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Review Article

A REVIEW ON DEVELOPMENT OF HPMCP BASED AQUEOUS ENTERIC COATING POLYMER

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INTRODUCTION

Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules. A simplified flow-chart of the relationship of pharmaceutical dosage forms is shown in Figure 1. These dosage forms are designed either for improving the physical and mechanical properties of materials during manufacture and/or for providing a desired drug delivery system. The tablets and capsules can be made directly from powders or from granules and pellets, or from filmcoated multiple units. Tablets are now the most popular dosage form, accounting for some 70% of all ethical pharmaceutical preparations produced (Rubinstein, 2000).

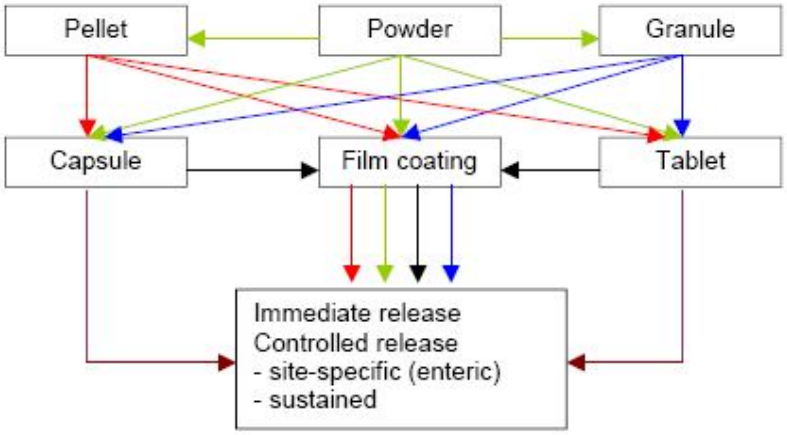


Fig. 1 Relationship of pharmaceutical solid dosage forms.

Enteric cellulose esters, such as cellulose acetate phthalate (CAP) and hydroxypropyl methylcellulose Phthalate (HPMCP), are widely used for film coating of granules, pellets and tablets to obtain controlled site-specific release of drug in the human intestinal tract Enteric-coated dosage forms are designed to resist the acidic environment of the stomach and to disintegrate in the higher pH environment of the intestinal fluid. Polymers

for enteric coating can be applied to solid dosage forms (i.e. granules, pellets or tablets) from aqueous latex or pseudolatex dispersions, aqueous solutions of alkali salts or organic solvent solutions.

Aqueous polymeric dispersions and solutions of alkali salts have been used extensively or enteric film coating of pharmaceutical solid dosage forms. These coating systems have numerous advantages over e.g. organic solvent-based systems with respect to ecological, toxicological and manufacturing safety concerns. However, the potential limitation related to many aqueous enteric coating formulations is the risk of premature drug release (permeation) through the enteric coat in the stomach. This can be due to an increased permeability of the aqueous film coating (Chang, 1990) or to a high water solubility of the drug (Bianchini et al., 1991). If the active ingredients are freely watersoluble, they may dissolve in the spray mist during the coating process, resulting in active ingredients being included in the film.

Aqueous enteric film coating

Film coating can be applied to solid dosage forms (i.e. granules, pellets or tablets) for protecting ingredients from the environment, particularly light and moisture, or masking unpleasant taste. Functional film coatings are used to impart site-specific (enteric) or controlled-release properties to the coated dosage form.

The advantages of an aqueous-based coating system have been recognized. This is derived from the drawbacks of organic solvents, including pollution, explosion hazards and solvent toxicity. Especially, there are risks for operators. For these reasons, waterbased systems are now gradually being applied instead of organic coating systems. There are, however, also problems associated with aqueous film coating, e.g. poor volatility of water, migration of drug to the film coating or water into the core, microbial growth in aqueous dispersions, and instability of the colloidal dispersions (Baudoux et al., 1990).

Enteric-coated dosage forms are designed to resist the acidic environment of the stomach and to disintegrate in the higher pH environment of the intestinal fluid. The reasons for using an enteric coating are to protect the stomach wall from the effect of the drug contents in a dosage form or to protect the drug contents in a dosage from the harmful effect of the gastric contents. Enteric coating can also be used to deliver the active ingredients to a particular region of the intestine, e.g. the upper part of the small intestine,

so as to enhance the bioavailability of the drug.

Aqueous enteric film coatings have been used widely in recent years. Many of these systems are pseudolatex dispersions of polymers such as CAP, latex dispersions of

methacrylic acid copolymers and aqueous solutions of alkali salts. Finely divided colloidal polymer dispersions are classified as true latexes or pseudolatexes largely on the

basis of the technique of production (Wheatley and Steuernagel, 1997). Aqueous solutions of alkali salts can be prepared using neutralization of enteric polymers of cellulose ester containing carboxylic groups with a base such as ammonium.

Cellulose esters

The most commonly used pH-sensitive enteric polymers today include cellulose esters such as cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate (HPMCP) and methacrylic acid copolymers. The general chemical structures of pharmaceutical cellulose esters are shown in Figure 3 (Baudoux et al., 1990). In gastric fluid these polymers are protonated and therefore insoluble in the low pH of the stomach, but ionize and become soluble in the higher pH of the small intestine.

The CAP and CAT are prepared by dissolving cellulose acetate in acetic acid. Phthalic or trimellitic anhydride is added to the solution and heated to allow for transesterification of the phthalic or trimellitic acid onto the cellulose backbone in the presence of basic catalysts.

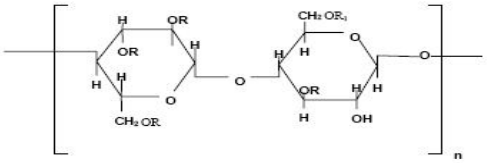
The polymer properties, e.g. molecular weight of the polymer, degree of substitution of acidic functional groups and pKa value determine the applicability of an enteric coating polymer. The mechanical strength of an enteric coating is a function of the molecular weight of the polymer. The pH-dependent solubility is mainly determined by the degree of substitution of acidic functional groups and the pKa value. The CAT film dissolved completely at pH 5.5, but CAP at pH 6.5. The difference in the pKa values may account for the difference of the dissolution characteristics of these two polymers (Wu et al., 1997).

Most of the studies on cellulose esters in the literature concerned their permeability properties, such as the water vapor transmission through free films of cellulose esters as a function of temperature and film thickness (Patel et al., 1964), the influence of plasticizers on the water vapor transmission

through free films of CAP (Lachman and Drubulis, 1964), the effect of an increasing concentration of plasticizer and pigment on the permeability to both water vapour and simulated gastric juice of CAP (Porter and Ridgway, 1982) and the permeability coefficients of CAP (Raffin et al., 1996). Except for the permeability properties, the monomolecular film properties of cellulose esters have been studied at the air-water interface (Zatz and Knowles, 1970) and thermal, mechanical and functional properties of CAP were also investigated from neutralized aqueous solutions (Béchard et al., 1995). Both CAP and HPMCP have been successfully applied in ammoniated aqueous solutions, but this approach has not been used commercially due to the difficulty of quantitatively removing ammonia from the final film (Edgar et al., 2001).

Many of the aqueous enteric coating systems are pseudolatex dispersions of polymers such as CAP and latex dispersions of methacrylic acid copolymers. Aquateric is a pseudolatex based on CAP polymer spray-dried into a chemically stable powder. This powder is reconstituted in water by mild agitation to the original colloidal or nearcolloidal size. The dispersion is manufactured by an emulsion process in which the CAP polymer is converted into a latex. The liquid product is then converted into a spray-dried powder with the aid of a barrier dispersant (McGinley and Tuason, 1985). A barrier dispersant is necessary in the manufacture of this aqueous enteric polymer dispersion because without it when CAP latex is spray-dried the particles would coalesce into a continuous film of CAP polymer.

In addition to use as an enteric coating material, cellulose esters can be used in preparing matrix tablets. Modified-release matrix tablets may be produced by compressing material made by spray drying theophylline slurried in an aqueous solution of enteric polymers of cellulose ester (e.g., CAP) (Wu et al., 1997).



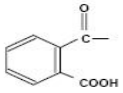
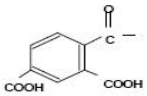
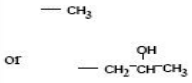
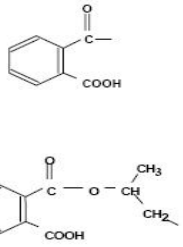
	R	R_1
CAP		
CAT		
HPMCP		

Fig. 2: Chemical structures of pharmaceutically used cellulose esters (Baudoux et al., 1990)

Film formation of aqueous enteric polymer dispersions

Since polymers for enteric coating are insoluble in water, they are usually applied as aqueous dispersions. The mechanism of film formation from an aqueous polymeric dispersion is more complex than that from an aqueous or organic solution (O'Donnell and McGinity, 1997) because the polymeric particles dispersed in the water must coalesce to form a continuous film (Fig. 3).

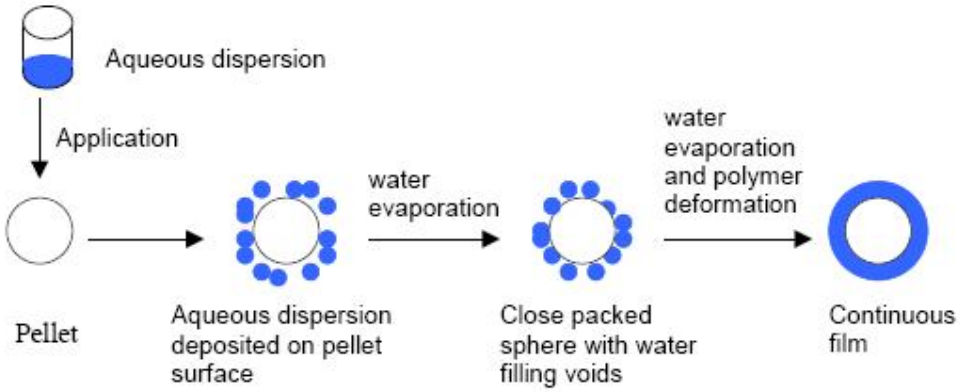


Fig. 3: Film formation from aqueous polymer dispersion (Wheatley and Steuernagel,1997)

An aqueous polymer dispersion is deposited from aqueous polymer spheres and coalesce into a continuous film by water evaporation. As water evaporates, interfacial tension between water and polymer pushes particles into a closely packed ordered array. Capillary force caused by the high interfacial surface tension of water provides the driving force to fuse the polymer spheres, facilitating coalescence and reducing minimum film formation temperatures (MFT) (Wheatley and Steuernagel, 1997). Several studies have been reported on the mechanisms of film formatiom in the literature (Ho and Suryakusuma, 1988; Eckerssley and Rudin, 1990; Roulstone et al., 1991; Chevalier et al., 1992; Winnik and Wang, 1992). An important factor for film formation is the driving force that causes the coalescence of polymeric particles that result from water evaporation or capillary force. Since coalescence occurs only above a certain temperature, i.e., MFT, temperature and water evaporation are considered to be major factors that affect the film properties of coating materials (O'Donnell and McGinity, 1997). With dispersions it is particularly important to avoid sedimentation or coagulation of the film-former and incomplete film formation (Lehmann, 1982). The volatility of plasticizers in water vapour during the coating process can cause problems in film formation from aqueous dispersions (Nakagami et al., 1991).

Limitations of aqueous enteric film coating

A potential problem associated with enteric-coated formulations made of aqueous disperse systems or solutions is the lack of resistance against gastric fluid. According to Chang (1990), enteric films prepared from organic-solvent-based solutions showed considerably lower permeability to a basic drug, theophylline, than films prepared from aqueous latex and pseudolatex dispersions. Heinämäki et al. (1994) reported that the diffusion of a water-soluble drug was faster through films prepared from ammoniated aqueous solutions than through films prepared from organic-solvent-based (acetone) solutions. More recently, as different aqueous enteric coating systems were evaluated, tablets coated with aqueous enteric dispersions exhibited good performance in the USP dissolution test when a water-insoluble drug was used (Bianchini et al., 1991). With a water-soluble substance, however, enteric-coated tablets did not pass the USP test unless the tablet cores were insulated by sub-coating barriers or were coated with double amounts of the coating. Also a number of other studies (Chang, 1990; Plaizier-Vercammen and Suenens, 1991) have shown that the enteric-coated formulations made of aqueous film-coating systems gave poor gastric fluid resistance. The premature drug release (permeation) through the enteric coat

in the stomach can be due to an increased permeability of aqueous film coating (Chang, 1990) or to a high water solubility of the drug (Bianchini et al., 1991).

According to the literature, dissolution of a small amount of drug from the core tablet to the aqueous film may occur during the coating process (Dansereau et al., 1993; Yang and Ghebre-Sellassie, 1990). The higher release rates of coated pellets were attributed primarily to drug diffusion into the film layer during the coating process (Yang and Ghebre-Sellassie, 1990). The undesired presence of a drug or an excipient in an applied film coating substantially alters the mechanical adhesion and permeation characteristics of the coating (Okhamafe and York, 1989). If the active ingredients are freely atersoluble, they may dissolve in the spray mist during the coating process, resulting in active ingredients being included in the film. Although a suitable method to prevent this phenomenon completely has not yet been found, a fairly effective method is to keep the droplet size of the spray mist small and to use a low spray rate (Nagai, 1997). Recently, Guo et al. (2000) reported that the pellet core containing amylopectin as a co-filler provides considerably low premature permeability to a freely water-soluble active agent in the acidic environment of the simulated gastric fluid. Cunningham et al. (2001) investigated the combination of excipients in a tablet core that would be suitable for use in an aqueous enteric film-coating process.

RESEARCH ENVISAGED

The advantages of an aqueous-based coating system have been recognized. This is derived from the drawbacks of organic solvents, including pollution, explosion hazards and solvent toxicity. Especially, there are risks for operators. For these reasons, waterbased systems are now gradually being applied instead of organic coating systems.

The objective of current study is to develop a HPMCP based enteric coating material which satisfy the need of enteric coating and contains the advantages of aqueous coating material.

REFERENCES

1. Tom Sam, “regulatory implications of excipients changes in medicinal products, drug information journal. 2000;34:875-894.
2. Giorgio pifferi and patrizia restani. The safety of pharmaceutical excipients, journal of Elsevier. 2003;58:541-550.
3. Leon lachman. The theory and practice of industrial pharmacy, third edition, Varghese publishing house, Bombay.
4. Remington. The science and practice of pharmacy, 20th edition, vol.2, published by lipincott Williams and Wilkins.
5. Aulton ME. Pharmaceutics the science of dosage form design, international student edition, 1999,
6. Hand book of excipients