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REVIEW ARTICLE

Potential Applications of Carbomer in Oral Mucoadhesive Controlled Drug Delivery System: A Review

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ABSTRACT

Carbomers are extensively being used in controlled drug delivery systems (CDDS). They are also finding numerous applications in oral mucoadhesive drug delivery because of their ability to interact with the mucus glycoprotein and to remain localized to a specific site. The present review aims at giving an insight into the potential application of carbomers in mucoadhesive CDDS. This review deals with the physicochemical properties of carbomers and various mechanisms of mucoadhesion. The mechanism for the release of the drug, both water soluble and water insoluble, is discussed. The use of carbomers in oral delivery of peptides or protein-based drugs is also covered.

Key Words: *Carbomer; CDDS; Drug release mechanism; Mucoadhesion; Oral peptide delivery.*

INTRODUCTION

In recent years, increasing attention is being paid to the development of controlled drug delivery systems (CDDS). The advantages of CDDS over conventional therapy are numerous, including better plasma level profile, increased patient compliance, lower dosage and toxicity, possibility of targeting, and more efficient utilization of the active agent.

Improvements in the technology to develop the CDDS have been ongoing for decades, with the formulation varying from simple matrix or reservoir-type devices to transdermals, osmotic pumps, nanoparticles, liposomes, microspheres, bioadhesives, implants, and more. Most of these formulations invariably require the incorporation or utilization of polymeric substances, which could vary from the widely accepted and used celluloses to acrylates and methacrylates, chitin and its derivatives, polyvinyl alcohols, polyethylene oxides, polyvinyl pyrrolidones, and others.

As seen in recent literature, carbomers are being extensively used in the formulation development of CDDS.

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Thus, it is imperative to provide a comprehensive review about carbomers and their possible uses in oral controlled drug delivery.

Carbomers are carboxyvinyl polymers of extremely high molecular weight that are available as dry fluffy powders. Various grades of carbomers are commercially available that differ from each other depending on their molecular weight and architecture as well as on the use of either allylsucrose or allylethers of pentaerythritol for cross-linking acrylic acid (1). These find official status in the BP 93 and in USP 23. It is important to note here that the BP has a single monograph for carbomers, whereas the USP has several different monographs that describe individual carbomer grades. Carbomer resins intended for oral and mucosal applications are designated by a ''P'' (934P, 974P, 971P).

PHYSICOCHEMICAL PROPERTIES OF CARBOMERS

The molecular and chemical structure of carbomer resins in acid form are depicted in Fig. 1. They contain between 56–58% of the carboxylic groups calculated on a dry basis.

A high percentage of carboxylic acid groups allow the polymer to be water swellable. When dispersed in water, carbomer resin molecules partially swell and build some viscosity. On neutralization with a water-soluble base, the resin molecules swell completely, with a dramatic increase in their viscosity (1). Table 1 summarizes the physicochemical properties of carbomer resins (1,2).

The carboxyl groups of carbomer dissociate highly in an alkaline environment (3); electrostatic repulsions between the negatively charged carboxyl groups cause uncoiling and expansion of the molecule, resulting in swelling of the polymer and gel formation (4,5). The gel is composed of closely packed swollen particles (6,7) with swelling that increases with an increase in pH. The swelling of carbomers is illustrated in Fig. 2 (8).

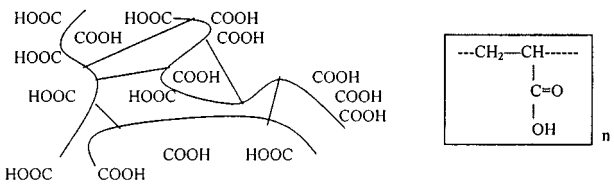

Figure 1. Molecular (acid form) and chemical structure of carbomer resins. (Adapted from Ref. 1.)

Table 1

Summary of the Physicochemical Properties of Carbomers

pH (0.5% w/v aqueous dispersion)	2.7–3.5
pH (1.0% w/v aqueous dispersion)	2.5–3.0
Bulk density	1.76 g/cm^3
Tapped density	1.40 g/cm^3
Melting point	260°C[a]
Moisture content	2% w/w (normal conditions), 10% w/w (25°C and 50% RH)
Particle size distribution	2–7 μm
Solubility	Soluble in water and after neutralization in ethanol and glycerin
Equivalent weight	76 ± 4
pK_a	6.0 ± 0.5
Glass transition temperature	100°C–105°C
Molecular weight	700,000 to 3 or 4 billion
Ionic nature	Polyanionic

[a]With decomposition.

ADVANTAGES OF CARBOMERS IN CONTROLLED DRUG DELIVERY SYSTEMS

There are several advantages of carbomers in CDDS:

Polycarbophil is physiologically inert (9) and is not absorbed from the gastrointestinal tract into systemic circulation (10).

Carbomers have been reported to have good mucoadhesive properties (11). By localizing the drug to their site of absorption, these polymers could increase the drug concentration at the absorption site,

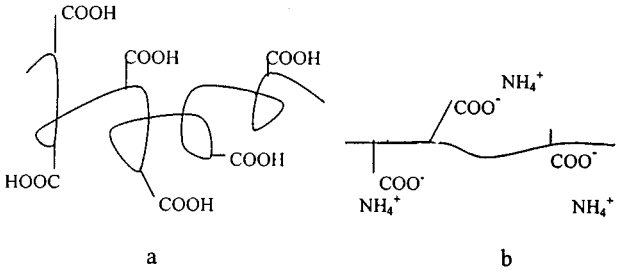

Figure 2. Swelling of the carbomer resin: (a) an unneutralized, partially solvated resin molecule (dispersion); and (b) a neutralized, fully solvated resin molecule (mucilage). (Adapted from Ref. 8.)

thus resulting in enhanced and faster bioavailability.

Carbomer formulations demonstrated sustained release (12). Under both simulated gastric and intestinal fluids, carbomers provide control release (CR) at a lower concentration than other CR systems (8). Depending on the drug solubility, pK_a, resin concentration, and test medium pH, all polyacrylates can show nearly zero-order release.

Polycarbophil may protect the underlying cell layer, forming a thick barrier that separates the cells from the environment due to its continuous cross-linking and to the fact that it is water insoluble (13). Carbomer 934 has a potential as a mucosa protective agent in vivo due to its ability to inhibit the hydrolysis of pepsin (14). In the case of nonsteroidal antiinflammatory drugs (NSAIDs), polycarbophil reduced gastric ulcers in rats (15). On the other hand, it was reported by Bjarnason et al. (16) that the intestinal permeability of indomethacin was unaffected by the presence of carbomer, indicating that carbomer did not limit the immediate damage of NSAIDs to the small intestine.

A frequently encountered problem with the peptide drugs is that these agents have to be administered parenterally. Therefore, there is considerable research interest in alternate delivery routes. Peptides may be administered orally as bioadhesives, as has been tried in the case of insulin (17) and DGAVP (9-desglycinamide,8-arginine vasopressin) (18,19). Studies have indicated that the problems of delivering the peptides by noninvasive means could be minimized, although the delivery by these routes may not be bioequivalent to the invasive methods, the convenience to patient in some cases will outweigh the demand for complete bioequivalence.

For tablet dosage forms, polycarbophil appears to be a good disintegrant and a directly compressible vehicle (20). Carbomers produce tablets with excellent hardness and friability over a range of compression forces (21).

Carbomer 974P exhibits semienteric behavior, which is particularly beneficial in formulations targeted to the intestine (21).

DISADVANTAGES OF CARBOMERS

Carbomers are highly sensitive to the ionic environment. Their use in an ion-rich environment may interfere with adhesive and release properties of the polymer. Their sensitivity to the changes in pH of the dissolution medium in vitro and to the extremes of pH in vivo makes it difficult to correlate in vitro drug release with in vivo drug absorption.

Since these polymers give a highly viscous solution, the viscosity of the system could impede the delivery of the drug to the absorbing surface (22–24).

For orally administered products, ingestion with an insufficient amount of water may result in the adherence of the dosage form to the esophageal mucosa, thus aggravating the local toxicity of such drugs.

APPLICATIONS TO PHARMACEUTICAL TECHNOLOGY

Carbomers are extensively being used in the pharmaceutical and cosmetic industry due to

excellent thickening efficiency even at low resin concentration, allowing it to be used for suspending insoluble substances and viscosifying and stabilizing emulsions, pastes, ointments, jellies, and the like

excellent temperature stability even when subjected to heating and cooling cycles

microbial resistance since dry powder forms of the resin do not support the growth of molds and fungi; however, aqueous carbomer dispersions require the addition of a suitable antimicrobial

Use in Mucoadhesive Controlled Drug Delivery Systems

In addition to the hydrophilic nature of carbomer, its cross-linked structure and essential insolubility in water makes carbomer a potential candidate for use in CDDS (25). Carbomer was first synthesized and patented in 1957 (26). Since then, a number of extended-release tablet formulations and novel drug delivery systems involving carbomer matrices have been thoroughly investigated. The development of CDDS for targeted drug delivery to the defined areas of the body has often been utilized in the bioadhesive process (27), which has resulted in application of bioadhesive polymers to various sites of drug delivery, such as buccal (28–30), peroral (31), nasal (32–34), vaginal (35), conjunctival (36–38), rectal (39,40), and cervical (41).

Good (42) defined bioadhesion as the state in which two materials, at least one of which is biological in nature, are held together for an extended period of time by interfacial forces. When the biological membrane is cov-

ered with a mucous layer, the phenomenon is referred to as *mucoadhesion*. This phenomenon of mucoadhesion requires the incorporation of polymers that bind to mucin, owing to their sticky nature, after being wetted by the gastrointestinal fluids or bind to the epithelial cells and thus are retained at a particular site for extended periods of time (43).

The desirable properties of a polymer for it to be chosen as a bioadhesive are (44) that the polymer should

- have a strong hydrogen bond–forming group as hydroxyl or carboxyl
- carry a strong anionic charge
- have a high molecular weight
- have sufficient chain flexibility
- have surface energy favoring spreading onto the mucus
- be nontoxic, nonabsorbable, and noninteracting with the drug

Various workers have indicated the potential use of CR systems of carbomers as mucoadhesives, probably due to the interaction of their carboxylic groups with the functional groups of mucous (45). Carbomers are being extensively studied for their mucoadhesive potential. Table 2 summarizes the use of carbomers in oral mucoadhesive CDDS.

Mechanism of Mucoadhesion of Carbomer Resins

Various theories have been put forth for the mechanisms responsible for the mucoadhesion of carbomers. These studies have utilized the measurements of viscos-

Table 2

Use of Carbomers in Oral Mucoadhesive CDDS

Carbomer Type	Drug	Route of Administration/Dosage Form	Reference
Polycarbophil	Diclofenac sodium	Peroral/tablet	13
Polycarbophil	Indomethacin	Peroral/tablet	15
934P	Miconazole nitrate	Buccal/tablet	46
934P	Miconazole nitrate	Buccal/tablet	47
934P	Sulpiride	Peroral/tablet	48
974P	Chlorpheniramine maleate	Peroral/spheronized beads	49
934	Tenoxicam	Peroral/tablets	50
934P	Hydrochlorothiazide	Peroral/suspension	51
Polycarbophil/940	Benzydamine HCl Lidocaine HCl	Buccal/patches	52
974P	Clotrimazole Chlorhexidine Benzocaine Hydrocortisone	Buccal/tablet and patches	53
Polycarbophil	Propranolol HCl	Buccal/tablet	54
934P	Sodium fluoride	Oral/tablet	55
934P	Acitretin	Buccal/tablet	56
934P	Metronidazole	Peroral/tablet	57
940	Propranolol HCl	Peroral/disk	58
934P/974P/EX 55	Aminophylline	Peroral/tablet	59
Polycarbophil	Hydrocortisone hemisuccinate	Buccal/tablet	60
934P	Cetylpyridinium chloride	Lozenges	61
		Buccal/tablet	62
934P	Captopril	Peroral/tablet	63
934P	Verapamil HCl	Peroral/tablet	64
974P	Ibuprofen	Peroral/tablet	65
934P	Metronidazole	Peroral/tablet	66
934P/polycarbophil	Codeine phosphate	Sublingual/tablet	67
974P	Mesalamine	Oral/tablet	68

ity, surface energy, water movements, and the like to assess the interactions between mucous glycoprotein and carbomers.

Carbomers were observed to increase dramatically the viscosity of porcine gastric mucin solution, which was found to be 19-fold greater than that of the sum of the individual polymers. After an initial 30 min, this interaction was found to be stable for up to 36 hr at 25°C or 37°C and was unaffected by either the pH or the ionic strength of the medium. The magnitude of the interaction was observed to be dependent on the polymeric structure of mucin and the level of cross-linking of carbomer. This interaction was reversible and increased with an increasing carbomer and mucin concentration. The dramatic increase in the viscosity was explained in terms of space filling by the mucin molecules that led predominantly to carbomer-mucin interactions (14).

In another study (69), good correlations were obtained between the mucoadhesive strength and the calculated free energies of interaction between mucin and polymer in the presence of simulated gastric and intestinal fluids. Increased mucoadhesion was observed with carbomers (when compared with the predicted values based on the results of un-ionizable polymers), thereby indicating some sort of ionic interaction between carbomer and mucin. On the other hand, Achar and Peppas (70) found that the mucoadhesion was not related to the ionic charges of the polymer, but rather were due to hydrogen bonding. In yet another study (71), it was observed that the addition of such hydrogen bond–breaking agents as urea and potassium thiocyanate (72,73) caused a reduction in the mucoadhesive strength. Findings suggested that the presence of an un-ionized carboxyl group within carbomer 934P was critical in the formation of a strong interaction with mucus. These interactions were thought to be a result of the hydrogen bonds between carbomer and the proton-accepting groups within the mucous glycoprotein. Since, at the experimental pH (6.2), the mucous gel carried a net negative charge (74) due to the presence of the sialic acid and sulfate ion residues on the oligosaccharide chains of the mucous glycoprotein (71), these interactions were unlikely to be electrostatic in nature. It was concluded that the mucoadhesive polymer could interact with the mucin molecule by physical chain entanglements followed by hydrogen bond formation with the sugar residues on the oligosaccharide chains, resulting in the formation of a strengthened gel network, thus, allowing the mucoadhesive to remain adhesive for extended periods of time.

Madsen et al. (75) recently reported that the polymers having a high density of available hydrogen bond–forming groups, such as carbomers, would be able to interact more strongly with the mucin glycoproteins. As the polymer would be in an expanded uncoiled state at the pH of the medium (6.2) due to the electrostatic repulsion arising from the ionized functional groups (74), thus making the polymer more susceptible to mechanical chain entanglement and secondary interactions with the mucous glycoprotein. Due to the presence of numerous carboxy groups in carbomer, there is a likelihood that the polymer could adopt a more favorable macromolecular conformation and an increased accessibility of its hydrogen-bonding groups when compared to other polymers. Hydrogen bond formation, as a possible mechanism for mucoadhesion of carbomers with mucus glycoproteins, has also been reported by other researchers (76,77).

Ranga Rao and Buri (78) reported that the relaxation of the polycarbophil chains in the intestine could facilitate the penetration and interlinking of the polymer with the glycoprotein network of the mucus, leading to better adhesion. Contrary to this, Mortazavi and Smart (79) observed that the water movement could play a significant role in mucoadhesion involving dry and partially hydrated dosage forms and may prove to be more important than molecular interpenetration. This study attempted to assess the possibility of water movement from mucus to a contacting mucoadhesive dosage form by evaluating the water uptake of the dry and gel formulations of carbomer 934P, Carbopol EX 55, hydroxypropyl cellulose (HPC), and gelatin. Carbomers were found to dehydrate the mucus more than the neutral polymers. Further, the adhesive and cohesive structure of the mucous gel was seen to increase with a decrease in the water content. This was predicted to result in the strengthening of the weakest component of a mucoadhesive joint.

Mechanism of Drug Release from Carbomer Matrices

In the dry state, the drug is entrapped in the glassy core of carbomer matrix. On hydration of the surface, a gelatinous layer is formed that consists of discrete microgels made up of many polymer particles in which the drug is dispersed. When the hydrogel is fully hydrated, it does not dissolve, but osmotic pressure from within works to break up the structure, mainly by sloughing off discrete pieces of the hydrogel. These hydrogels remain intact, and the drug continues to diffuse through the gel layer at a continuous rate. It is postulated that, as the concentration of the drug becomes high within the gel matrix and its thermodynamic potential increases, the gel layer around the tablet core then acts as a rate-controlling membrane, resulting in a linear release of the drug. Factors that influence the dissolution rate are the molecular

structure of the polymer and the rate of hydration and swelling, which in turn is dependent on the pH of the dissolution medium.

Drugs exhibiting poor solubility tend to partition into the more hydrophobic domains of the system. Since the hydrogel layer is stable, it results in linear drug release. On the other hand, in the case of highly water soluble drugs, the Fickian diffusion CR rate is due to the fast dissolution of the drug through the water-filled interstitial spaces between the hydrogels of such highly cross-linked carbomers as 974P and 934P. With lightly cross-linked carbomer (971P), the drug is more likely to partition preferentially in the hydrophilic matrix of the resin and exhibit nonlinear diffusion.

Due to the chemical nature of carbomers, peak swelling is seen between pH 5 and pH 9. Thus, release rates tend to be more Fickian in simulated gastric fluid (SGF). However, in simulated intestinal fluid (SIF), the drug release mechanism may be described as a special case of non-Fickian anomalous release, ideally suited for CR dosage forms (21). In the SIF environment (pH 6.80), the effect of further ionic repulsion of the polymer, which is manifested on a macrolevel as swelling, is apparent in addition to the hydration effect seen at lower pH levels. Increasing the amounts of carbomer in the tablets results in a decrease in the drug release rate and a linearization of the drug release curve, leading to a shift toward a swelling-control mechanism. This could be attributed to the closure of micropores and a reduction in the regions of low viscosity in the swollen tablet. Due to this added effect, the linearization and slowing of the drug release kinetics are observed more quickly in SIF than in SGF as the polymer concentration is increased. However, with highly water soluble drugs, this dramatic linearization of the curves may not be seen as the drug release mechanism is not swelling driven (21).

It was observed from studies (80) carried out with thin sheets of various concentrations of sodium salicylate pressed in Carbopol® 934P matrix in synthetic gastric fluid that the transfer of the liquid and the drug took place with the swelling of the matrix, resulting in the release of the drug in the fluid. These matter transfers were found to be controlled by transient diffusion with concentration-dependent diffusivities.

The potential of three varieties of carbomer (934, 940, 941) as excipients for hydrophilic matrix tablets containing a hydrosoluble drug (atenolol) was assessed (81). In all cases, the drug release profile fit the Higuchian square root kinetics and showed a strong dependence on the proportion of the polymer present in the tablet. The compression force and the microporous structure were not found to be important in this respect. Contradictory to these results, in a study with furosemide (82), it was observed that the variables associated with the type and proportion of carbomer, with insignificant effect on porosity, played an important role in the release characteristics of the active principle. It was further reported that carbomer 941, which produced a higher viscosity than carbomers 934 and 940, showed the slowest release profile. In all cases, furosemide dissolution profiles fit a zero-order release kinetics, pointing toward an erosion mechanism. On the other hand, Khan and Jiabi (65) observed, from the data of the release of a slightly soluble drug (ibuprofen) from Carbopol 974P matrices, that the drug release could be prolonged and controlled by Carbopol 974P in a concentration-dependent manner. Increasing the amounts of the polymer in the tablets resulted in a reduction in the drug release rate and a linearization of the drug release curve, leading to a shift from an anomalous type toward a case II type release mechanism. However, in a study (25) involving the release of a relatively neutral molecule (theophylline) in carbomer 934 matrix, it was observed that the release of the drug in phosphate buffer (pH 7.2) appeared to exhibit nearly zero-order kinetics via a diffusion-controlled mechanism for all polymer levels studied (10–85%). Drug release characteris-

Table 3

Drug Release Characteristics from Carbomer Resin Formulations

Polymer Type	Degree of Cross-Linking	Highly Water Soluble Drugs		Poorly Water Soluble Drugs	
		pH 1.2	pH 7.5	pH 1.2	pH 7.5
934P	High	Fickian	Fickian	Non-Fickian/anomalous type	Anomalous/case II type
971P	Low	Fickian	Fickian	Non-Fickian/anomalous type	Anomalous/case II type
974P	High	Fickian	Fickian	Non-Fickian/anomalous type	Fickian

Source: Adapted from Ref. 21.

tics for highly water soluble and poorly water soluble drugs, in acidic and alkaline pH, from carbomer resin formulations are given in Table 3 (21).

Stability data of dyphylline tablet formulation containing Carbopol 971P, magnesium stearate, talc, and lactose after subjecting the tablets to exaggerated temperature (4°C, 25°C, 37°C, 45°C, and 55°C) and humidity (37°C/11% relative humidity [RH], 37°C/51% RH, and 37°C/91% RH) conditions exhibited sorption of large amounts of moisture at 37°C/91% RH, although the samples were found to be fairly stable at lower humidity and at all the temperatures studied. Storage of the tablets at higher humidity produced changes in the crystalline form and thermal behavior of dyphylline from the anhydrous to the hydrate form with a corresponding decrease in dissolution (83).

Carbomers in Combination with Other Substances

Carbomers have been widely used in combination with other polymers, particularly celluloses (hydroxypropylmethylcellulose [HPMC], HPC, ethyl cellulose). Being polyanionic, it is very likely that carbomers may complex with either cationic or nonionic excipients or the active ingredient of the formulation, thereby modifying the release profile and bioadhesive characteristics of the formulation. Indeed, complex formation between carbomer and propranolol HCl has been reported (84,85).

Bioadhesive CR systems for metronidazole were prepared by compressing HPMC and carbomer 934. The release behavior of the system containing 50% w/w of metronidazole and varying amounts of the two polymers was found to be non-Fickian. The bioadhesive strength was found to be solely dependent on the carbomer content (57). Similarly, with propranolol HCl buccoadhesive tablets prepared with HPMC and polycarbophil, the release behavior of the drug was non-Fickian, but the adhesion force was found to be affected significantly by the mixing ratios of HPMC and polycarbophil in the tablet, and the weakest adhesion force was observed at the ratio 1:1 (HPMC:polycarbophil) (54). Interpolymer complex formation was confirmed between the two polymers in acidic medium by turbidity, viscosity, and Fourier transform infrared (FTIR) measurements. Likewise, propranolol HCl matrices prepared with a combination of HPMC and carbomer 974P exhibited higher cloud points for gel containing either carbomer or HPMC alone than those of any of their mixtures, indicating the ability of the polymers to reduce mutually the solubility of each other, thereby indicating a potential for controlling dissolution from their matrices by erosion (85). Complex formation between carbomer 934 and a nonionic polymer (HPC) in bioadhesive tablets was also reported by Satoh et al. (86). It was found that the adhesion force was significantly affected by the mixing ratios of HPC and carbomer in the tablet, and that the weakest adhesion force was observed in the ratio 3:2 (HPC:carbomer). The interaction between the carbomer carboxy groups and the HPC molecules was considered to be a possible mechanism for this complex formation, which was confirmed by turbidity and viscosity measurements in the acidic medium. These observations suggested that the adhesion force of the HPC/carbomer tablet to the mucous membrane was significantly affected due to the formation of the complex.

The disintegration and dissolution characteristics of tablets consisting of HPC and carbomer 934, employing brilliant blue as a model water-soluble drug, were also evaluated by Satoh et al. (87). Rapid disintegration was observed for tablets prepared with HPC/carbomer (3:2) complex, while the tablets with its physical mixture were able to maintain their original shape during the disintegration test (0–24 hr). It was further observed that the slowest dissolution was obtained with a physical mixture of the two polymers, and this has led to the conclusion that the drug release from the tablet prepared with the physical mixture was being controlled by the three-dimensional network structure produced by the complex formation [in situ] between the polymers following water penetration into the tablets.

In another study (59) involving a combination of various grades of carbomers (934P, 974P, and EX 55) with sodium carmellose and hypromellose, it was observed that the 934P grade had low adhesion work (3 ± 0.1 mJ). Addition of hypromellose significantly increased the adhesion work of the tablets containing carbomer 934P, with a maximum adhesion force being observed at 50 and 100 mg of hypromellose (6.7 ± 0.15 mJ and 9.60 ± 0.16 mJ, respectively). Carbomer 974P in combination with hypromellose (10 mg) was found to be more adhesive (detachment force 3.2 ± 0.38 N) than a combination of carbomer 934P and hypromellose (10 mg, adhesion force 2.2 ± 0.28 N). On the other hand, the addition of polyvinylpyrrolidone (PVP) K30 to carbomer 934P was found to reduce significantly ($p < .01$) the observed mucoadhesion of carbomer (88). The possible explanation for this was that the PVP structure had an electron deficient region that could act as a hydrogen bond acceptor, resulting in an interaction between PVP and the carboxylic acid moiety of carbomer. No significant ($p > .05$) difference was found on the addition of up to 10% soluble starch to carbomer.

A polyacrylate gel network is destroyed by ions that affect the hydration of the carboxylate groups, thereby generating turbid dispersions of low viscosity (89,90). Divalent cations are very effective in destroying this hydrogel network. They serve as a cross-linker, reacting simultaneously with two carboxylic groups of the same or different polyacrylate chains. To study the effect of calcium ions and other components on the release of a model water-soluble drug (saccharin sodium), Ca^{++} was added to carbomer 934P to act as a simple cross-linking agent to form bridges between the polymer chains by interacting with the carboxylic groups. HPMC was included as a sparingly soluble component and stearic acid as a hydrophobic component (91). The inclusion of HPMC and $CaCl_2$ in the formulation was found to be successful in extending the drug release from carbomer 934P matrix. The formulation containing $CaCl_2$ gave release kinetics nearest to the ideal zero order ($n = 0.830$). The inclusion of stearic acid, although observed to reduce the extent of swelling, increased the rate of drug release, whereas formulations with polycarbophil and carbomer 1342 exhibited prolonged, near-Higuchi-like release ($n = 0.562$ and 0.613, respectively). Similarly, in another study (12), using tartrazine as a model drug, it was found that the inclusion of an insoluble or sparingly soluble macromolecule was a successful method of sustaining drug release. The formulation containing ethylcellulose appeared to be the most successful (t_{50}-638 min and t_{90}-1316 min) and was nearest to ideal zero-order kinetics. On the other hand, the formulation containing HPMC showed a prolonged near-Higuchi-like release (t_{50}-287 min and t_{90}-799 min), but the inclusion of stearic acid or $CaCl_2$, although observed to reduce swelling, had a limited effect on drug release.

The incorporation of a penetration enhancer (sodium glycodeoxycholate, SGDC) at 5% levels to an 8:2 mixture of HPMC/carbomer 910 resulted in no significant difference ($p > .05$) in bioadhesion between the SGDC-containing and SGDC-free tablets. This study concluded that SGDC could be an acceptable excipient for a buccoadhesive drug delivery system (92). In another study, Realdon et al. (93) investigated the possibility of incorporating a cationic drug (procaine) in carbomer 934P gels in two different forms: in the state of salt in solution in the aqueous vehicle of the gel or in the base form with which the polymer itself was salified, totally or partially substituting the usual bases to produce the gel. Gels that were salified with carboxyvinylic polymer had a faster release rate than those with procaine in the hydrochloride form dissolved in the aqueous phase. This behavior could not be attributed solely to a physical mechanism; therefore, the intervention of a chemical mechanism was hypothesized. Since the acceptor aqueous phase consisted of phosphate buffer at pH 7.2, the greater release of the procaine base was attributed to an ionic exchange between the hydrogel and the buffer solution throughout the pores of the interposing membrane (94). It was in fact observed that Na^+ and K^+ from the buffer solution could be diffused in the hydrogel sample and be exchanged with the procaine salifying the polymer carboxylic groups, in turn diffusing into the adjacent aqueous phase as a function of the concentration gradient.

CARBOMERS AND PEPTIDE DELIVERY

Recently, bioadhesive polymers have been gaining considerable interest as auxillary agents for the peroral administration of proteins and peptide drugs (95,96). In general, poor absorption of the peptides across the mucosal surfaces is caused by the high polarity and molecular weight of this class of compounds and their susceptibility to proteolytic degradation, both by the brush border and cytosolic enzymes. Intestinal peptide absorption is further reduced by the strong pH extremes and the abundance of very potent luminal enzyme systems (18).

Polycarbophil has been found to protect the peptide drugs from proteolytic degradation (18,97–100) by inhibiting the activity of trypsin at a pH of 6.7, which could lead to increased stability of the peptide drug in the intestine. The pronounced affinity of carbomers for such divalent cations as Ca^{++} and Zn^{++} was reported to be a major reason for the inhibitory effect. Interaction between polycarbophil and Ca^{++} was studied (101) under physiological conditions. The swelling of the polycarbophil particles was found to be dependent on the degree of neutralization and the presence of electrolytes, particularly Ca^{++}, the addition of which caused a decrease in the particle size due to the dehydration of the polymer. Also, the depletion of Ca^{++} out of the incubation medium due to the Ca^{++}-binding properties of polyacrylates could be the possible mechanism of action (18) as Ca^{++} has been found to be an essential cofactor for trypsin activity (102).

Chelation of calcium and other metal ions by carbomers could provide an explanation for several biological effects, such as the disruption of the structure of epithelial monolayers (103), resulting in an increased junction permeability (101). Woodley and Kenworthy (104) reported the ability of polycarbophil to loosen the tight junctions in the intestinal mucosa, thus enhancing the transport of hydrophilic molecules via the paracellular route. However, circular dichroism indicated (100) that, under the

depletion of Ca^{++} from trypsin, the secondary structure of trypsin changed conformation, followed by increased autodegradation. Polycarbophil and carbomer 934 were reported to inhibit ∝-chymotrypsin, carboxypeptidase A, and cytosolic leucine aminopeptidase, but failed to inhibit microsomal leucine aminopeptidase and polyglutaryl aminopeptidase.

Carbomer 974P was observed (98) to increase the pharmacological availability of colonic insulin. It was demonstrated that the carbomers with numerous carboxylic acid groups could release the protons in the intestinal lumen, creating a local temporary acidic shield and thus protecting the peptides from being attacked by the luminal enzymes. Similar results have been observed by Bai et al. (105) in that carbomers were able to inhibit almost 100% of trypsin and chymotrypsin activities against insulin in saline medium, but at a concentration of 0.1%, these polymers weakly inhibited the degradation of insulin by both the enzymes in 50 mM tris buffer. However, as the polymer concentration increased to 0.4%, a complete inhibition of the degradation of insulin, calcitonin, and insulin-like growth factor I was observed. This effect was reversed at 0.1% polymer concentration in 100 mM tris buffer, but not with 0.4% polymer concentration. The inhibitory effects of carbomer were found to correlate with the final pH of the medium. This led to the conclusion that, in a medium of no or low buffer capacity to buffer the protons released by carbomers, these polymers were able to reduce the pH to a level (<5.0) that was much lower than the optimum pH for the enzyme activities and thus to inhibit proteolytic degradation.

Recently, it has been reported (106) that freeze-dried sodium salt of carbomer 934P (FD934) significantly improved the small intestinal absorption of insulin after oral administration of the capsule formulation, whereas carbomer 934P and lactose did not. In the in vitro experiments, both FD934 and carbomer in solution increased the mucoadhesion of the model compound (fluorescein isothiocyanate–dextran 40000, FD40) and inhibited the enzymatic degradation of insulin to almost the same extent. FD934 and carbomer in the solution did not change the membrane resistance or the permeability of FD40 in the rat jejunum. Carbomer formed a swollen gel barrier for the drug release layer at the boundary between the medium and the capsule, but FD934 did not (3). However, the latter significantly improved the small intestinal absorption of insulin after the oral administration of a capsule, but the former did not. The effects of FD934 were thought to be due to the adhesion on the intestinal mucosa and the inhibition of the enzymatic degradation of insulin. Since the adhesive effects and the enzymatic inhibitory effect of FD934 and carbomer in the solution were almost the same, the difference between these two polymers was thought to be due to the rapid dissolution of insulin as observed in the FD934 capsule, but not in the carbomer 934P capsule. Some peptide drugs that have been tried for oral delivery with carbomer are given in Table 4.

CONCLUSION

Carbomers are being used extensively in the formulation of mucoadhesive CDDS. These are capable of providing controlled drug release at lower concentrations than other CR excipients. The availability of different grades of carbomers provides a flexibility in drug release profiles and mucoadhesion. In combination with other suitable substances such as celluloses, divalent ions, and hydrophobic materials, a greater latitude in mucoadhesive characteristics and drug release profile may be provided in the dosage form. Also, their ability to chelate divalent ions could provide an alternate noninvasive route for the administration of peptides, thus obviating the problems associated with invasive methods of drug delivery. However, sensitivity to the changes in pH and

Table 4

Examples of Peptide Delivery via the Peroral Route

Peptide	Polymer	Dosage Form	Reference
Insulin	Carbomer 934P	Tablet	17
9-Desglycinamide, 8-arginine vasopressin (DGAVP)	Polycarbophil Carbomer 934P	Dispersion	18, 19, 107
Desmopressin acetate	Carbomer 940	Submicron emulsion	108
Buserlin	Carbomer 934P and freeze-dried sodium salt of carbomer 934P	Dispersion	109

the ionic strength of the medium could restrain its use. Nevertheless, the advantages associated with the use of carbomers far outweigh the disadvantages, and it is for this reason that they find myriad uses in CDDS.

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