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Mini review

Hydrogen-bonded interpolymer complexes as materials for pharmaceutical applications

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Abstract

Association of poly(carboxylic acids) and non-ionic polymers in solutions via hydrogen bonding results in formation of novel polymeric materials—interpolymer complexes. These materials can potentially be used for design of novel mucoadhesive dosage forms, development of solid drug dispersions and solubilisation of poorly soluble drugs, encapsulation technologies, preparation of nanoparticles, hydrogels, in situ gelling systems and electrically erodible materials. This review is an attempt to analyse and systematise existing literature on pharmaceutical application of hydrogen-bonded interpolymer complexes.

Keywords: Interpolymer complexes; Mucoadhesion; Solid drug dispersions; Multilayered materials; Nanoparticles; In situ gelling systems

1. Introduction

Mixing poly(carboxylic acids) with non-ionic polymers in solutions often results in a phase separation and formation of interpolymer complexes (IPC). These complexes are novel individual compounds and their properties are entirely different from the properties of their component polymers. This research topic has received much attention since 1959, when Smith et al. (1959) and then later Bailey et al. (1964) reported the complexation between poly(carboxylic acids) and poly(ethylene oxide) (PEO). They demonstrated that the interaction between these polymers is driven by hydrogen bonding and the IPC stoichiometry approaches 1:1. While at low pH (pH < 3.8), the interaction results in phase separation; at higher pH, the polycomplex exists in solution. In the neutral pH region, they also observed some interaction between the two polymers.

Much research has been focused on investigating interpolymer reactions, properties of IPC in solutions and solid state, as well as their applications. The information accumulated on IPC has been systematised in a number of reviews (Kabanov and Papisov, 1979; Bekturov and Bimendina, 1981; Tsuchida and Abe, 1982; Jiang et al., 1999; Nurkeeva et al., 2001a, 2003a).

Hydrogen bonding is a major driving force for interpolymer interactions between poly(carboxylic acids) and non-ionic polymers. The energy of a single hydrogen bond is comparatively low (2–167 kJ/mol) and its length is in 1.2–3.0 Å range (Desiraju, 2004). However, when there is a simultaneous formation of a large number of intermacromolecular hydrogen bonds between two macromolecules (cooperative phenomenon) the strength of the interaction is very significant. The cooperativeness of the interaction provides a sufficiently stable ladder-type structure of IPC in comparison with small molecules, which associate via single hydrogen bonds. In most cases, these ladder-type structures begin compacting immediately after their formation in order to reduce the surface contact with solvent molecules and the compact IPC particles continue to aggregate further (Fig. 1).

The most commonly used poly(carboxylic acids) for preparing interpolymer complexes are poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMAA). These polyacids have been complexed with various classes of water-soluble non-ionic polymers (Nurkeeva et al., 2003a):

1. polymers containing lactam groups such as poly(vinyl pyrrolidone), poly(vinyl caprolactam);
2. polymers containing ether groups in the backbone such as poly(ethylene oxide), poly(propylene oxide) or as pendants such as poly(vinyl methyl ether);

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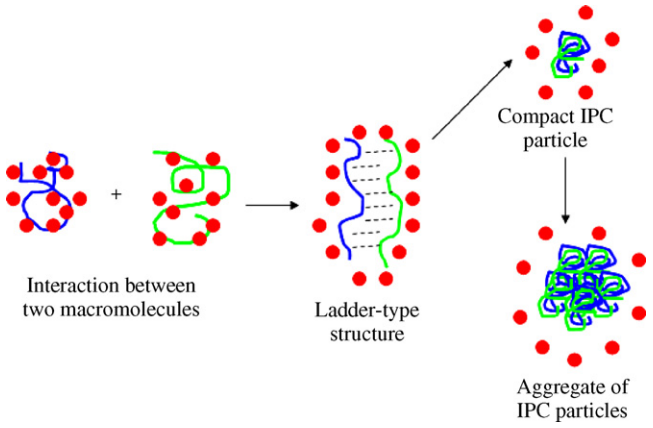

Fig. 1. Scheme of IPC formation (circles are molecules of solvent).

3. acrylic type polymers, such as polyacrylamide (PAAM), poly(*N*-isopropylacrylamide) (PNIPAAM), poly(*N*,*N*-dimethyl acrylamide);
4. polymeric alcohols such as poly(vinyl alcohol), poly(2-hydroxyethylacrylate), poly(vinyl ether of ethyleneglycol), and poly(vinyl ether of diethyleneglycol);
5. other synthetic polymers such as poly(ethyloxazoline) and poly(*N*-acetyliminoethylene);
6. polysaccharides such as water-soluble non-ionic cellulose ethers (e.g. hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose).

Since hydrogen bonding occurs between proton-accepting groups of non-ionic polymers and non-ionised carboxylic groups of poly(carboxylic acids), complex formation also depends on the degree of ionisation of a poly(carboxylic acid) and thus on environmental pH. As a rule, complexes are formed in weakly or strongly acidic media and dissociate upon increase in pH (Fig. 2). The pH below which the IPC starts to precipitate is called critical pH of complexation (pH_{crit}) (Ikawa et al., 1975). It has been found that the pH_{crit} is a specific value for a given polymer–polymer system. It is dependent on the nature of both polymers, their molecular weight and concentration as well as the presence of various small molecules and ions in solution (Mun et al., 2000, 2001, 2002, 2003; Nurkeeva et al., 2000, 2001a,b, 2003a,b). An increase in molecular weight and hydrophobicity of interacting polymers as well as their concentration in solutions leads to higher pH_{crit} values. Fig. 3 shows an example of solution turbidity dependence of PAA–PAAM mixtures on pH. A sharp increase in turbidity corresponds to the pH_{crit}, which increases with increase in polymers concentration in solutions.

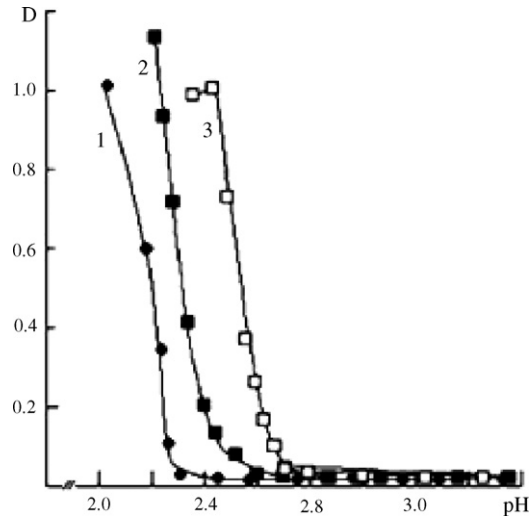

Fig. 3. Dependence of solution turbidity of PAA–PAAM (1:1, mol/mol) mixtures on pH. $C_{polymers}$ = 0.005 base-mol/L (1), $C_{polymers}$ = 0.01 base-mol/L (2) and $C_{polymers}$ = 0.05 base-mol/L (3). M_W (PAAM) = 6000 kDa; M_W (PAA) = 250 kDa. Reproduced from Mun et al. (2003).

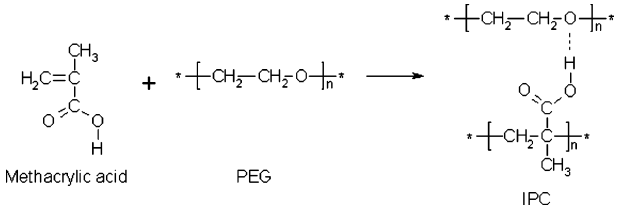

Fig. 4. Formation of IPC by template polymerisation of methacrylic acid in the presence of PEG.

Hydrogen-bonded IPC can be prepared by mixing interacting polymers in a common solvent and also by so-called template (matrix) polymerisation. Template polymerisation is defined as polymerisation of a monomer in the presence of complementary macromolecules (Papisov and Litmanovich, 1988; Polowinski, 2002). For example, Baranovsky et al. (1992) have reported the formation of IPC by polymerisation of methacrylic acid in the presence of polyethylene glycol (PEG) and poly(*N*-vinyl pyrrolidone) (PVP) (Fig. 4). There have been also reports on formation of hydrogen-bonded IPC at different interfaces: liquid–liquid (Jaycox et al., 1982), liquid–solid (Permyakova et al., 2003; Sukhishvili and Granick, 2000), liquid–air (Shaikhutdinov et al., 2002; Vorobeva et al., 1992) and liquid–hydrogel (Bekturov et al., 1999; Budtova et al., 1994; Mun et al., 1998; Starodubtsev, 1991).

Although most of the studies report the formation of IPC in aqueous media, there are publications on existence of

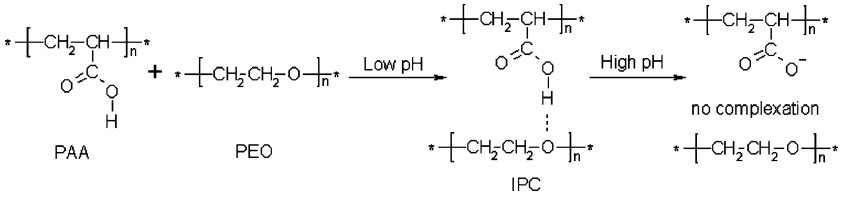

Fig. 2. Formation and dissociation of IPC based on PAA and PEO.

polymer complexes in some organic solvents (Jiang et al., 1999; Tsuchida and Abe, 1982). The nature of solvent plays an important role in complexation and IPC can only be formed once polymer–polymer interactions are stronger than polymer–solvent ones.

The thermodynamic aspects of IPC formation via hydrogen bonding have been considered in a number of studies (Papisov et al., 1974; Abe et al., 1978; Tsuchida et al., 1980; Eagland et al., 1994; Staikos et al., 1997; Bokias and Staikos, 1999). The thermodynamic parameters were determined by potentiometric titration and direct calorimetric measurements. The heats of mixing of PMAA with PVP were found to be positive in water (+5.8 kJ/mol), but negative (−1.0 kJ/mol) in *N*,*N*-dimethylformamide (Abe et al., 1978). The positive enthalpies were also reported by Bokias and Staikos (1999) for complexation of PAA with poly-*N*-isopropylacrylamide in water (+160 kJ/mol), whereas for complexes formed by PAA and polyacrylamide these values were negative (−75 kJ/mol). Although there is some discrepancy in the magnitude of the thermodynamic parameters reported for different polymer–polymer–solvent systems by different authors (Papisov et al., 1974; Abe et al., 1978; Tsuchida et al., 1980; Eagland et al., 1994; Staikos et al., 1997; Bokias and Staikos, 1999), the positive enthalpy values indicate an important role of hydrophobic effects in stabilisation of IPC.

One of the most important factors that influence the interpolymer complexation in solutions is environmental temperature. Hydrogen bonds begin to dissociate at higher temperatures, whereas the contribution of hydrophobic effects into IPC stabilisation is getting stronger. Hence, the stability of IPC greatly depends on a delicate balance between the contribution of hydrogen bonding and hydrophobic effects. The IPC, which are formed by the polymers with lower critical solution temperature, are quite stable and form larger aggregates upon heating. These include the complexes of PAA with PNIPAAM, HPC or poly(vinyl methyl ether) (Staikos et al., 1997; Khutoryanskiy et al., 2004a; Dubolazov et al., 2004). On the other hand, when the contribution of hydrophobic effects into stabilisation of IPC is less important, the complexes dissociate at elevated temperatures. This situation is observed for complexes of PAA with polyacrylamide and HEC (Staikos et al., 1997; Khutoryanskiy et al., 2004a; Dubolazov et al., 2004).

In solid state the hydrogen-bonded IPC exhibit the mechanical and thermal properties, which are entirely different from the parent polymers. A complexation between amorphous PAA and semi-crystalline PEO results in formation of fully amorphous IPC (Smith et al., 1959). The tensile strength and ultimate elongations for PAA-PEO complexes are moderately lower than PEO alone. The polymers are fully miscible within IPC and exhibit single glass transition temperatures (Khutoryanskiy et al., 2004b). The solid complexes formed by poly(carboxylic acids) and PAAM, polymeric alcohols or polysaccharides can be partially cross-linked upon heating at 80–150 °C (Baranovsky et al., 1984; Nurkeeva et al., 2001a; Khutoryanskiy et al., 2003). These partially cross-linked materials form hydrogels upon exposure to aqueous environment.

A number of technical applications of hydrogen-bonded IPC have been suggested. These include ion-conducting materials (DeLongchamp and Hammond, 2004), reagents for prevention of soil erosion (Shulga et al., 2001) and capture of radioactive elements in soil (Orazzhanova et al., 2003), metal chelating materials (Rivas and Moreno-Villoslada, 1998), emulsifiers (Mathur et al., 1998; Mun et al., 2004), and polymeric membranes (Kurokawa et al., 1980). This review is an attempt to systematise a research on application of hydrogen-bonded complexes in pharmaceutics. Since most of IPC are formed by water-soluble polymers, which are widely used as pharmaceutical excipients, there is a huge potential in application of polymeric complexes in dosage forms design.

2. Bio- and mucoadhesive dosage forms

Mucoadhesion is defined as interfacial force interactions between polymeric materials and mucosal tissues. In the last two decades mucoadhesive polymers have received considerable attention for design of novel drug delivery systems due to their ability to prolong the residence time of dosage forms and to enhance drug bioavailability (Edsman and Hagerstrom, 2005; Grabovac et al., 2005; Harding, 2003; Lee et al., 2000; Smart, 2005; Yang and Robinson, 1998). Various administration routes, such as ocular, nasal, gastrointestinal, vaginal and rectal, make mucoadhesive drug delivery systems attractive and flexible in dosage forms development.

Some of the polymeric structural characteristics necessary for mucoadhesion can be summarised as (1) strong hydrogen bonding groups, e.g., carboxyl, hydroxyl, amino and sulphate groups; (2) strong anionic or cationic charges; (3) high molecular weight; (4) chain flexibility; (5) surface energy properties favouring spreading onto mucus (Lee et al., 2000). Typical polymers that have been used as mucoadhesive carriers include poly(acrylic acid), poly(methacrylic acid), chitosan, carboxymethylcellulose, cellulose ethers, and sodium alginate.

Poly(acrylic acid) (PAA) and its lightly cross-linked derivatives Carbopol®, Carbomer® and Polycarbophil® usually exhibit strong mucoadhesion and have been extensively used in the design of mucoadhesive dosage forms. It is known that PAA or its derivatives form hydrogen bonds with mucin glycoproteins and this interaction is pH sensitive (Park and Robinson, 1987; Patel et al., 2003). At acidic pHs, the carboxylic groups are non-ionised and show the strongest mucoadhesion. However, an increase in pH results in a significant decrease in the mucoadhesive ability of PAA (Luessen et al., 1994).

When the dosage form consists of a blend of poly(carboxylic acid) and a non-ionic polymer, its mucoadhesive properties can be significantly affected by formation of hydrogen-bonded IPC under acidic conditions. One of the earliest studies reporting the effect of interpolymer interactions on bioadhesive properties was the work of Satoh et al. (1989a). This work demonstrated that mixing the aqueous solutions of Carbopol 934 (CP) with hydroxypropylcellulose (HPC) at pH 3.0 results in formation of insoluble IPC stabilised by hydrogen bonding. The stoichiometric ratio of the precipitated complex was found to be HPC/CP 3:2 (w/w). Using the tablets of HPC/CP compressed powder

mixtures in 4:1, 3:2, 1:1, 2:3 or 1:4 ratios, they studied their adhesion to peritoneal mouse membrane. The weakest adhesion force was observed at HPC/CP 3:2 (w/w), which corresponds to the IPC stoichiometry. It also confirms that mucoadhesive properties are strongly dependent on the interpolymer complex formation. Satoh et al. (1989a) hypothesised that the interpolymer complex formed during the swelling of tablet acts as an inhibitor of the adhesion due to its hydrophobicity. The same group (Satoh et al., 1989b) have studied the disintegration and dissolution characteristics of compressed tablets consisting of HPC/CP physical mixtures and solid IPC. A rapid disintegration of the tablets based on solid IPC was observed in distilled water, whereas the HPC/CP physical mixture tablets maintained their original shape during the test (0–24 h). This difference was also explained by a hydrophobic nature of IPC, which particles may have weaker inter-particle binding force.

Gupta et al. (1994) have attempted to establish a relationship between the complex formation among different polymers and buccal adhesion of tablets as well as drug dissolution behavior. By measuring the turbidity of polymer solution mixtures at different pHs they found that CP forms strong complexes with PVP and HPC, but very weak complexes with sodium carboxymethyl cellulose (NaCMC). It was also observed that the complexation is more pronounced at acidic pH and the maximum of turbidity corresponds to the weight ratios HPC/CP 3:2, PVP/CP 1:1 and NaCMC/CP 1:4. The dissolution of HPC/CP and PVP/CP tablets containing verapamil hydrochloride as a model drug revealed that the drug release increases with an increase in the percentage of HPC and PVP. A lag time was observed in drug release and its maximal values were found for the formulations, which contained the polymers in a ratio corresponding to the maximum of complex formation. Using a hamster cheek pouch to study mucoadhesive properties it was found that the highest mucoadhesive strength is observed for the formulations containing 68 wt.% of PVP or HPC. Unfortunately the authors have not discussed this result, but it is clear that it contradicts the data reported by Satoh et al. (1989a). The difference between these studies may be due to a number of factors, including different animal tissue, different pH, and presence of drug in the formulation.

Hao et al. (2004) studied the complexation between poly(methyl vinyl ether-*co*-maleic acid) (Gantrez) and PVP in aqueous solutions using viscometric technique and Raman spectroscopy. They found that the addition of PVP to Gantrez decreases the solution viscosity and the dependence of viscosity on concentration is not linear. The greatest deviation from the linearity was observed at 1:1 weight ratio, which would appear to correspond to the complex stoichiometry. The Raman spectra of PVP/Gantrez complex (1:1) have shown a slight shift in the wave numbers compared to parent polymers, which the authors attributed to hydrogen bonding between the polymers. Polymeric films containing diclofenac sodium as a model drug have been prepared by casting PVP/Gantrez aqueous mixtures in the presence of 1.5 wt.% *N*-methyl-2-pyrrolidone. All the films were clear in dry state, but opaque on contact with distilled water, which was attributed again to the complex formation. The presence of *N*-methyl-2-pyrrolidone was found to be critical in formulating clear and homogeneous films as it disrupts the formation of insoluble IPC. The bioadhesive properties of the films were studied by measuring the detachment force from a silicone elastomer substrate used as a model of skin. The films composed of PVP/Gantrez mixture exhibited larger detachment force compared to the films based on individual polymers. The highest bioadhesive property was observed for the samples with the weight ratio PVP/Gantrez 1:1. The high bioadhesive performance of PVP/Gantrez films was explained by existence of insoluble complex, which increases the cohesiveness and thus the adhesiveness of the composite. Unfortunately in this study there was no control of solution pH that is believed to be critical both for the degree of the complex formation and adhesive properties of IPC.

Dubolazov et al. (2006) have reported a successful attempt to design mucoadhesive polymeric films based on blends of poly(acrylic acid) and hydroxypropylcellulose by carefully adjusting the pH of casting solutions. The mixing of aqueous solutions of PAA and HPC results in formation of insoluble IPC, which precipitation does not allow preparation of uniform films by casting technique. A previous attempt to cast the films by mixing HPC with completely neutralised PAA has resulted in immiscible polymeric blend with irregular morphology, poor transparency and mechanical properties (Khutoryanskiy et al., 2004b). In later attempt (Dubolazov et al., 2006) the films were prepared by mixing polymer solutions at pH above pH_{crit1} (pH, below which insoluble IPC are formed) and below pH_{crit2} (above which the hydrogen bonding is completely disrupted). This careful selection of solution pH allows preparing uniform polymeric blends, where miscibility is ensured by weak hydrogen bonding between the component polymers. Cross-linked PAA/HPC films were prepared by gamma-irradiation treatment of dry samples, with 0.2–0.5 mol% *N*,*N*′-methylenebisacrylamide added to the casting mixture. The mucoadhesive properties of soluble and cross-linked PAA/HPC films towards porcine buccal mucosa were assessed using rotating disc method. It was found that soluble films undergo dissolution within 30–110 min depending on the polymer ratios in the blend, whereas the cross-linked samples are retained on the mucosal surface for 10–40 min and then detached. Different PAA/HPC ratio dependences of mucosal adhesion were observed for soluble and cross-linked films still require further systematic studies to reveal the role of interpolymer interactions in mucoadhesion. The analysis of the pH effects on the properties of films composed of PAA and different non-ionic polymers allowed formulating the following guidelines for preparation of uniform materials (Dubolazov et al., 2006; Khutoryanskiy et al., 2004c; Nurkeeva et al., 2005). Casting solution mixtures of PAA and a non-ionic polymer at pH below pH_{crit1} results in precipitation of insoluble IPC and formation of non-uniform films (Fig. 5). Casting solution mixtures at pH above pH_{crit2} results in polymeric films with inhomogeneous morphology. This is due to immiscibility of fully ionised PAA and non-ionic polymers (Fig. 6). Homogeneous films can be prepared by casting from solution mixtures at pH between pH_{crit1} and pH_{crit2}.

Tan et al. (2001) investigated the interpolymer complexation between CP and various pharmaceutical grades of PVP

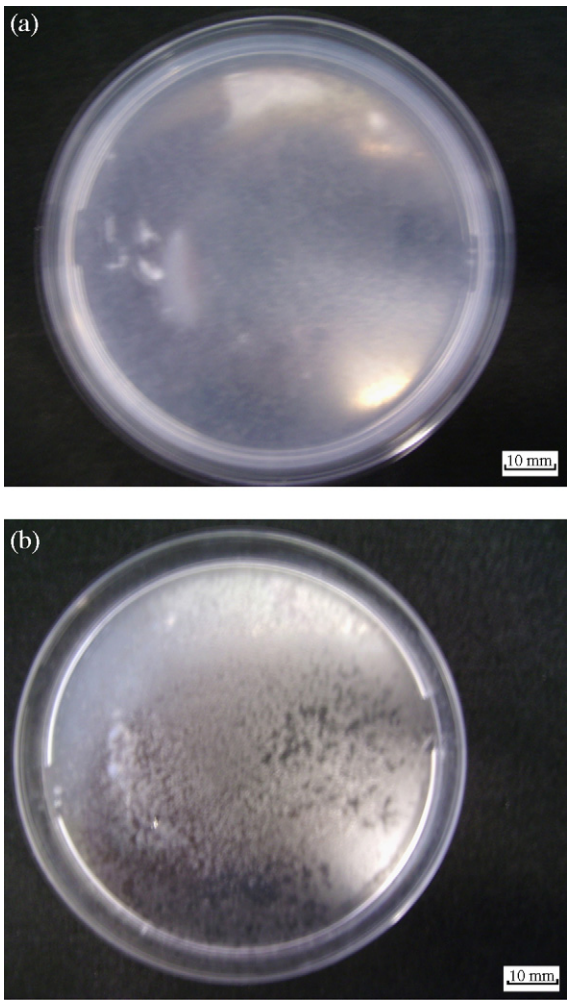

Fig. 5. Solution mixture of PAA and PEO prepared at $pH < pH_{crit1}$ (a) and resulting non-uniform films after solvent evaporation (b).

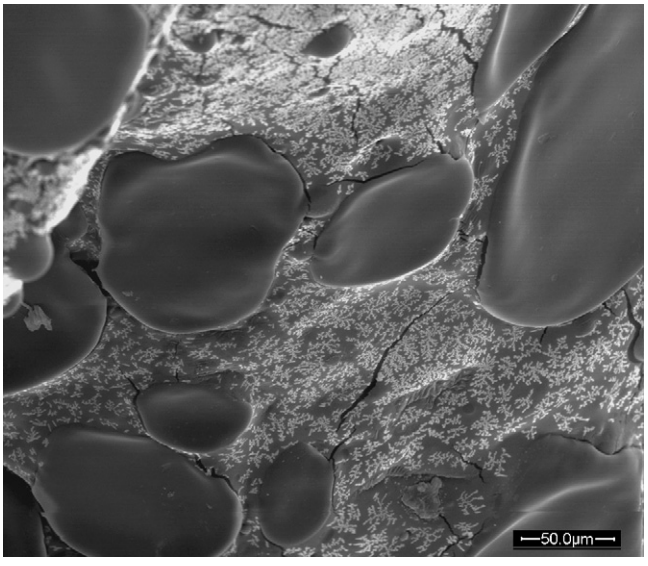

Fig. 6. SEM image of PAA-MC (1:1, w/w) blend cast from solution with $pH > pH_{crit2}$ (pH 8.0).

(K90, K32, C15 and VA/S-630). It was found that complexation occurred between CP and all PVPs, but most significantly with PVP K90, possibly due to its higher molecular weight. Tablets were prepared from both the physical mixtures and solid complexes of CP–PVP K90 and their bioadhesion towards chicken pouch membrane was studied by determination of detachment force (D_f) and work of adhesion (W_{adh}) using Texture Analyser (Stable Microsystems, UK). Both D_f and W_{adh} were found to be linearly correlating with CP content. A higher bioadhesion was observed for the formulations containing more CP. The tablets composed of IPC were less bioadhesive compared to the physical mixtures. The authors suggest that this was due to suppression of interactions between polymers and biological tissue caused by interpolymer interactions.

Tomic and Filipovic (2004) have prepared the interpolymer complexes of poly(itaconic acid) and PEG by solution mixing and by template polymerisation of itaconic acid in the presence of PEG. They studied the adhesive properties of these complexes towards a polypropylene plate as a model substrate and found that the IPC are more adhesive than a commercial mucoadhesive polymer Carbopol 971P. The complexes obtained by template polymerisation were found to be more efficient adhesives compared to the IPC prepared by solution mixing.

Mucoadhesive properties of tablets composed of PAA, hydroxypropylmethylcellulose (HPMC) have been studied by Taylan et al. (1996). They found that tablet adhesion towards bovine sublingual mucosa is significantly affected by PAA/HPMC mixing ratio. The weakest adhesive properties were observed for 50:50 (wt.%) formulation, which corresponds to the stoichiometry of IPC determined by turbidimetric technique in solution. The tablets containing propranolol hydrochloride as a model drug exhibited lower adhesive ability compared to drug-free polymer formulations. Similar results were reported by the same group (Capan et al., 1994) for the tablets composed of PAA, HPMC and morphine sulphate.

An interesting mucoadhesive system utilising interpolymer complexation has been reported by Lele and Hoffman (2000). They designed a new drug delivery formulation by conjugating poly(ethylene glycol) with indomethacin via hydrolysable anhydride bonds and then by forming a complex between this PEGylated drug and PAA at pH 3.0. The complexes are designed first to dissociate as the formulation swells in contact with mucosal tissue at pH 7.4, releasing PEG-indomethacin, which then undergo hydrolysis to release the free drug. It was found that an increase in PAA molecular weight decreases the dissociation rate of the IPC and results in decreased rate of drug release. A comparison of the drug release from PEG-indomethacin alone, PEG–indomethacin–PAA physical mixture and from H-bonded IPC showed that the slowest rate was observed in the case of the polymeric complex system. The possibility of using this dosage form for ophthalmic drug delivery is suggested.

A series of mucoadhesive dosage forms have been synthesised and studied by researchers from South Korea using template polymerisation. These polymeric complexes were prepared by polymerising acrylic acid in the presence of PEG (Choi et al., 1999), PVP (Chun et al., 2002) and poly(vinyl alcohol) (PVA) (Oh et al., 2003). The adhesion of polymeric complexes

towards polypropylene plate was found to be superior compared to the adhesive force of the corresponding polymeric blends or Carbopol 971. It was demonstrated that the adhesive properties can be controlled by changing the molar ratios of polymers.

The same group (Chun et al., 2005a,b) also reported a novel method for preparation of mucoadhesive microspheres based on interpolymer complexes of PAA and PVP. In this method the solutions of PAA and PVP in water–ethanol mixtures (3:7, w/w) were sequentially dropped into corn oil, which contained sorbitan monooleate as a surfactant and was used as an external phase. The mixture was then stirred until microspheres hardened. These were then separated by filtration, washed with *n*-hexane and dried. The adhesive properties of the microspheres towards polypropylene plate were similar to Carbopol. The possibility of loading of these microspheres with amoxicillin or clarithromycin has been also demonstrated.

In summary, hydrogen-bonded complexes of poly(carboxylic acids) and non-ionic polymers exhibit mucoadhesive properties, which sometimes may be superior to the adhesion ability of individual polymers. However, some authors reported a decrease in mucoadhesive ability caused by interpolymer complexation. A disagreement between the results reported by various authors may be due to different experimental conditions (solution pH, hydration of polymers, nature of substrates, etc.). Interpolymer complexation offers a simple and cheap approach for manipulating with mucoadhesive properties of dosage forms and more systematic studies are required to establish a correlation between adhesive ability and structure of IPC.

3. Formulation of poorly water-soluble drugs using interpolymer complexes

The problem of poorly water-soluble drugs has attracted increasing attention during the last 5 years and it is currently one of the "hot topics" in pharmaceutical formulation development. About 10% of the drugs currently on the market are poorly water soluble and have bioavailability problems. About 40% of drugs being in the pipeline of the pharmaceutical companies are poorly soluble (Merisko-Liversidge, 2002; Speiser, 1998).

The method of solid dispersions is one of the techniques currently used for improving the dissolution properties and bioavailability of poorly water-soluble drugs. In a series of papers Ozeki et al. (1998a,b, 1999, 2000) have reported the application of interpolymer complexes of PEO and Carbopol for developing solid dispersions of phenacetin. They have also studied the effect of various factors affecting the release of this drug from the formulations. Solid drug dispersions were prepared by dissolving PEO, CP and phenacetin in water/ethanol (1:1, v/v) with subsequent evaporation of solvents. It was demonstrated that the release of phenacetin from these solid dispersions is controlled by the degree of the complex formation between CP and PEO, which was varied by changing CP/PEO ratio. Using differential scanning calorimetry to analyse IPC formulations and the powder mixtures they revealed that the melting peak 136 °C – typical for phenacetin crystals – is observed in physical powder mixtures and disappears in the IPC dispersions. This indicates that the drug exists in amorphous form. The amorphous structure of phenacetin in IPC solid dispersions was also confirmed by analysis of X-ray diffraction patterns. The release of the drug from solid dispersions can also be affected by the molecular weight of PEO and the cross-linking degree of CP. A similar study has been recently published by the same group on formulation of phenacetin using interpolymer complexes of CP and methylcellulose (Ozeki et al., 2005).

Poorly soluble drugs can be also formulated using the ability of some amphiphilic polymers such as block-copolymers (Kataoka et al., 1993; Kwon and Okano, 1996; Kwon, 2003; Torchilin, 2001) or hydrophobically modified polysaccharides (Khutoryanskiy, 2005; Qu et al., 2006) to form intra- and intermolecular micelles and aggregates with hydrophobic cores capable to solubilise non-polar molecules. Hydrogen-bonded IPC also have micellar structure with hydrophobic cores and hydrophilic shells, which opens up the possibility of their application for solubilisation of drugs. It has been demonstrated recently that the IPC can enhance the solubility of non-polar organic molecules such as pyrene (Dubolazov et al., 2006; Khutoryanskiy et al., 2004c; Nurkeeva et al., 2005). However, poor colloidal stability of IPC and their precipitation poses a challenge for their development as drug solubilisers.

4. Layer-by-layer assembling and encapsulation

Layer-by-layer (LBL) sequential adsorption of polymers on solid surfaces is a simple and versatile technique for producing ultrathin polymeric films and coatings (Decher, 1997). The principle of the LBL technique exploiting electrostatic interactions is the following: an anionic substrate is exposed to a cationic polymer solution and rinsed with distilled water. Then it exposed to an anionic polymer solution and rinsed with water again. Each exposure results in formation of adsorbed polymer monolayer and multiple repetition of this procedure leads to a multilayered film, which thickness is controlled by a number of cycles.

The complex formation between polymers via hydrogen bonding can also be used for development of multilayered materials using the LBL technique (Fig. 7). Stockton and Rubner (1997) first demonstrated this possibility based on complexes of polyaniline with a variety of different non-ionic water-soluble polymers such as PVP, PVA, PEO and PAAM. These materials exhibited unique electric conductivity. Later, Sukhishvili and Granick (2000, 2002) applied the LBL technique for preparation of ultrathin polymeric films based on complexes of PMAA and PAA with PVP and PEO. They found that these materials are highly pH sensitive and can be completely disintegrated at higher pH values. It was also demonstrated that dyes or drugs can be incorporated into such multilayers and then released at

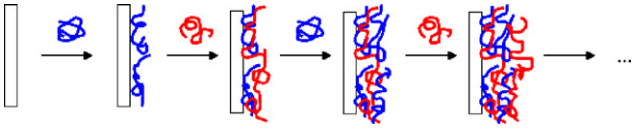

Fig. 7. Layer-by-layer deposition of hydrogen-bonded IPC by alternative immersion of a substrate in solutions of poly(carboxylic acid) and non-ionic polymer.

pre-selected conditions. Yang and Rubner (Yang and Rubner, 2002) reported that hydrogen-bonded multilayers based on PAA and PAAM can be stabilised by either thermal or photoinduced cross-linking reactions.

The use of LBL technique for preparation of hydrogen-bonded capsules was reported by Kozlovskaya et al. (2003, 2005). To produce capsules they used cadmium carbonate as a substrate and PMAA/PVP or PEO as complex forming components. Similar strategy was applied by Yang et al. (2004), who reported the preparation of bioinert multilayer deposition on colloidal particles. These multilayers were based on complexes between PAA and PAAM and after self-assembly they were additionally stabilised by cross-linking using carbodiimide chemistry. It was also shown that multilayer-coated surfaces exhibit excellent resistance to mammalian cells adhesion.

The new developments in the area of hydrogen-bonded layer-by-layer polymer films were analysed in a recent review by Kharlampieva and Sukhishvili (2006). The effects of different factors including molecular weights of polymers, ionic strength, pH and temperature on the growth and stimuli-responsive properties of LBL films were summarised and compared with the trends known for electrostatically assembled films.

5. Micro- and nanoparticles

The concept of interpolymer complexation via hydrogen bonding has recently been exploited for design of micro- and nanoparticles. Lu et al. (2002) have reported a surfactant-free synthesis of PAA nanogels based on its complexation with HPC. The method involved polymerisation of acrylic acid in the presence of HPC and *N*,*N*′-methylenebisacrylamide as a cross-linking agent. The polymerisation was initiated by ammonium persulphate in the presence of tetramethylethylenediamine and was carried out under stirring. The resulting nanogels were characterised by dynamic light scattering, which data shown narrow size distribution dependent on solution pH. The average hydrodynamic radius of nanogels at pH 3.2 was found to be smaller than at pH 7.4, which was attributed to strong hydrogen bonding under acidic conditions.

A similar strategy was used by Sun and co-workers (Dou et al., 2005; Tang et al., 2006) in synthesis of nanoparticles based on PAA and dextran. The synthesis of nanoparticles also involved polymerisation of acrylic acid in the presence of dextran and *N*,*N*′-methylenebisacrylamide. However, in this case the polymerisation was initiated by cerium (IV) ammonium nitrate and was performed at pH 2.0 under gentle stirring with the stirring rate of 200 rpm. The synthesised nanoparticles had a spherical morphology and dimensions between 40 and 140 nm. It was found that the nanoparticles are remarkably sensitive to pH due to the complexation/decomplexation between PAA and dextran via hydrogen bonding.

Dou et al. (2003) have demonstrated the possibility of preparation of hollow spheres based on graft-copolymer of hydroxyethylcellulose-*g*-polyacrylic acid. Under acidic conditions this graft-copolymer formed intramolecular complex stabilised by hydrogen bonding. This complex was then intramolecularly cross-linked by addition of 2,2′-(ethylenedioxy)-bis(ethylamine) as a cross-linker in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide. These cross-linked structures exhibited the ability to undergo transition from micellar structures to hollow spheres, when the pH was increased.

Another interesting approach was reported by Henke et al. (2005), which involved irradiation of PAA–PVP complexes by pulses of fast electrons in dilute, deoxygenated solutions. The radiation treatment of IPC induces intramolecular (intra-complex) cross-linking leading to the formation of permanent PAA–PVP nanogels. The nanogels prepared by using radiation are sterile and do not require further purification.

Although the nanoparticles based on IPC reported in the above-mentioned papers have not yet been studied as materials for design of dosage forms, they are potentially useful for drug delivery due to controllable size, presence of functional groups (carboxylic groups) on their surface and relatively hydrophobic cores. These nanoparticles (nanogels) are expected to be mucoadhesive and be able to bind cationic drugs electrostatically and non-polar drugs via solubilisation in hydrophobic cores.

6. In situ gelling systems

Solutions that undergo sol–gel transformations when exposed to physiological conditions may serve as an in situ gelling drug delivery system (Jeong et al., 2002). Haglund et al. (1996) have developed an injectable parenteral formulation which transforms into a gel under physiological conditions. They used the ability of PMAA and PEG to form insoluble complex in an aqueous medium at low pH and to dissolve in the presence of ethanol due to the weakening of hydrogen bonds. The gel is formed by mixing concentrated solutions of PMAA and PEG at low pH and is dissolved upon addition of ethanol along with a drug. The solution is injected into the site of administration where gelation occurs as ethanol diffuses out quickly. The IPC gel slowly dissociates at physiological pH, releasing the drug. Although this system was tested by the authors in vitro, the injections containing ethanol may be quite painful, which will limit the application.

Another potential application of in situ gelling polymeric systems is for administration of drugs in ophthalmology. The conventional liquid ophthalmic formulation is eliminated from the precorneal area immediately upon instillation due to lacrimal secretion and drainage. Lin and Sung (2000) have developed an in situ gelling system by combining Carbopol with Pluronic F-127. It was demonstrated that a combination of 0.3% solution of Carbopol with 14% solution of Pluronic F-127 results in formation of the gel at physiological conditions (pH 7.4 and 37 °C), whereas at non-physiological conditions the mixture can flow freely. Both the in vitro and in vivo results indicated that the combined polymer systems performed better in retaining drugs than the individual polymer solutions.

Srividya et al. (2001) reported on development of a pH-triggered in situ gelling system based on Carbopol and hydroxypropylmethylcellulose. Carbopol was used as a gelling agent in combination with HPMC, which acted as a viscosity-enhancing agent. The formulation was liquid at the formulated

pH 6.0 and underwent rapid gelation upon raising the pH to 7.4. The gel formed in situ afforded a sustained release over an 8 h period, and the formulation was therapeutically efficacious, stable, and nonirritant. This pH-triggered in situ gelation is also based on the interactions between the polymers. At lower pH Carbopol forms complexes with HPMC, which lowers solution viscosity. An increase in pH leads to a destruction of the IPC and a significant enhancement in viscosity.

7. Hydrogels with interpolymer complexation

Hydrogels are three-dimensional polymer networks of hydrophilic polymer, which are cross-linked either by chemical or physical bonds. The unique ability of hydrogels to swell in water and living tissue-like consistency makes them important candidates for developing various biomaterials and dosage forms. The applications of hydrogels in biomedical and pharmaceutical sciences include soft contact lenses, drug delivery systems, and wound dressings. Many hydrogel formulations are already commercialised and are produced in large scales (Peppas, 1987).

If hydrogels are based on combinations of complementary hydrophilic macromolecules, the specific interactions between them may govern the properties of the whole network. For example, Nishi and Kotaka (1985, 1986) have prepared interpenetrating networks by polymerising acrylic acid inside a cross-linked PEG network. These hydrogels exhibited reversible complex formation, and swelled to over thirty times of their dry weight when pH was changed from acidic to basic.

Kim and Peppas (2002) reported the preparation of sugar-containing copolymer networks of poly(methacrylic acid-*co*-methacryloxyethyl glucoside), in which the complex formation between carboxylic groups of methacrylic acid units and carbohydrate groups within the network results in the appearance of pH-responsive properties. In acidic media, hydrogen bonds forming in the networks rendered the hydrogel more hydrophobic, resulting in a collapsed state. However, in neutral or basic conditions, electrostatic repulsion occurred, leading to a high swelling.

Peppas and co-workers (Peppas and Klier, 1991; Bell and Peppas, 1996; Madsen and Peppas, 1999) prepared the complexing networks based on graft-copolymers of PEG and PMAA. These networks were synthesised by copolymerising poly(ethylene glycol) methacrylate macromonomers with methacrylic acid in the presence of tetraethylene glycol dimethacrylate as a cross-linking agent. Complexation between PEG and PMAA within these networks strongly influenced their equilibrium swelling and solute release. The degree to which complexation occurred varied with the copolymer composition and the molecular weight of the PEG chains grafted to the polymer backbone. The hydrogels exhibited minimal swelling at approximately a 50:50 molar ratio of PMAA units to PEG units, which corresponds to the IPC stoichiometry found for complexes of linear PMAA and PEG. Results suggest that these hydrogels are good drug delivery carrier candidates due to their pH sensitive and controllable swelling behavior. Additionally, they possess some protease inhibition effect along with their bioadhesive properties which makes them promising carriers for peptides or proteins.

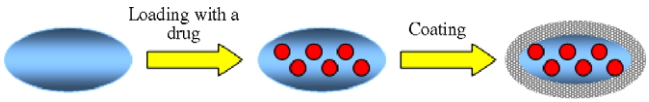

Fig. 8. Scheme showing the possibility of a drug encapsulation within a hydrogel coated with IPC: hydrogel swollen in water (1); hydrogel swollen in a drug solution (2); hydrogel containing a drug immersed in a solution of a non-ionic polymer.

8. Hydrogel and tablet coatings

Formation of hydrogen-bonded complexes has also been reported at hydrogel–linear solution interfaces (Osada, 1987; Starodubtsev, 1991; Budtova et al., 1994; Karybiants et al., 1996; Mun et al., 1998; Bekturov et al., 1999). When fully swollen hydrogel based on PAA or PMAA is immersed in solution of a non-ionic polymer it undergoes significant changes in the swelling behavior. Depending on pH, ionic strength of solution, concentration and molecular weight of a linear polymer, hydrogels can either reduce their volume or alternatively may swell (Budtova et al., 1994; Mun et al., 1998). These changes in sample swelling are accompanied by absorption of linear macromolecules and formation of interpolymer complexes. A careful manipulation with interpolymer complexation at hydrogels interfaces can be used for encapsulation technologies. Previously we have demonstrated the possibility of drug encapsulation via electrostatic complexation between PAA hydrogel containing antibiotic and cationic polysaccharide—chitosan (Yin et al., 2001). Similar encapsulation technique may utilise hydrogen bonding, when hydrogel is swollen in a drug solution and then immersed into solution of a non-ionic polymer (Fig. 8). Formation of hydrogen-bonded interpolymer complex at the hydrogel surface will ensure the protection of a drug from an acidic environment of a stomach as IPC is insoluble at low pH. Once the delivery system will pass stomach, the solution pH will increase leading to dissociation of the IPC layer and release of a drug.

Similar technique can also be applied for tablet coating. Immersion of tablets based on Carbopol® 946 in 0.2 wt.% solution of methylcellulose (MC) at pH 2.0 was found to result in penetration of MC macromolecules into the gel layer of a tablet and formation of more hydrophobic hydrogen-bonded IPC outer-layer (Khutoryanskiy and Jafri, 2006, unpublished results). Fig. 9 shows the swelling of Carbopol® 946 tablet in MC solution and water (blank experiment) at pH 2.0. This interpolymer complexation may offer a new approach in tablets coating. The thickness of the coating can be controlled by the contact time between tablet and linear polymer solution. The application of non-ionic polymers of different nature in tablet coating may lead to dosage forms with pH-controlled solubility.

9. Electrically erodible polymer gels

The possibility of using interpolymer complexation driven by hydrogen bonding for design of a novel polymeric system,

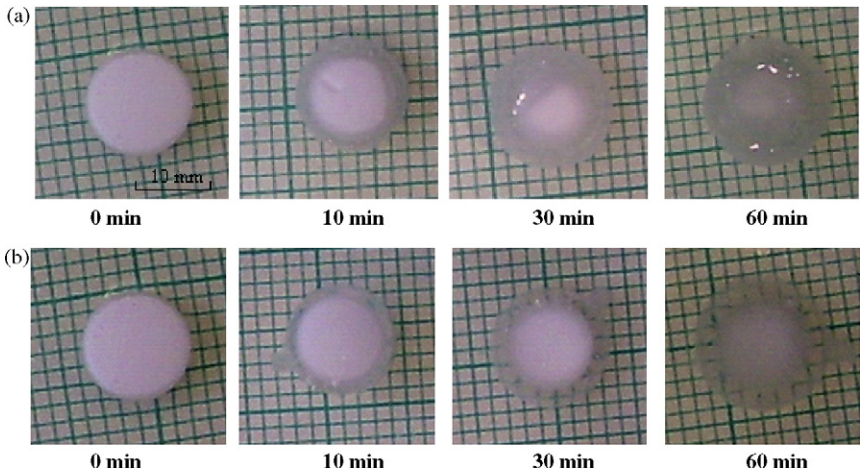

Fig. 9. Swelling of Carbopol® 940 tablets in 0.2% MC solution (a) and in water (b) (pH 2.0).

which rapidly changes from a solid state to solution in response to electric field stimulation, was demonstrated by Kwon et al. (1991). They used the ability of PMAA to form insoluble IPC with poly(oxazoline) at pH < 5.0, which dissolves instantly at pH > 5.4. The IPC was prepared by mixing the polymer solutions at pH < 5.0, which resulted in precipitation of IPC. The precipitate particles were filtered, washed with acetone/water mixture for 1 h and then the swollen polymer was compressed to make a disc-shape matrix. This matrix was dried in vacuum and then pre-swollen in 0.9% saline solution for 10 days. The swollen sample was attached to a woven platinum wire cathode, which together with the anode were immersed in 0.9% saline solution. The application of an electric current has resulted in dissolution of a polymeric matrix caused by disruption of interpolymer hydrogen bonding due to a local increase in pH near the cathode. A linear weight loss of a polymer sample with time was observed and related to a surface mechanism of IPC erosion. The possibility of applying this system for drug release was demonstrated using insulin as a model compound. Insulin was loaded into the matrix during IPC precipitation and its loading content was 0.5 ± 0.2 wt.%. The amount of insulin released at pre-swelling stage was less than 4%. An application of an electric current has resulted in a release of up to 70% of insulin in a stepwise manner.

10. Conclusion

Hydrogen-bonded interpolymer complexes exhibit unique physicochemical properties, which can be widely used for development of novel dosage forms. The complexation between poly(carboxylic acids) and non-ionic polymers affects the mucoadhesive properties of formulations, which allows development of novel materials with regulated adhesiveness. The core–shell structure and amorphous nature of interpolymer complexes can be used for formulation of poorly soluble drugs. A pH-dependent solubility of these materials can be used in development of stimuli-responsive microcapsules, nanoparticles, hydrogels, in situ gelling systems and electrically erodible materials.

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