solution preparation and casting film formation. In the experiment, ethanol was selected as the main solvent to reduce the viscosity of the polymer solution. In industrial production, an internal mixer should be used to grind and Banbury. After the Banbury is allowed to stand, the molecular solution will be more uniform and there will be no obvious bubbles. During the casting process, the polymer solution showed good spreading ability. After drying at elevated temperature, the ethanol in the film after casting was almost completely volatilized.

Banbury mixer：

The internal mixer is a machine that is equipped with a pair of rotors with a specific shape and relatively rotating, which can intermittently plasticize and mix polymer materials in a closed state with adjustable temperature and pressure. It is mainly composed of a mixing chamber and a rotor. Rotor sealing device, feeding and pressing device, unloading device, transmission device and machine base and other parts。

The working principle of the internal mixer:

When the internal mixer is in the mixing process, after the material is added from the hopper, it first falls into the upper part of the two relatively rotating rotors, and is brought into the gap between the two rotors under the pressure of the top bolt and the action of friction, Subject to kneading. The material is divided into two parts by the protruding edge of the lower top bolt. As the rotor rotates, it passes through the gap between the rotor surface and the front wall of the mixing

chamber. After being subjected to strong mechanical shearing and kneading, it reaches the dense the upper part of the refinery room. [69] Under the influence of the different speeds of the rotors, the two strands of rubber material converge on the upper part of the two rotors at different speeds, and then enter the gap between the two rotors to circulate repeatedly. During the entire work of the internal mixer, when the material is plasticized in the internal mixer, it is subjected to both strong mechanical stress and thermal oxidative cracking, so the required plasticity can be achieved in a short time, and the required form can also ensure that the two materials interact, fully mix and swell. As shown in Figure 3.8.

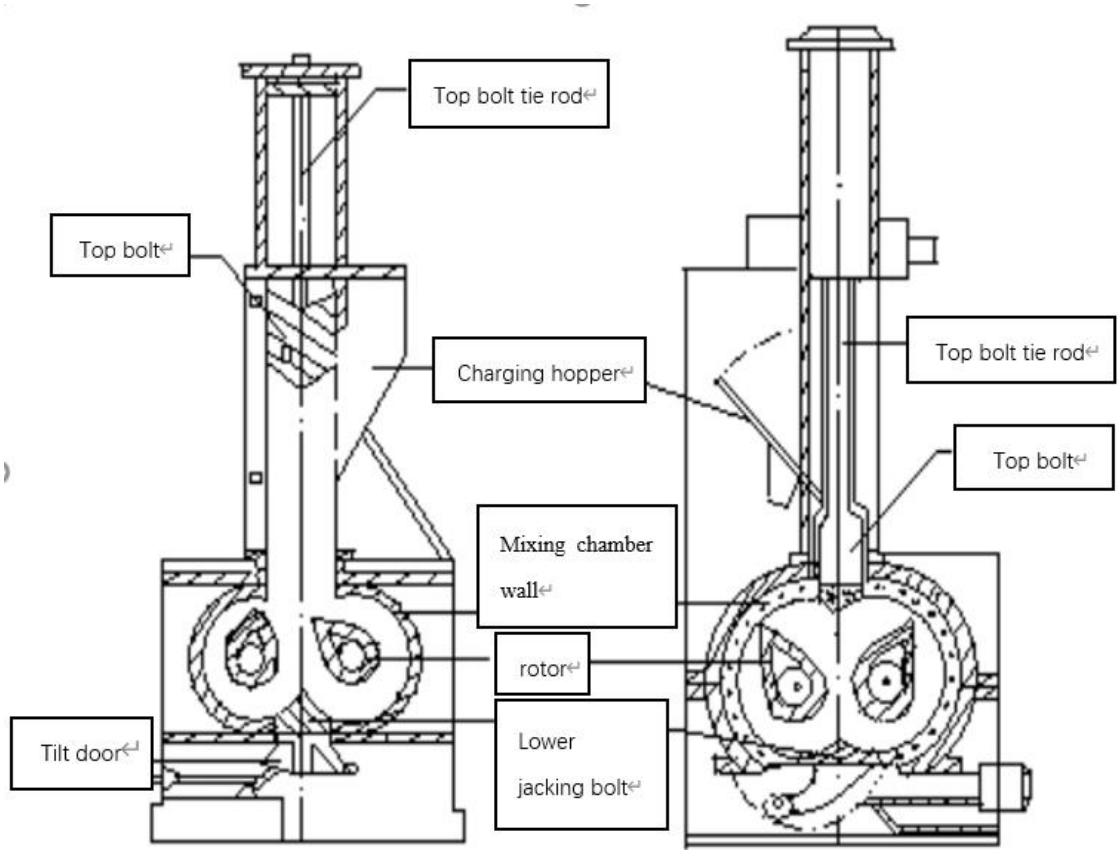


Fig.3.8-Basic structure diagram of two classic internal mixers

In the preparation process of the adhesive layer of the oral adhesive tablet, only in the laboratory preparation system, we use simple manual fusion and banburying. The banburying effect is average. There are a lot of bubbles in the

material, agglomeration, and the temperature cannot be precisely controlled. In the process of industrial production, these problems can be better solved by using internal mixers to ensure the full reaction and mixing of the matrix and auxiliary materials, which will greatly help the improvement of tablet quality.

② Casting process:

A film production process that first plasticizes and melts the raw materials through an extruder. Extruded through a T-shaped structure forming die, cast in a sheet shape onto the surface of a smoothly rotating cooling roller. The film is cooled and shaped on the cooling roller, and then pulled and trimmed to obtain a film product.

Casting machine:

Casting machine refers to the special equipment used to make cast film. Using high-precision electronic ceramic casting machine, using alumina as the main raw material for ceramic casting, first mix the crushed powder with the binder, plasticizer, dispersant, and solvent to form a slurry with a certain viscosity. It flows down from the hopper and is scraped and coated on the special base tape with a certain thickness by a scraper. After drying and curing, the film that becomes the green tape is peeled off from the top, and then the green tape is punched and cut according to the size and shape of the finished product. Laminating and other processing treatments to make finished products to be sintered. It has the advantages of low cost, high quality, non-toxicity, and simple production process.

The principle of the casting process:

First, the prepared materials and other auxiliary materials are mixed according to the prescription ratio to form a slurry with a certain viscosity. The slurry flows down from the container and is scraped and coated on the special base tape with a certain thickness by a scraper. After drying and curing, it is removed from the top. The film that becomes the green tape is peeled off, and then the green tape is punched and laminated according to the size and shape of the finished product to make a preliminary finished product. As shown in Figure 3.9

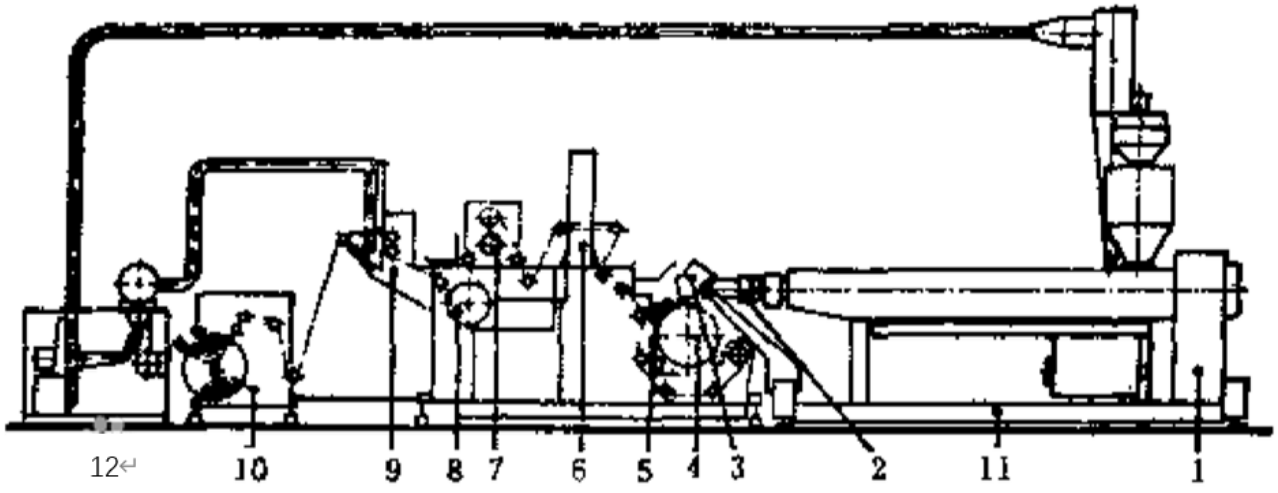


Fig.3.8- 1-Extruder; 2-connector and filter; 3-head; 4-cold roll; 5-air knife; 6-thickness gauge; 7-pretreatment device; 8-post cooling roll; 9-cutting device; 10-winding machine; 11-positioning device; 12-side strip recovery device.

In the preparation of the oral adhesive, the most critical part is the preparation of the film. In the laboratory, the thickness of each layer is controlled by the thickness of the tetrafluoroethylene frame; the solvent volatilization condition is 35°C, 6 h; finally, the solvent evaporates the cast film was cut into 10 mm diameter discs to obtain the preliminary product. In this process, the thickness control of the film is not very accurate. The casting process is passed, manual casting, manual control of the casting speed, there are big uncertain factors, the casting speed is not uniform, and the film collection inconvenient. [70] In

industrial production, the use of a casting machine can solve this problem, the speed of the casting machine can be set uniformly, the thickness of the film can be accurate to a thinner unit, and the degree of automation is high.

Summary of this chapter

This chapter first conducts experiments on the safety and dissolution performance of oral adhesive tablets containing Periplaneta extract. From the experimental results, it can be seen that the main body of the film made by using carbomer and HPMC as the matrix and combining with other excipients is correct. The cell is non-toxic, indicating that the material made by the prescription is non-toxic and harmless, and has high safety performance. Secondly, the dissolution of oral adhesive tablets was also tested. The test was to detect the content of specific amino acids in the dissolution solution of the cockroach extract. The experimental results showed that the cockroach extract can be used in the tablet. Better release under the system.

However, the above preparation experiments are all obtained under laboratory conditions. In industrial production, the three most critical production processes are: ① the extraction of the cockroach extract, ② the mixing of materials, ③ the preparation of the membrane. There is a huge difference between realization and in the laboratory. The extraction process of periplaneta extract should ensure the purity and output of the extract. Only by adopting a unified industrial process can the quality and output of industrial production be adapted. For the internal mixing of materials and auxiliary materials, the use of an internal mixer can ensure the full mixing and reaction of the materials, and the polymer materials can fully swell, which can remove the bubbles generated during the process and the uneven reaction, which can be effectively avoided through the use of internal mixers. The occurrence of undesirable phenomena improves the quality of the product by improving the quality of the process reaction. In the preparation of membranes, casting film formation is a process method for making membranes.

In industrial production, the use of casting machines can effectively avoid the disadvantages of artificial membrane production in the laboratory. The thickness of the film after forming can be freely controlled with high precision, fast production speed, high control precision of materials, and the film has a regular and beautiful shape.

CONCLUSION

The main body of the Periplaneta americana oral patch developed in this subject is a combination of Periplaneta americana extract and the oral patch. We use the Bioadhesive Drug Delivery System (BDDS), the purpose is to directly contact and adhere the material and the loaded drug to the lesion area of the oral ulcer while retaining the efficacy of the original dosage form, thereby maximizing the length of the drug Action time, improve the effect of drug treatment, has high clinical significance.

Carbomer 941 and hydroxypropyl methylcellulose (HPMC) are selected as the bioadhesive materials for this subject, and the polymer adhesive film formed can be adhered to the surface of biological mucosa and loaded with drugs. For the adhesive material, the adhesive performance is very important. This paper verifies the adhesive performance of the adhesive tablet through mechanical experiments. It was found that although the polymer material combined with Carbomer 941 and HPMC has strong adhesion, the adhesion performance of the patch after drug loading has decreased. At the same time, under the same other conditions, applying external pressure to the adhesive tablet to prolong the adhesion time and increase the drug concentration, the adhesion performance will tend to decrease. When the content of HPMC in the tablet formulation is increased, the adhesion performance tends to increase.

Secondly, because the oral patch will directly act on the oral cavity of the human body, attention should be paid to the safety of the tablet material and the contained drugs. This subject also conducted cytotoxicity tests on oral adhesive tablets containing Periplaneta americana extract, including cytotoxicity tests including polymer adhesive materials and extracts of Periplaneta americana. The experimental results show that the polymer adhesion material is safe and non-

toxic, and the periplaneta extract has certain toxicity at high concentrations, and the drug content must be strictly controlled in the production and preparation. Secondly, the release effect of the periplaneta extract in the obtained tablets was tested. By detecting the content of specific amino acids, the dissolution effect of the drug can be reflected. The results show that the drug can be released and dissolved well, thereby ensuring the therapeutic effect of the tablet.

The preparation of oral adhesive tablets in the laboratory is quite different from industrial production. The extraction process of Periplaneta extract should have a complete purification process to ensure the high quality and high purity of the extract. In the internal mixing process, internal mixers are used in industry to fully swell and react between the polymer materials and auxiliary materials. In the process of preparing the film, the process of casting should be used. Casting machines are used in industrial production to better improve the precision and quality of the film.

Recommendations for follow-up work: The stability of the oral adhesive tablets of Periplaneta extract remains to be further studied, as well as pharmacokinetic tests.

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COMPLEMENT

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
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MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
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Збірник містить матеріали IX Міжнародної науково-практичної Internet-конференції «Сучасні досягнення фармацевтичної технології» (5 листопада 2021 р.).

Розглянуто теоретичні та практичні аспекти розробки, виробництва, перспективи створення, контролю якості, стандартизації та реалізації лікарських засобів природного, синтетичного та біотехнологічного походження на сучасному етапі у промислових умовах та екстемпоральних лікарських засобів, питання підготовки здобувачів вищої освіти за освітніми програмами «Фармація», «Технології фармацевтичних препаратів», «Біотехнологія», «Промислова біотехнологія» та «Фармацевтична біотехнологія» тощо.

Для широкого кола науковців, співробітників фармацевтичних та біотехнологічних підприємств, науково-дослідних установ, фармацевтичних фірм, викладачів закладів вищої освіти.

Collection contains materials of the IX International Scientific-Practical Internet-Conference «Modern achievements of pharmaceutical technology» (November, 5th 2021).

Theoretical and practical aspects of development, production, prospects of creation, quality control, standardization and realization of medicines of natural, synthetic and biotechnological origin at the present stage in industrial conditions and extemporaneous medicines, questions of preparation of applicants for higher education on educational programs "Pharmacy", “Technologies of pharmaceuticals", "Biotechnology", "Industrial biotechnology" and "Pharmaceutical biotechnology", etc are considered.

For a wide range of scientists, employees of pharmaceutical and biotechnological enterprises, research institutions, pharmaceutical companies, teachers of higher education institutions.*Редколегія не завжди поділяє погляди авторів статей.*

Автори опублікованих матеріалів несуть повну відповідальність за підбір, точність наведених фактів, цитат, отриманих даних, висновків, власних імен та інших відомостей.
Матеріали подаються мовою оригіналу.

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ADHESIVE PLASTERS FOR ORAL USE

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Chronic inflammatory conditions in humans can cause erosive and painful oral lesions. Mouth ulcers are a common inconvenience to a person. They significantly reduce the quality of life - they interfere with speaking, chewing and swallowing, and sometimes they cause painful sensations. Anyone can face an unpleasant symptom, since it is provoked by a decrease in the body's immune forces or a stressful situation, short-term hormonal disruptions.

Most often, oral ulcers and lesions are treated with creams, gels, or mouth rinses without targeting a specific area and therefore making them less effective. The moist surface and the constant movement of the mucous tissue in the mouth prevent the firm fixation and long-term maintenance of traditional dosage forms (DF) on its surface.

The use of bioadhesive materials for muco-adhesive patches that have the ability to be in close connection with mucosal surfaces due to physical attachment of molecules or intermolecular bonds between contact surfaces is a promising direction.

Recently, the range of plasters has been expanding, their production has been improved through the introduction of the latest technologies, which make it possible to obtain products that meet the requirements of international standards ISO 9002.

The use of a mucoadhesive polymer, which is able to attach to the surface of the mucous membrane, makes it possible to increase the residence time of the drug in the oral cavity, increases the bioavailability and therapeutic efficacy of the drug.

Scientists at the University of Sheffield School of Clinical Dentistry, working closely with Dermtreat A / S in Copenhagen, have developed a unique patch using special polymers that adhere to wet surfaces. The patch successfully injects steroids directly into oral ulcers or lesions, while simultaneously creating a protective barrier around the affected area, accelerating the healing process.

For the treatment of various injuries of the skin and mucous tissue in traditional Chinese medicine for more than 40 years, the liquid preparation Kangfuchsin (Periplaneta americana extract, PAE) has been used to restore tissues, exhibit antibacterial, antitumor effects and increase immunity. In addition, PAE is widely used to treat a variety of wounds, ulcers, fistulas, pressure ulcers, and burns.

According to the literature, the PAE contains such compounds as cytosine, cytidine, thymine, uracil, guanosine, adenine, hypoxanthine, inosine, uridine, cyclo- (L-Val-L-Pro) arbutin and (E) -3-hexenyl - β-D-glucopyranoside promoting wound healing.

The preparation of an adhesive plaster for the oral cavity using RAE will allow combining the thousand-year experience of traditional Chinese medicine, providing a stable supply of medicinal substances to the body, dosing accuracy, safety, a wide range of actions and convenience for the patient.

SIMVASTATIN-LOADED PLGA MICROSPHERES FOR DRUG DELIVERY

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Abstract

In this paper, simvastatin-loaded poly(L-lactide-co-glycolide) (PLGA) microspheres, with a uniform size about 35 μm and loading simvastatin amount about 18%, were prepared by emulsion-solvent evaporation method. The drug release behavior was determined in mimic sink condition, which shows an obvious burst release about 40.59% in the first 15 min, and then slowly released for over 14 h. This simvastatin-loaded microsphere may have potential application in bone regeneration and repair field by injection.

1. Introduction

Simvastatin can induce the expression of BMP-2 gene in osteoblasts and bone marrow cells, which can promote osteogenesis. [1] Oral preparation shows low bioavailability due to first-pass effect in liver, resulting in failing to promote the formation of new bone tissue at defect site. Moreover, high dosage simvastatin will have serious toxicity and side effects on liver, muscle and other tissues. Therefore, it is important to develop a new simvastatin delivery system. Injectable bio degradable microspheres have been extended studied as drug carrier and tissue engineering scaffolds. One side, drug-loaded biodegradable microspheres can release drug slower at injection site, on the other side the microspheres can promote cell growth, proliferation and tissue repair. [2] Herein, Simvastatin-loaded PLGA microspheres were prepared by emulsion-solvent evaporation method, and microspheres morphology and drug release behavior were studied.

2. Materials and methods

Materials

Simvastatin and medium viscosity polyvinyl alcohol (PVA) were purchased from Aladdin Chemical Reagent Co., Ltd. (Shanghai, China). Poly(L-lactide-co-glycolide) (glycolide/L-lactide=25/75, mol/mol, Mw=100000 Da) was synthesized in our lab.

Preparation of Simvastatin-loaded PLGA microspheres

Simvastatin (1 g) and PLGA (1 g) were dissolved in 10 mL dichloromethane to obtain homogeneous oil phase solution. The oil phase solution was poured into 1% PVA aqueous solution (40 mL) precooled at 4°C, and then stirred at 5000 rpm for 10 min by a emulsifier to obtain O/W emulsion. Finally, the emulsion was transferred into an open beaker, and mechanically stirred overnight at 600 rpm at room temperature to remove the organic solvent. Simvastatin-loaded PLGA microspheres were collected by centrifugation, and then lyophilized to obtain drug-loaded microspheres.

Characterization

Microsphere morphology was observed by optical microscope (Smartzoom 5, Germany), and its size distribution was determined by Laser particle size analyzer

(Zetasizer Nano ZS90, USA). 100 mg drug-loaded microspheres were dispersed in 900 mL dissolution medium of sodium dihydrogen phosphate buffer solution (0.01 mol, pH 7.0) with 4.5 mg sodium dodecyl sulfate stirred at 100 rpm at 37 °C. The medium of 5 ml was taken out and replaced with the same volume fresh dissolution medium at preset time intervals to mimic sink condition, and simvastatin concentration in dissolution medium was determined at 238 nm by a UV-vis spectrophotometer and calculated according to standard curve (y=0.0685x+0.0631 R^2=0.9986). Drug loading amount was calculated as total release simvastatin.

3. Results and discussion

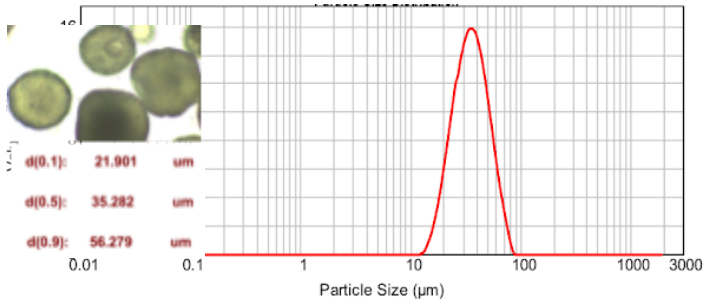

Fig. 1 Simvastatin-loaded PLGA microsphere morphology and size distribution

As shown in Fig 1, The simvastatin-loaded microspheres showed spherical structure, and obvious drug crystallization could be observed on its surface. The microsphere shows uniform size distribution, and the median particle size was about 35 μm, indicating injection can be administered by a very fine needle.

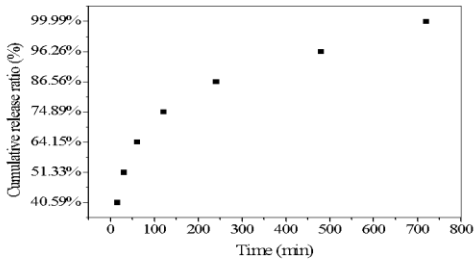

Fig.2 Cumulative release of simvastatin from the drug-loaded PLGA microspheres

Cumulative release ratio of simvastatin from drug-loaded microspheres is shown in Fig 2. In the first 30 min, an obvious burst release was observed, which was mainly ascribed to the drug crystals on the microsphere surface. Simvastatin was fully released from the microspheres after 14 h. Considering the slow degradation rate of PLGA,[3] it can be concluded that the release rate of simvastatin was mainly controlled by diffusion. Simvastatin is difficult to dissolve in water, but the encapsulation ratio and loading amount of simvastatin are low (~18%). This may be ascribed to the presence of PVA in water phase that increases the solubility of drugs,

resulting in drug loss during the preparation of microspheres by emulsification and solvent evaporation method.

4. Conclusion

Simvastatin-loaded microspheres can be prepared by emulsion-solvent evaporation method. The microsphere shows uniform size distribution with a median particle size about 35 μm. Loading amount of simvastatin in the biodegradable microspheres is about 18%, which can be slowly released for over 14 h.

Reference

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