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Review

The development of polycarbophil as a bioadhesive material in pharmacy

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ABSTRACT

Polycarbophil (PCP), a kind of pharmaceutical polymers with superior bioadhesive properties has been widely used in the field of controlled drug delivery systems. It could be used as a highly efficient thickener, bioadhesive agent, suspending aid and emulsion stabilizer when dispersed in water or other polar solvents. These exceptional utilities of the polymers result from their hydrophilic nature. Hydrogen bonding plays an important role in most adhesion behaviours and becomes the main adhesion force. This paper reviews the applications of PCP in pharmacy over the past decades, and clarifies its unique advantages in the bioadhesive formulations. After an introduction discussing its structural characteristics and action mechanism, the focus turned to the description of its available applications in detail with particular emphasis on the ocular, nasal, vagina and oral drug delivery systems. The other less developed formulations are also described, including the buccal and the transdermal delivery systems.

1. Introduction

Currently, the bioadhesive drug delivery system (BDDS) has got much attention, and a great progress has been made by researchers [1–3]. John D. Smart [4] and Sharma *et al* [5] had discussed the mechanisms of mucoadhesion in detail, including electronic theory, wetting theory, adsorption theory, diffusion theory, mechanical theory and fracture theory. These numerous theories should be regarded as complements in the different stages of the mucus/substrate interaction, rather than individual and absolute theory.

The wetting theory is mainly applicable to liquid or low viscosity bioadhesive systems and is essentially a measure of spread-ability of the drug crossing the biological substrate [6]. The electronic theory describes adhesion characteristic depending on electron transfer between the mucoadhesive

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system and the mucus, which was arised by the differences in their electronic structures. The electron transfer causes the formation of a double layer of electrical charges at the interface of mucus and mucoadhesive, as well as produces the attractive forces within this double layer [7]. According to the fracture theory, the adhesive bond is related to the force of separating the two surfaces between systems. This theory relates the force for polymer detachment from the mucus. The work fracture will increase when the polymer network chains are longer or the degree of cross-linking is low [6]. The diffusion-interlocking theory proposes a time-dependent diffusion between mucoadhesive polymer chains and the glycoprotein chains of the mucus layer. This is a two-way diffusion process, the permeability of the polymers depends on the diffusion coefficients of the interacting polymers. And the main factors affecting the diffusion process are the molecular weight (MW), cross-linking density, chain mobility/flexibility and scalability of both networks [8]. It has been reported that longer polymer chains can diffuse, interpenetrate and entangle to the surface mucus, and the critical MW to obtain interpenetration is at least 100,000 Dalton (Da). Furthermore, excessive chain cross-linking will decrease the polymer mobility and interfacial penetration [9].

In the adsorption theory, adhesion is defined as the result of various surface interactions (primary and secondary bonding) between the mucus substrate and adhesive polymers. The primary bonding is produced by ionic, covalent and metallic bonding, which is generally considered undesirable due to their permanency. And the secondary bonding is arised mainly due to hydrogen bonding, hydrophobic interactions and van-der-Waals forces. Meanwhile because these interactions require less energy to 'break', the secondary bonding has become the most prominent form of surface interaction in mucoadhesion processes as it has the advantage of being semi-permanent bonding [6,10].

As is known to all, polymer properties can affect mucoadhesion. According to the adhesion theory, the different molecular structures and functional groups have a great influence on the polymer/mucus interaction. As the attachment and bonding of bioadhesive polymers to biological organisms occurs mainly through interpenetration followed by secondary bonding. And the secondary bonding is mainly aroused by hydrogen bonding which is well accepted that polymers possessing hydrophilic functional groups such as, carboxyl (COOH), hydroxyl (OH), sulphate groups (SO_4H) and amide (NH_2) may be more appropriate for formulating targeted drug delivery platforms. Typically, secondary interactions (mainly refers to hydrogen bonding) play a significant role on the formation of stronger network. Therefore polymers containing a high density of available hydrogen bonding groups could combine with mucin more strongly [11]. The hydration degree of polymers is another important factor affecting the mucoadhesive strength. Generally the higher the degree of hydration, stronger the biological adhesion. However, excess hydration may cause a decline in mucoadhesion because of the formation of a slippery mucilage. So polymers with stronger hydration ability are more conductive to play biological adhesion. The higher degree of cross-linking allows greater control of drug release as well as increases the surface area for polymer/mucus interpenetration.

PCP is a high-molecular-weight acrylic acid polymer cross-linked with polyalkenyl ethers or divinylglycol. There is a large number of carboxyl (COOH) on the molecular chain. As a pharmaceutical excipient, PCP is generally considered safe and does not produce allergies and irritation to the skin [12]. It is insoluble in aqueous media but in the neutral pH conditions, it has a high swelling capacity and the volume can be increased to 100 times, allowing high levels of entanglement within the mucus layer. Comprehensive adhesion and the inherent characteristics of PCP, the bioadhesive effect is produced by the carboxylic acid groups binding to the mucosal surfaces via hydrogen bonding interaction [9]. As shown in Fig. 1, the structures of PCP before and after swelling or neutralizing are different in a suitable medium. In the non-swollen state, the macromolecules are tightly coiled, so the volume and viscosity are very small. When dispersed in water, the molecules will hydrate and uncoil to some extent, though the molecular chains don't achieve the greatest degree of expansion, the viscosity of the system could be improved to a greater extent. The performance of polymers will be maximized when they are fully uncoiled and extended, which can be accomplished by neutralization or hydrogen bonding. The hydrogen bonding force makes the viscosity increased significantly. Fig. 2 depicts the detail of the hydrogen bonding process and action principle of PCP from the perspective of atomic three-dimensional structure. Furthermore, the gel is formed in such platforms, which is caused by the electrostatic repulsion between anionic groups [13].

The environmental pH value and ionic strength have a strong impact on the viscosity of PCP [14]. As a pH-sensitive gel, the carboxyl groups in molecular chains are neutralized by adding the neutralizer (alkali, etc.). Negative charges will be produced on the backbone of the molecular chains after the polymers ionized by the neutralizer, which may turn the molecules into an extended state with the repulsions of homogeneous charges. This reaction occurs rapidly and leads to thickening effect, therefore it plays a strong role in viscosity. Adjusting its pH value to 5 or above after the PCP dispersed in the water with the concentration of 0.2%, the system would turn into a gel immediately. But when a large number of ions presented in the solution system, the concentration of the polymer should be increased significantly to make it to a gel. Studies showed that when the concentration of ions in the solution reached 0.1 mol/l, the system would not convert to a gel, even the concentration of PCP was up to 0.7%. So when PCP is used as a gel matrix or a bioadhesive agent, the researchers must pay special attention to the concentration of the ions in the system, especially the divalent or trivalent cationic. The mechanism of this phenomenon is the combination of dissimilar charges. In the highly dispersed systems of PCP, there are many carboxyl negative charges exposing on the extended molecular chain, making cations associated which reduces the repulsion effect of the same charges, leading the system lower degree of stretching, therefore the viscosity is decreased. As a consequence, PCP is very sensitive to the pH and ionic concentration in the host system, special attention must be paid in this aspect.

Tang Xing *et al* [15] compared a series of bioadhesive polymer materials, and found PCP has the highest values for various properties such as swelling, humidification, viscosity

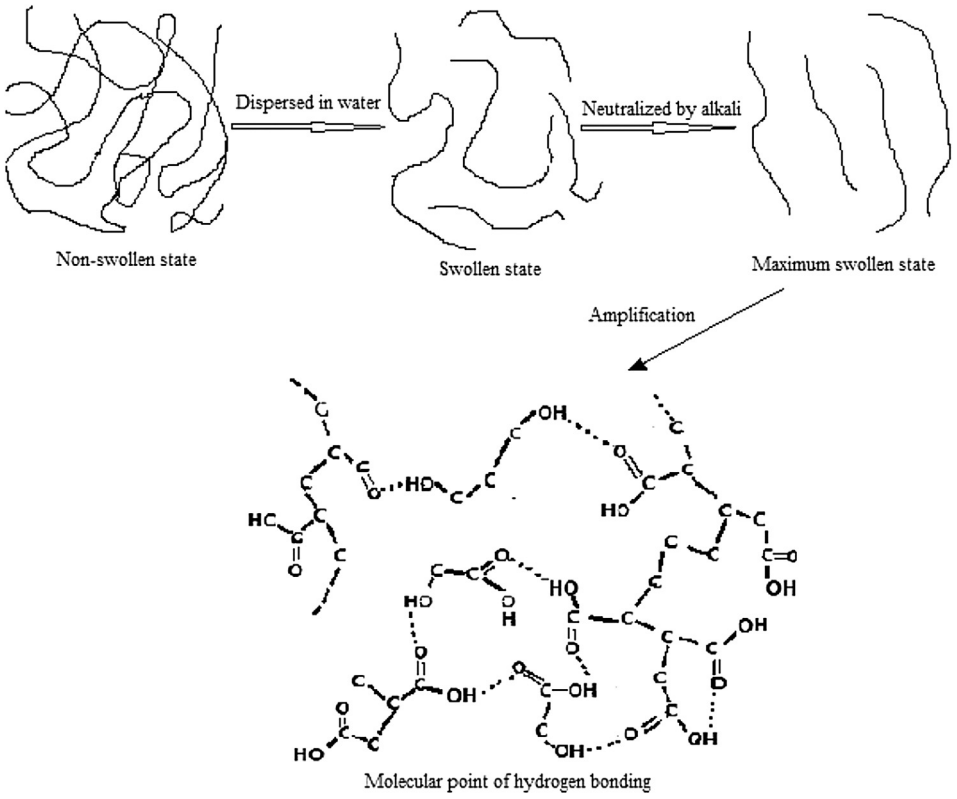

Fig. 1 – Schematic depicting the structure of PCP before and after swelling or neutralizing.

and adhesion force. The adhesion decreases with the following sequence by their comparison: PCP > Xanthan gum > Carbopol 1342P > Carbopol 974P > Chitosan > Carbopol 971P > hydroxypropylmethyl-cellulose (Methacel K100M) > CMC-Na > hydroxypropylmethyl-cellulose (Methacel K15M) > gelatin > Acacia gum.

Many studies have showed that the carboxylic acid groups can bind to the mucins by hydrogen bonding, in other words, mucoadhesion is based on non-covalent bonds or entanglement between mucus and polymers [9,16,17]. When the drug containing PCP contacts with mucosal tissue, hydrogen bonding makes the carrier and mucus adsorption occur. At present, there is not any systematic biological adhesivity theory. In view of the good bioadhesive properties of PCP, a large number of studies have been conducted on drug delivery systems. It has been proved that bioadhesive agents can be adhered to the target sites in order to extend the retention time of the drug in the lesion, and improve the treatment effect of local disease. Higher local drug concentration and the close contact with the site of absorption can not only promote absorption of the drug, but also increase concentration gradient. Meanwhile, PCP modulates transport pathways by opening epithelial tight junctions to promote the drug diffusion. In addition, the drug adheres to the mucosa directly and is absorbed by the mucosal capillaries to avoid the first-pass effect of the liver, thereby to increase the bioavailability [18]. Furthermore, the use of bioadhesive slow (control) release formulations can reduce the frequency of administration, and thus improve patients' compliance.

This paper reviews the usage of PCP as a carrier of controlled release preparations in recent years, and focuses on the different routes of administration. The development and application of new formulations aim to provide new ideas for BDDS.

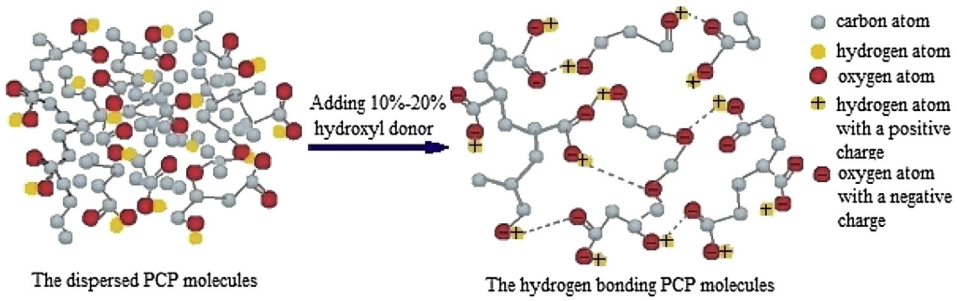

Fig. 2 – Schematic depicting hydrogen bonding process of PCP.

2. The applications of PCP in the mucosal administration systems

2.1. *In the ocular drug delivery systems*

The traditional ocular preparations are usually lost quickly from eyes by flowing away with tears, and gelatinous eye preparations are easy to cover the surface of the cornea resulting in blurred vision. Therefore, the current study focuses on selecting the appropriate bioadhesive materials to extend residence time in the eyes. Although there are many applications of carbomer in ocular formulations, carbomer is usually used as a promoting agent rather than an adhesion agent. PCP used in ocular drug delivery system has many superior characteristics, such as small irritation, long residence time in the corneal surface, which can enhance the bioavailability of drugs, and can be used as gels or emulsions matrix.

Lehr *et al* [19] investigated that PCP had the ability of improving ocular penetration of gentamicin in the pigmented rabbit. They designed two gentamicin formulations containing PCP (neutralized versus non-neutralized) group and saline control group, and they were dropped into the rabbit eyes respectively. After analysing the concentrations of gentamicin in the different tissues of the eyes including cornea, bulbar conjunctiva, anterior sclera, aqueous humour and vitreous humour, which were measured by fluorescence polarization immunoassay, they got the conclusion that both formulations containing PCP increased the uptake of gentamicin by conjunctiva two times. Considering only approximately 50%–60% of the drug was released from the molecular *in vitro* experiment, therefore the promoting effect was very significant. But only the drug in the non-neutralized polymers formulation penetrated into the aqueous humour was observed, the authors believed that the penetration enhancement was probably caused by its low pH, because it was consistent with the fact that mucoadhesive performance of poly(acrylic acid) was achieved under conditions when its carboxyl groups were not or only partly dissociated, such as at pH < 4.5 [20].Their study concluded that the biological adhesivity of PCP played a major role in helping permeation of the drug at pH < 4.5, and when the molecules turn into a gel under the pH > 4.5, the increased viscosity would play a leading role. It means whether PCP was neutral or not, it was certain of the effect of extending residence time of drugs in the lesion sites and making their bioavailability improvement in comparison with conventional eye drops.

Sensoy *et al* [21] prepared bioadhesive sulfacetamide sodium (SA) microspheres using mixture of polymers such as PCP, hydroxypropylmethyl-cellulose (HPMC) and pectin at different ratios, and made the microspheres by spray drying method. The particle size and distribution, thermal behaviour, morphological characteristics, encapsulation efficiency, mucoadhesion and drug release studies *in vitro* have been investigated. After optimization studies, they chose the formulation of SA-loaded PCP microsphere with the ratio of polymers:drug as 2:1. They carried out the *in vivo* studies on New Zealand male rabbit eyes with keratitis caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The rabbit eyes treated with PCP microspheres showed prominently less clinical symptoms than those treated with SA alone. It means that the bioadhesive microspheres were highly effective in the treatment of ocular keratitis. This research also confirmed that PCP had the bioadhesive effect and the function of improving bioavailability.

Using liposomes as a carrier in ocular administration can solve many shortcomings of the conventional solution eye drops. They have the ability to entrap hydrophilic compounds in their aqueous compartments and to embody hydrophobic molecules in their lipid bilayers. The potential of liposome used in ocular delivery has been researched many years, and got confirmed previously [22]. Nagarsenker *et al* [23] prepared cationic and neutral liposomes of tropicamide, and made neutral liposomes gel by dispersing the neutral liposomes in PCP simultaneously. After giving them to the rabbit eyes, they recorded the pupil dilatory effect. Relative mydriatic strength by curves showed that t_{max} after the neutral liposomes gel administration was significantly greater than the aqueous solution; after the treatment of simple drug gel and neutral liposomes gel, the AUC was almost the same. It showed the improvement of AUC because of the increased viscosity of the formulation rather than liposome-encapsulated drug. γ–Scintigraphic studies had confirmed the limitation usage of neutral liposomes in ocular drug delivery because of no specificity in the cornea.

2.2. *In the nasal mucosal drug delivery systems*

The nasal mucosa has a relatively large surface area, rich submucosal blood supply as well as a relatively high mucosal permeability with a porous endothelial basement membrane, which is conducive to the absorption of drugs. Meanwhile the blood from the nose passes directly into the systemic circulation, avoiding first-pass metabolism of the drug, which achieved more rapid attainment of therapeutic blood levels with lower doses, quicker onset of pharmacological activity and fewer side effects [24,25].

However there are a number of factors limiting the intranasal absorption of high-molecular-weight and hydrophilic drugs, such as mucociliary clearance, enzymatic activity, and the barriers formed by epithelium and mucus layer to the nasal absorption. The applications of absorption enhancers, proteolytic enzyme inhibitors, and suitable dosage formulations, such as mucoadhesive and inhaled delivery systems, have been investigated to enhance the nasal bioavailability of drugs [26]. Unfortunately, many traditional absorption enhancers, such as surfactants and bile salts, would cause significant damage to the nasal mucosa when used at very effective concentrations, particularly with long-term exposure. Lots of them have been limited in clinical for their irreversible damage to the nasal mucosa [27]. Therefore the bioadhesive preparations applied to nasal administration has drawn greater attention. In this approach, when the preparations contact with the mucus layer, the matrix could absorb water and swell to form a viscous gel, and extend the residence time of preparations in the absorption site. This kind of delivery system can protect the drug from enzymatic degradation by nasal secretions, and reduce the mucoliliary clearance rate [28,29]. At the same time the tight junctions between the epithelial cells are opened due to temporary dehydration

shrinkage and increasing the permeability, thus contribute to the absorption of the drug [30].

The bioadhesive polymers PCP have above properties. Ugwoke *et al* [31] conducted the bioavailability study in rabbits of apomorphine mucoadhesive drug delivery system for nasal administration with Carbopol 971P, PCP and lactose power respectively. The result showed that the former two t_{max} and MRT were significantly higher than the latter and the AUC was equal with subcutaneously value. Park *et al* [32] made the delivery of plasmid DNA successfully by using the thermoresponsive polymer, poloxamer in combination with PCP or polyethylene oxide. They found both the polymers decreased the gelation temperature of poloxamer, which indicated that the gelation temperature could be controlled within the temperature range available in the nasal mucosa. The results also showed that the preparation containing PCP and poloxamer was the best, leading to a 11-fold increase in DNA absorbed when compared to the saline group.

Recently thiolated polymers which are a kind of polymers containing thiol substructures have gained considerable attention [33–35]. Sarath [36] studied thiolated dendrimer as a feasible mucoadhesive excipient for the controlled drug delivery systems. The thiolated polycarbophil (PCP-Cys) is reported recently as PCP derivative. It is formed by the carboxyl groups of PCP which have been neutralized with NaOH covalent binding with amino groups of Cys under the activation of some activator. Grabovac [37] evaluated the adhesion of some mucoadhesive polymers by adhesion time and total work of adhesion on porcine small intestinal mucosa. Results of his study demonstrated that the adhesion of PCP was higher than PCP-Cys. Lqbal *et al* [38] has got the same conclusion. A nasal microparticulate delivery system for human growth hormone (hGH) had been studied by Leitner *et al* [8], the system based on the PCP-cysteine (PCP-Cys) in combination with the permeation mediator glutathione (GSH). In the experiment, they prepared three kinds of microparticles, and the composition of prescriptions were PCP-Cys/GSH/hGH (7.5:1:1.5), PCP/hGH (8.5:1.5), and mannitol/hGH (8.5:1.5) respectively. The size distribution of particles was evaluated by using a laser diffraction particle size analyzer. The release of hGH from microparticles was determined by fluorescence labeling in Franz diffusion cells. *In vivo* studies on rats were also performed comparing the nasal bioavailability achieved by three prescriptions above. The results showed that PCP-Cys/GSH/hGH and PCP/hGH microparticles had an equivalent size distribution, and the two preparations had almost the same sustained drug release profiles. The nasal administration of the PCP-Cys/GSH/hGH group resulted in a relative bioavailability of 8.11 ± 2.15%, which means a 3-fold and 3.3-fold improvement compared to that of PCP/hGH and mannitol/hGH group, respectively. The study suggests that the PCP-Cys/GSH/hGH for nasal microparticulate formulation might be a promising novel tool for the systemic administration.

2.3. *In the vaginal mucosa drug delivery systems*

Traditional vaginal delivery systems, such as effervescent, emulsions and others are easy to leak, thus result in shorter residence time, lower dose and shorter effective time of the active drug, which are inconvenient to the patients. The vagina is the best administration site of BDDS. As vaginal suppository base, PCP is able to overcome the shortcoming of stranded short time of the site, which was observed in traditional creams, suppositories and vaginal tablets, and it can also improve the hydration of the vaginal tissue.

The applications of the technology have achieved encouraging results [39]. The Columbia company has developed two kinds of bioadhesive formulations (Advantage – STM and Crinone) using PCP and carbomer as adjuncts. The former formulation is a bioadhesive gel of contraceptive, which takes the drugs into the cervix and around by using a special dosing device, and the drug continue releasing the trace effective spermicide slowly within 24 h, then the contraceptive effect will be achieved. The later formulation is Crinone, treatment of infertility, which can ensure the release time of progesterone no less than 48 h after one vaginal administration [40]. Robinson *et al* [41] prepared a vaginal adhesion gel containing PCP that could reserve the drug in the lesion for 3–4 days. Wang Chengwei *et al* [42] developed the nonoxynol vaginal sustained release gel used PCP, Carbopol 971P and glyceryl behenate, and examined the released results *in vitro*. The consequences showed that the preparation could prolong the contact time, release the effective dose quickly and continue for 24 h of an effective dose, which reduced the drug dose, the toxicity and adverse reactions it caused. Milani *et al* [43] compared the effects of two formulations on restoration vaginal pH value. One was a vaginal suppositories containing PCP, and the other was an ordinary acidic vaginal douche. The vaginal pH was a key factor in healthy vaginal ecosystem, when suffering from bacterial vaginosis, an increase in vaginal pH of patients was commonly observed. The result showed that PCP vaginal suppositories appeared to reduce high vaginal pH to physiologic levels for 80 h compared with acidic vaginal. Therefore, PCP vaginal suppository has a superior efficacy for treatment of bacterial vaginosis by changing the vaginal pH and extending the contact time in the vaginal surface.

2.4. *In the buccal mucosa drug delivery systems*

Due to its relatively small surface area, lower permeability and relatively short residence time of the drug in mouth, oral mucosa is not conducive to administration. However, because of the smooth oral mucosa surface, large number of submucous capillary aggregated to the internal jugular vein, not directly to the liver but to the heart, which can avoid the drug degradation by gastric intestinal juice, first-pass effect of liver and enzyme metabolism. Therefore, as an administration site, buccal is very suitable for bioadhesive drug delivery systems [44–47]. From another perspective, it is necessary for bioadhesive systems that mucus layer covering the buccal mucosa. Unfortunately, the mucus layer not only forms a physical barrier to the permeation of drugs, but also prevents sustained drug release by its short turnover time. Interestingly, it has been reported that the presence of bioadhesive polymers on a mucous membrane might alter the turnover of mucin because of the residence time of mucoadhesives is usually longer than the reported mucin turnover time [8].

The bioadhesive formulations possess a higher biocompatibility, allowing adhesion to the mucosa in the mouth, and

finally, they can be quickly eliminated through the normal catabolic pathways, which could reduce irritation or allergic reactions in the administration sites [48,49].

Robinson *et al* [50] prepared a trilamellar membrane agent for the oral cavity with an impermeable support membrane, a rate-limiting intermediate film and an adhesion film containing PCP. This adhesive film agent used in the human oral cavity could reserve 15 h at the site of administration, and even will not be effected by eating and drinking. The study confirmed that PCP applied in buccal mucosa drug delivery systems could prolong the residence time in the active site, and thus enhance the bioavailability of drugs.

3. The applications of PCP in oral drug delivery systems

There is no doubt that oral preparations are the most widespread and popular routes of administration, but they still present many limitations, such as mucus covering the GI epithelia, variable range of pH, high turnover rates of mucus, rapid luminal enzymatic degradation, first-pass metabolism by hepatic and longer time to achieve therapeutic blood levels, which are all possible issues with the oral delivery system [51–53]. The idea of bioadhesion arose from the need of localizing the drug at a certain site in the GI tract. Therefore, the primary objective of bioadhesive systems orally is to achieve the substantial increase in residence time and once-daily dosing [54]. The hydrophilic macromolecules are usually used in the development of mucoadhesive controlled release formulations, which contain a large amount of hydrogen bonding groups [55].

3.1. *In the controlled release drug delivery systems*

Robinson *et al* [1] studied the bioadhesive properties of a series of polymers and reported that the preparation containing chlorothiazide and PCP could sustained release for 8 h after administered orally to rats. Leung *et al* [56] showed that PCP gel provided a gastric retention system. The phenomenon was dependent on its viscosity, which was produced by swelling in the stomach. They studied the gastric emptying of the canine stomach by using a duodenal cannulation technique. Different concentration of PCP were administered orally to fasted canines, and it was found that the higher of the PCP's concentration, the longer lag time of the gastric emptying. The conclusion was that PCP increased gastric retention via its apparent viscosity. Ch'ng *et al* [57] found that the residence time of PCP labelled with ^{51}Cr in the rabbit stomach was 17 h, while the normal control group without the polymer was only 8 h. Carelli *et al* [58] elaborated a drug release mechanism of silicone microspheres containing nicotinamide (NAM) and PCP. In this system, NAM and PCP at the ratio of 1:4 were dispersed in silicone as the osmotically active particles, and the silicone was encapsulated in microspheres. When the osmotically active hydrogel granules swell in the dissolution medium, the drug dissolved and diffused in the swollen granules rather than silicone elastomers. In gastric juice (pH 1–2), the swelling degree was low, and the mechanism of drug release was the dissolution–diffusion. When the pH value increased in intestinal juice (pH ~7), the swelling degree was increased significantly, which made the contact surface among the adjacent particles augment, thus resulted in the apparent diffusion coefficient of the drug in the matrix increased. In conclusion, the change of the gel swelling degree was very beneficial to delaying the drug release in the gastrointestinal tract. And in some cases, the control release kinetics was close to a pseudo-zero order. In summary, PCP with its unique physical characteristics has a great advantage on the controlled release drug delivery systems.

3.2. *In the oral protein and peptide drug delivery systems*

In recent years, with the rapid development of biotechnology, especially in the progress of the recombinant protein technology, the therapeutic effects of the peptides and proteins have received a great concern [59–61]. But the applications have great limitations for their poor stability, short half-life *in vivo*, difficultly penetrating the biofilms and low bioavailability characteristics [62]. The common approach to solve above problems is to incorporate enzyme inhibitors in the delivery systems. Since most peptide drugs are large molecules and easily degradated by the proteasomes, therefore they require the absorption enhancers and protease inhibitors to overcome GI epithelial barriers [63–66]. At the same time, different carriers have also been studied, which are used to shuttle the peptide to the most optimal absorption sites or tissues of the gut, such as gastrointestinal patch systems [67–70] and bioadhesive systems for oral drug delivery.

A large amount of work has shown that polyacrylic acid materials have superior protection capability for protein and peptide drugs. Luessen *et al* [71] researched PCP and Carbopol® 934 *in vitro* with the peptide probe 9-desglycinamide, 8-arginine vasopressin (DGAVP), and reported that both the two polymers possessed the properties of enhancing absorption. Moreover, PCP and Carbopol® 934 were able to protect DGAVP free from mucosal homogenate degradation [72] and inhibit the activity of trypsin [73]. Bai *et al* [74] had verified that PCP had the proteolysis inhibition characteristic, which was found to be effective in aqueous suspensions.

PCP-Cys is also used for oral protein and peptide drug delivery systems, because it has some permeation-enhancing effects. The mechanisms of permeation-enhancing effects: (1) Reducing the concentration of extracellular calcium by binding action and opening the tight junctions between cells; (2) The activities of the protein tyrosine phosphatase in the cell membrane (e.g. PTP1B) may reduce the tight junctions opening. While the Cys in PCP-Cys could form a disulfide bonding with PTP1B, which would inhibit the activities of PTP1B and thus increase the penetration of the drug by opening close joints. *In vitro* experiments showed that PCP-Cys significantly increased sodium fluorescein, bacitracin FITC and insulin FITC intestinal epithelial absorption [75].

Martien *et al* [76] developed and evaluated an oral oligonucleotide (ODN) delivery system based on PCP-Cys/glutathione (GSH). They made the permeation studies with PCP-Cys/GSH versus control on Caco-2 cell and rat intestinal mucosa *in vitro*. As shown in Fig. 3A and B, apparent permeability increased by 8 times (Caco-2) and 10 times (intestinal

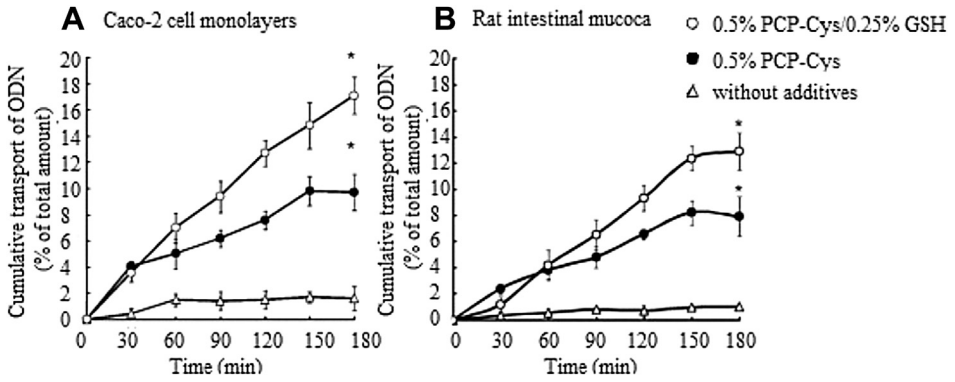

Fig. 3 – Cumulative transport of ODN across Caco-2 cell monolayers and rat intestinal mucosa [76].

mucosa) compared to the control group. Therefore, this system might be a promising tool for the oral administration of proteins or peptides, because it can protect the enzymatic degradation and promote drugs transport across intestinal membrane.

Vetter *et al* [77] designed a highly efficient small intestinal targeted drug delivery system for fondaparinux based on PCP-Cys and GSH combined with sodium decanoate. In the presence of PCP-Cys/GSH/sodium decanoate, the uptake of fondaparinux from the intestinal mucosa was 4.1-fold improved, the AUC in rat plasma from 0 to 24 h was 1.3-fold improved, and the absolute bioavailability was 6.2-fold improved compared with the ordinary tablets. This system showed strong potential of improving the bioavailability of oral drug.

4. The applications of PCP in transdermal delivery systems

Transdermal drug delivery has become a very attractive alternative to subcutaneous delivery as the skin has the largest area. It provides good compliance of patients and controls release characteristics of drugs, and avoids drug degradation from the GIT or first-pass liver effect. The skin can also provide a painless interface for systemic administration [78,79]. Except some remarkable advantages, skin administration could also form an extremely effective barrier to foreign molecules, especially large hydrophilic molecules. The low permeability of the skin was caused mainly by the stratum corneum at the outermost layer of the skin [80]. Therefore, a new method is badly needed to overcome the skin permeability barriers. There are some conventional techniques that weaken the obstacle with skin absorption enhancers, such as ultrasound, iontophoresis and microneedles [66,81–83]. It is a new method of biological adhesive system applied in transdermal delivery system, which can prolong the contact time greatly by adhesion effect and doesn't produce discomfort. Some adhesive materials which fixed with the skin stratum corneum could promote the permeability of skin by chemical bonding.

Valenta C *et al* [84] evaluated the possible usages of PCP-Cys as polymeric matrix for transdermal progesterone application. They compared the adhesive characteristics of PCP-Cys with two control formulations, polyvinylpyrrolidone/HPMC (PVP/HPMC) and polyvinylpyrrolidone/polyvinylalcohol (PVP/PVA). They analysed the progesterone content by HPLC and studied the emancipation and the percutaneous permeability through the *in vitro* permeation experiment, with full thickness skin of miniature pig as the model in modified Franz diffusion cells. It indicated that films based on PCP-Cys displayed higher cohesive properties than the control group due to the formation of interchain disulfide bonds. In addition, the progesterone permeation experiment showed that drug permeation from PCP-Cys was also higher compared with PVP/HPMC and PVP/PVA within 24 h. In the last, they got the conclusion that PCP-Cys might be a novel matrix for transdermal progesterone delivery system with its excellent adhesiveness.

5. Problems and prospects

As a bioadhesive matrix, PCP has the capability of adhering to the mucus gel layer or mucosal epithelial surfaces, extending the residence time in some specific sites, such as the administration sites, the lesion sites and the sites of absorption, improving the treatment of local or systemic diseases. *In vitro* and *in vivo* experiments have made remarkable achievements. However, the results of researching in human body are still unsatisfactory, which are mainly manifested in the following aspects.

(1) The update of the mucus layer *in vivo* is one of the important reasons for adhesion failure *in vivo* of bioadhesive formulations containing PCP. Meanwhile, the formulations are also likely to damage mucous or mucous membranes, and may stimulate the synthesis, secretion and update of mucus, thus affect the adhesion behaviour *in vivo*.
(2) For gastrointestinal bioadhesive drugs, polymers being hydrated excessively before adhering to the target tissue is another reason of decreasing their biological adhesivity. At the same time, the food and feces in gastrointestinal tract also affect adhesion to the surface of the mucus layer.
(3) Further research in irritation and toxicity of PCP on mucosal is badly needed.
(4) The evaluation methods *in vitro* and *in vivo* of this kind of preparations need to be further perfected.

With the further development and mutual penetration of polymer science, life sciences and pharmacy, the use of the new formulation technologies will overcome the existing deficiencies in certain extent. The bioadhesive formulations will also tend to be more mature and perfect under the development of new multi-functional bioadhesive materials and specific adhesion materials. In the future, the leading direction of BDDS is likely to be the bioadhesive microspheres and specific biological adhesion ligands or coated nanoparticles, used as sustained release and specific site of administration [85]. Especially in the bioadhesive particulate drug delivery system containing PCP, the administration system has important significance in improving the poor absorption, unstable drug (peptide, protein and vaccine) *in vivo*. With reference to the theories of mucoadhesion mentioned in the introduction, various polymer structures and functional groups can have an effect on the interaction of polymer/mucus. Thus, modification or control of such polymer structures may achieve specific mucoadhesive delivery systems. We may design and synthesise the modified PCP with smaller molecular structure, lower toxicity and immunogenicity. In short, by taking PCP or its modifications as the carrier, the bioadhesive drug delivery system will show great superiority in reducing the adverse reaction, improving the curative effect and the compliance of patients.

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