noveon

The Specialty Chemicals Innovator™

Pharmaceutical Polymers for Oral Solid Dosage Forms

Introduction

Carbopol® polymers and Noveon® polycarbophils are high molecular weight polymers of acrylic acid, chemically crosslinked with polyalkenyl alcohols or divinyl glycol. These polymers have been successfully formulated into a variety of different commercial tablet forms including swallowable (peroral), chewable, buccal and sublingual tablets.

Carbopol® polymers and Noveon® polycarbophils can provide highly effective controlled release properties at low concentrations. Typical usage levels in extended release tablets are 5 - 30%, depending on the drug properties, co-excipients and processing parameters. Additionally, the polymers can provide bioadhesion, taste masking and good binding characteristics. Carbopol® polymers and Noveon® polycarbophils offer formulation flexibility because they can be used with a variety of pharmaceutical active ingredients and excipients and can be processed by direct compression, dry granulation (roller compaction, slugging) or wet granulation (high/low shear, extrusion spheronization, pelletization) methods.

Noveon polymers are supported by substantial literature references citing their performance in solid dosage forms. Additionally, Noveon researchers support customers in the development of new product concepts, prototype formulations and custom formulations through regional technical service centers in the U.S., Mexico, India and China.

Key Benefits of Noveon Pharmaceutical Polymers

- Highly efficient controlled release agents in both monolithic and multiparticulate systems
  - *Data demonstrates slower release at lower use levels than other commercially available excipients, enabling overall formulation cost savings and smaller tablet sizes*
- Offer formulation flexibility
  - *Active pharmaceutical ingredients (APIs) with different properties can be formulated to achieve various extended release profiles*
  - *Can be used alone or in synergy with other:*
    - *Carbopol® polymer grades*
    - *Controlled release excipients (hypromellose – HPMC; hydroxypropyl cellulose – HPC; carboxymethyl cellulose sodium – CMC; sodium alginates, etc.)*
  - *Widely compatible with commonly used tablet excipients*
- Available in both powder and granular forms (Carbopol® 71G NF polymer) and can be used in all types of tablet manufacturing processes
- Compression force/tablet hardness does not affect drug release from carbomer matrices
- Provide excellent tablet hardness and low friability over a wide range of compression forces
- Synthetic, reproducible polymers
- Not affected by TSE/BSE or GMO matters
- Improve bioavailability of certain drugs
- Efficient binders in wet and dry granulation processes
- May impart functional attributes such as taste masking, bioadhesion and binding
- Products have global pharmacopeial status and are supported by Drug Master Files (DMFs) in the United States and Europe

Recommended Polymers for Solid Dosage Forms

Noveon recommends use of particular Carbopol® polymers and Noveon® polycarbophils for oral solid dosage forms as summarized in Table 1.

Table 1: Noveon Polymers for Solid Dosage Forms

Product Trade Name	Polymerization Solvent	Crosslinker Type	Physical Form	Comments
Carbopol® Polymers				
71G NF	Ethyl acetate	Allyl ethers of pentaerythritol	Granular	Chemically the same as Carbopol® 971P NF polymer with no additives. Ideal for use in direct compression processes due to its improved flow properties.
971P NF	Ethyl acetate	Allyl ethers of pentaerythritol	Powder	Lightly crosslinked polymer
974P NF	Ethyl acetate	Allyl ethers of pentaerythritol	Powder	Highly crosslinked polymer
934P NF	Benzene	Allyl ethers of sucrose	Powder	Some commercially available formulations contain Carbopol® 934P NF polymer, but this material is typically not used for new product development due to regulatory restrictions on benzene.
Noveon® Polycarbophils				
AA-1 USP	Ethyl acetate	Divinyl glycol	Powder	Ideal for buccal tablets due to its bioadhesive properties
CA-1 USP	Water	Divinyl glycol	Powder	Calcium salt of polycarbophil; Coarsely ground; Used in bulk laxatives
CA-2 USP	Water	Divinyl glycol	Powder	Calcium salt of polycarbophil; Finely ground; Ideal for chewable tablets or lozenges

Regulatory Status of Polymers

Noveon works with all relevant regulatory bodies in order to establish and maintain the global pharmacopeial status of its pharmaceutical ingredients. On January 1, 2006 the Carbomer Homopolymer monograph became effective in USP 29-NF 24. It is one of the umbrella monographs that separates the Carbomer products based on polymer structure/polymerization solvent and applies to homopolymer products that are not polymerized in benzene. As noted in USP 29-NF 24, the monograph includes a delayed labeling implementation date up to January 1, 2011. Prior to January 1, 2011 the practice of labeling products as Carbomer 941 or Carbomer 934P may be continued. The Carbomer Homopolymer monograph includes three categories of carbomers (Type A, Type B and Type C) which differ by viscosity range. A global regulatory summary is found in Table 2.

Drug Release Mechanism from Tablets with Noveon® Polymers

Carbopol® polymers and Noveon® polycarbophils are efficient matrix forming excipients. These polymers are not soluble, but only swellable in water. The polymers swell up to 1,000 times their original volume in water to form a gel when exposed to a pH environment above their pKa of 6 ± 0.5. In contrast, other hydrophilic controlled release excipients such as hydroxypropyl methyl cellulose and hydroxypropyl cellulose are linear polymers, not chemically crosslinked, and therefore water soluble. The drug is dispersed homogenously throughout the polymer matrix. Drug release from tablets with Carbopol® polymers or Noveon® polycarbophils is controlled by drug diffusion through the gel layer that the polymer forms in contact with aqueous medium.

When carbomer tablets are placed in contact with dissolution medium the following occurs:

- Drug in the outside layer exposed to the bathing solution is dissolved and then diffuses out of the matrix.
- The polymer swells to form a hydrated matrix layer (hydrogel) (Figure 1). Due to the crosslinked nature of the polymers, the hydrogel is not single entangled chains of polymers (as is the case with linear polymers), but discrete microgels made up of many polymer particles in which the drug is dispersed (Figure 2).

The hydrated matrix layer controls water penetration (into the non-hydrated core) and diffusion of the drug through the hydrated matrix (Figure 3). Unlike linear polymers, Carbopol® polymers and Noveon® polycarbophils do not dissolve during the release process.

Table 2: Global Regulatory Summary

Product Trade Name	Polymerization Solvent	Compendial Name				Drug Master File Number	
		United States (USP/NF)		Europe (Ph. Eur.)	Japan (JPE)	U.S.	Europe
		Current (Effective January 1, 2006)	Previous				
Carbopol® Polymers							
71G NF	Ethyl acetate	Carbomer Homopolymer Type A	Carbomer 941	Carbomers	Carboxyvinyl polymer	17095	
971P NF	Ethyl acetate	Carbomer Homopolymer Type A	Carbomer 941	Carbomers	Carboxyvinyl polymer	7170	
974P NF	Ethyl acetate	Carbomer Homopolymer Type B	Carbomer 934P	Carbomers	Carboxyvinyl polymer	7170	Yes
934P NF	Benzene	Carbomer 934P	Carbomer 934P	—	Carboxyvinyl polymer	153	
Noveon® Polycarbophils							
AA-1 USP	Ethyl acetate	Polycarbophil	Polycarbophil	—	—	7618	
CA-1 USP	Water	Calcium Polycarbophil	Calcium Polycarbophil	—	—	6542	Yes
CA-2 USP	Water	Calcium Polycarbophil	Calcium Polycarbophil	—	—	6542	Yes

Figure 1: Carbopol® Polymers Swelling Mechanism

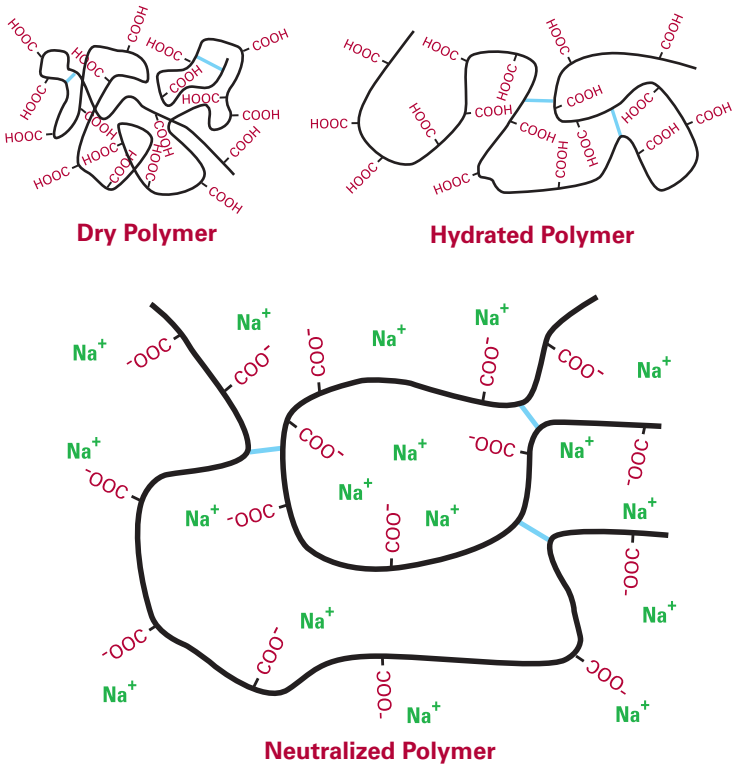
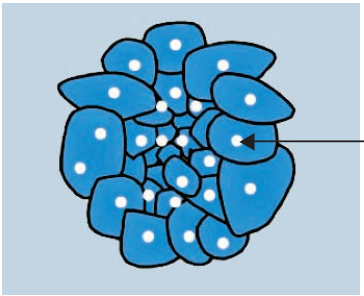
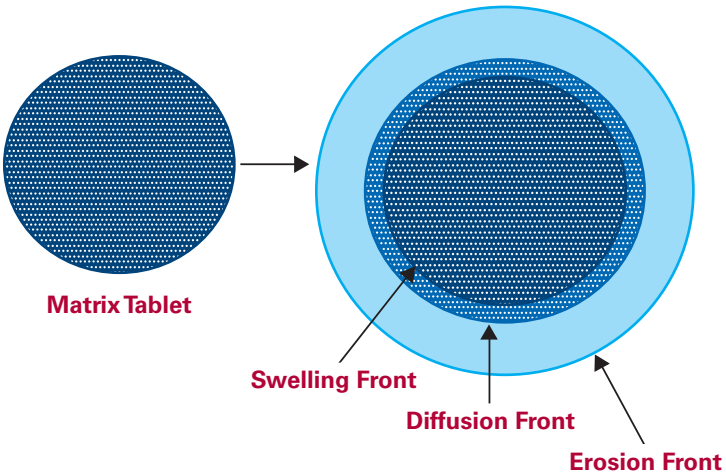


Figure 2: Microgel Structure in Hydrated Matrix Tablet



The white dots represent the API dispersed in the tablet. Similarly, the tiny white dots represent the API dispersed in the tablet in Figure 3.

Figure 3: Drug Release Schematic



Factors Affecting Drug Release

Polymer Type

- Lightly crosslinked Carbopol® polymers (971P NF) tend to be more efficient in controlling drug release than highly crosslinked Carbopol® polymers (974P NF).

Polymer Level

- Increasing the level of Carbopol® polymer in a formulation leads to slower and more linear drug release.
- At low usage levels, Carbopol® polymers can be more effective than cellulosic materials in sustaining the drug release.

Drug Solubility

- Release from Carbopol® polymer tablets is generally slower for drugs with low water solubility.

Dissolution Medium

- Drug release from Carbopol® polymer matrices may be medium-dependent due to the anionic nature of the polymer. The swelling and gel formation of the polymers is pH-dependent. At lower pH values the polymer is not fully swollen and the drug is released faster. As the pH increases, swelling of the polymer is greater resulting in rapid formation of the gel layer which prolongs drug release. However, it is important to note that the pH effect on the polymer does not significantly impact drug release in various media (Figures 4 - 7). The most significant factor impacting drug release is API solubility and how it is affected by pH.

Effect of Dissolution Medium on Drug Release

Figure 4: Theophylline release (USP apparatus 2) from tablets (50 mg) with 10% **Carbopol® 971P NF polymer** (wet granulation).

Theophylline

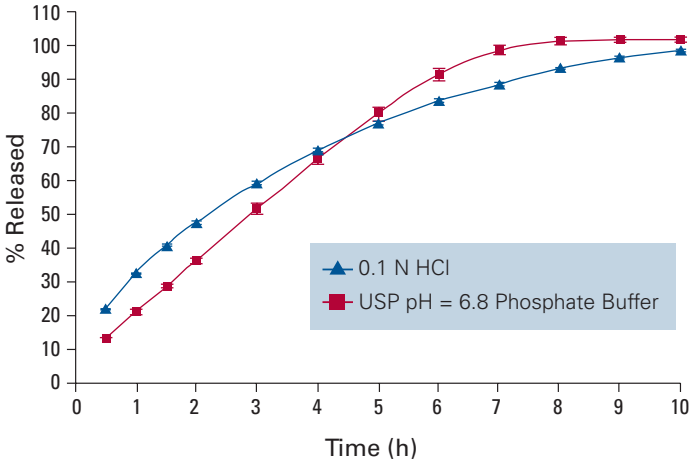


Figure 5: Theophylline release (USP apparatus 2) from tablets (50 mg) with 10% **Carbopol® 974P NF polymer** (wet granulation).

Theophylline

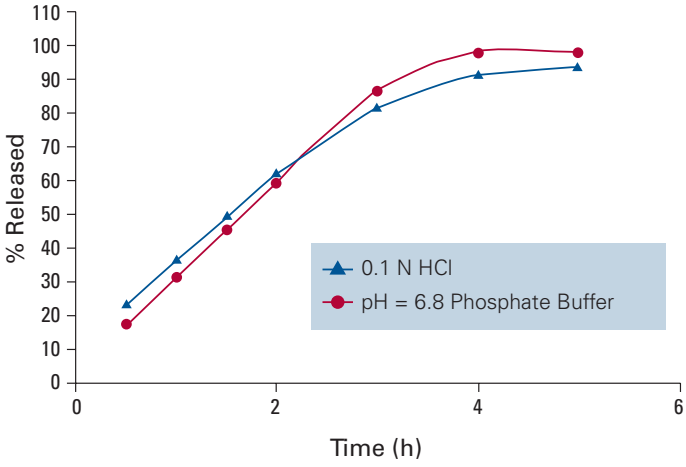


Figure 6: Acetaminophen release in different media from tablets (100 mg) with 10% Carbopol® 971P NF polymer (wet granulation).

Acetaminophen

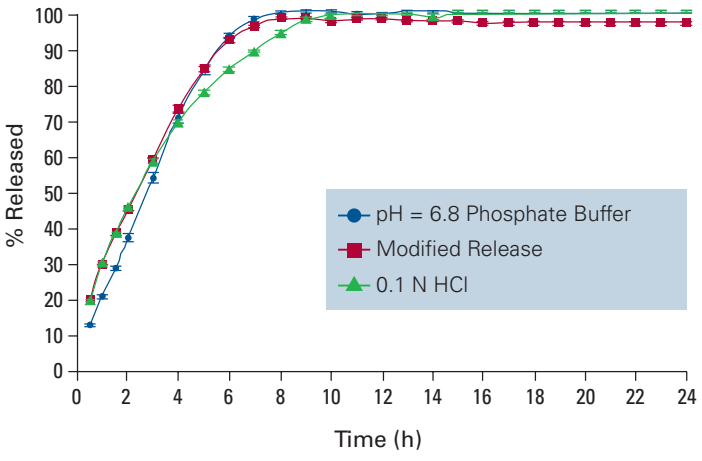
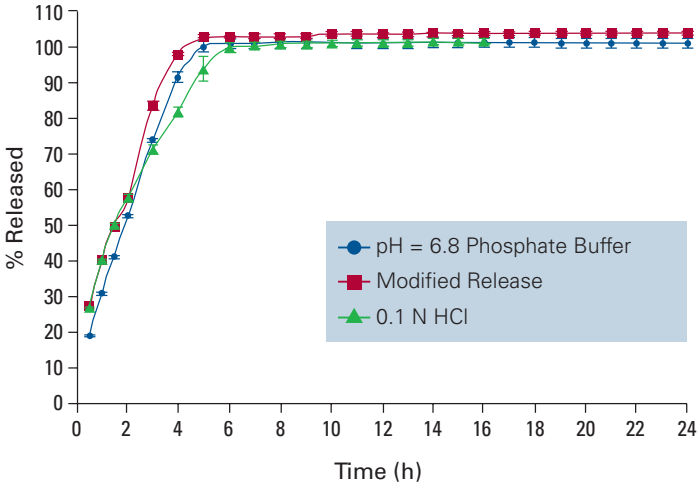


Figure 7: Guaifenesin release in different media from tablets (100 mg) with 10% Carbopol® 971P NF polymer (wet granulation).

Guaifenesin



The effect of dissolution medium on drug release is not major if the API solubility is pH-independent (so no major effect on the matrix itself).

Synergistic Effects of Carbopol® Polymers and Hypromellose for Matrix Tablets

Carbopol® polymers can be used alone as a controlled release agent in matrix tablets or in combination with hypromellose. Potential benefits to be derived from the polymer combination matrix (Carbopol® polymer/hypromellose) versus use of a single polymer matrix (Carbopol® polymer or hypromellose) are as follows:

- Lower total polymer level needed
  - *Formulation cost savings*
  - *Better patient compliance with smaller tablets*
- Performance consistency with regard to drug release
- Flexibility in modulating drug release
- Ability to further extend the release of some cationic drugs

The synergistic effects of a polymer combination matrix have been demonstrated in a variety of APIs with different solubilities. Benefits were observed in matrix tablets manufactured by direct compression and wet granulation with both low and mid dose tablets. Results for tablets manufactured by wet granulation are shown in Figures 8 - 13.

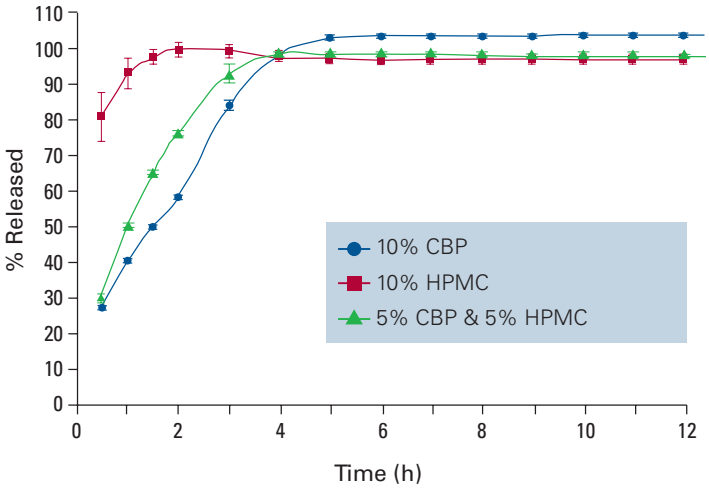
Table 3: Polymer Combination Study Overview

Type of Tablet Manufacture	Tablet Composition	APIs Evaluated
Direct Compression	Active Pharmaceutical Ingredient (API) • 50 mg/tablet (16.67%) Release controlling agents • Carbopol® 71G NF polymer and/or Methocel® K4M premium cellulose ether (1:1 ratio; 30% total polymer) Fillers • Avicel® PH 102 microcrystalline cellulose (7.33%) • Emcompress® dibasic calcium phosphate dihydrate (q.s.) Glidant • Cab-O-Sil® M5 fumed silica (0.5%) Lubricant • Synpro® magnesium stearate (0.5%)	• Propranolol hydrochloride • Hydrochlorothiazide • Carbamazepine • Ketoprofen
Wet Granulation	Active Pharmaceutical Ingredient (API) • 100 mg/tablet (33.3%) Release controlling agents • Carbopol® 971P NF polymer and/or Methocel® K4M premium cellulose ether (1:1 ratio; 10% total polymer) Fillers • Lactose and Emcompress® dibasic calcium phosphate dihydrate (1:1 mixture) Lubricant • Synpro® magnesium stearate (0.5%)	• Chlorpheniramine maleate • Propranolol hydrochloride • Verapamil hydrochloride • Ketoprofen • Acetaminophen • Guaifenesin

Results for Tablets Manufactured by Wet Granulation

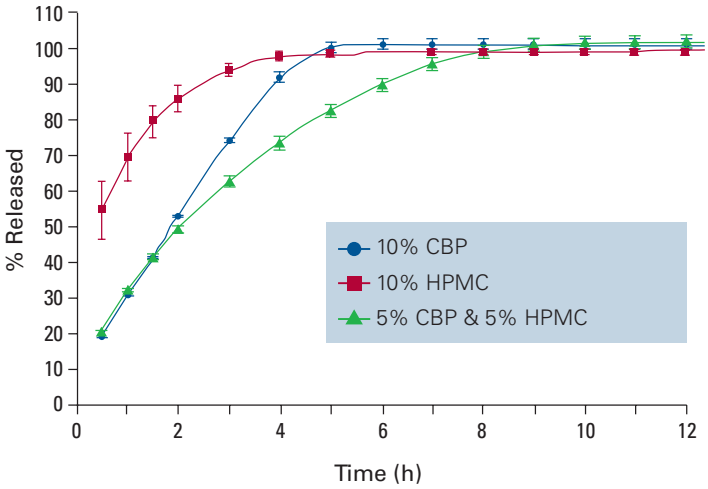
Guaifenesin (High Solubility)

Figure 8: Guaifenesin release (USP modified release method) from tablets (100 mg) with 10% polymer



In USP modified release, Carbopol® 971P NF polymer was the most efficient in extending the release. Partial replacement of the hypromellose with Carbopol® polymer led to slower release.

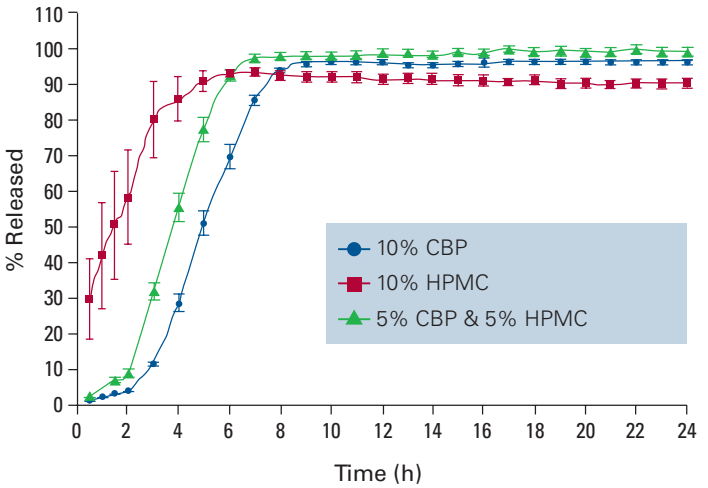
Figure 9: Guaifenesin release (pH = 6.8 buffer) from tablets (100 mg) with 10% polymer



In buffer, the polymer combination released slower than the Carbopol® polymer matrix.

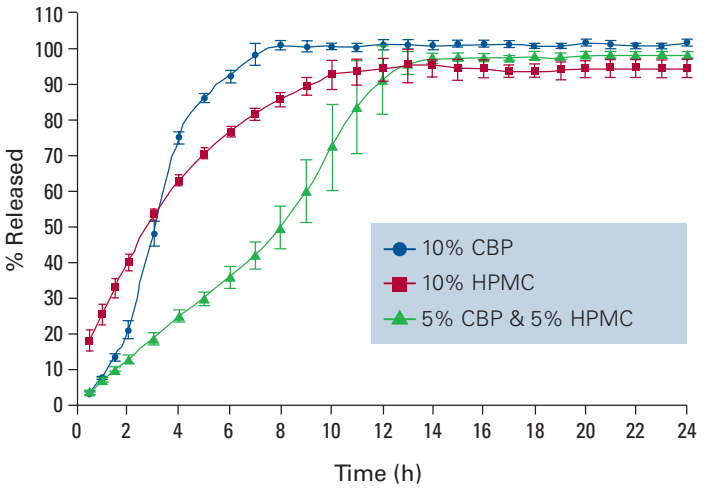
Ketoprofen (Anionic; Low Solubility)

Figure 10: Ketoprofen release (USP modified release method) from tablets (100 mg) with 10% polymer



In USP modified release, Carbopol® 971P NF polymer was the most efficient in extending the release and hypromellose release was the fastest with high variability. Change in drug solubility (higher in buffer) determined the shift in the release profile at 2 hours.

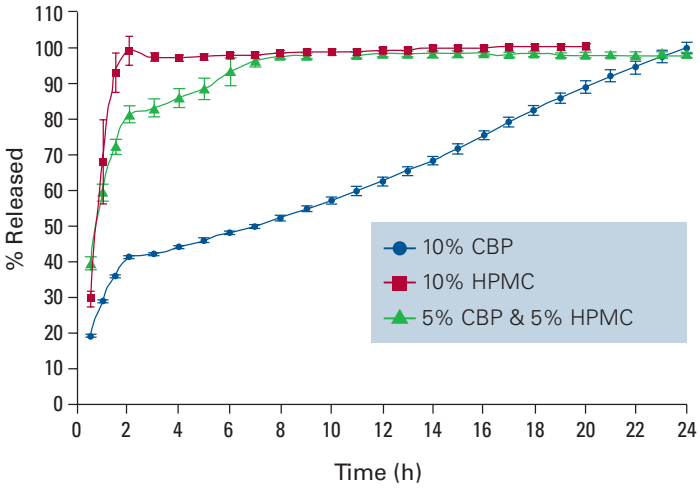
Figure 11: Ketoprofen release (pH = 6.8 buffer) from tablets (100 mg) with 10% polymer



In buffer, the polymer combination released slower than the Carbopol® polymer matrix.

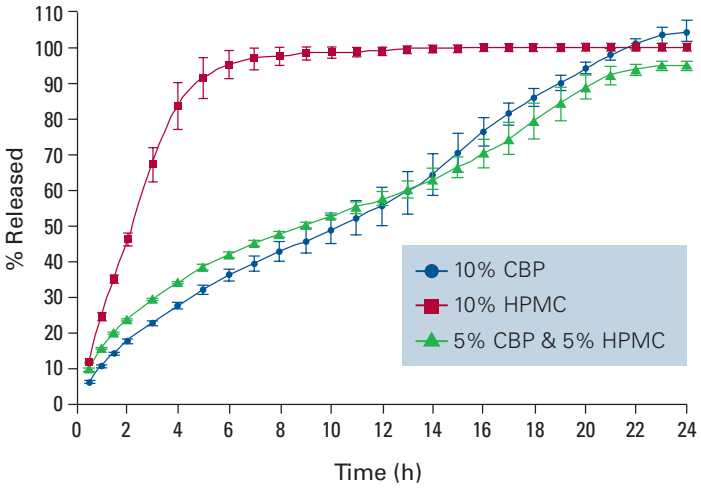
Verapamil (Cationic; Soluble)

Figure 12: Verapamil release (USP modified release method) from tablets (100 mg) with 10% polymer



In USP modified release, Carbopol® 971P NF polymer was the most efficient in extending the release and hypromellose release was the fastest.

Figure 13: Verapamil release (pH=6.8 buffer) from tablets (100 mg) with 10% polymer

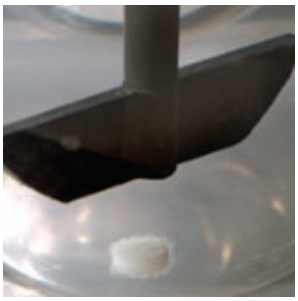


In buffer, the polymer combination released slower than the Carbopol® polymer matrix.

The Carbopol® polymer / hypromellose combination forms an efficient / advantageous matrix forming system. In buffer, the synergistic inter-polymer interaction is by chain entanglements between hypromellose and swollen carbomer particles. The polymer combination forms a more cohesive network, more resistant to diffusion and erosion.

Carbopol® 71G NF polymer (granular form)

Carbopol® 971P NF polymer (powder form)



Formulation Tips for Use of Carbopol® Polymers in Extended Release Tablets

API Dose

- Higher API dosages generally require higher polymer levels.

API Solubility

- Higher API solubility requires higher polymer levels.
- For water soluble drugs, 10% polymer (wet granulation) or 25% polymer (direct compression) may be a good starting concentration. Lower polymer levels may be sufficient for low solubility drugs.
- For highly soluble/high dose drugs, some other approaches may be required in conjunction with increasing the polymer level. For example, use of a polymer combination matrix or combined technologies (addition of the polymer intra- and extra-granularly, coating of the matrix tablets, etc.)

API Ionic Character

- Cationic APIs can interact with Carbopol® polymers and this interaction requires the ionized form of the polymer (occurs in the buffer).
- The molar ratio of API to Carbopol® polymer (carboxyl) is important for the interaction. A high stoichiometric ratio of carboxyl to API is favorable for interaction.
- API properties are important for the ionic interaction (solubility, amine group strength, steric orientation, molecular weight and size).
- Ionic interaction can slow the drug release and provide taste masking properties.
- The acidic nature of Carbopol® polymer can modulate the microenvironmental pH in the tablet. This is important for API stability and solubility inside the matrix.

Method of Tablet Manufacture

- Direct compression generally requires higher polymer levels (15 - 30%) than wet granulation (5 - 15%) mainly due to differences in polymer surface area. Specifically, there is a smaller surface area for the granular grade used in direct compression than for the powder grades used in wet granulation.
- Roller compaction generally requires low polymer levels (starting at 2.5%).

Coexcipients

- Fillers can have an impact on the release due to their solubility and disintegrating properties.
- Synergistic effects of Carbopol® polymers with other polymeric excipients (hypromellose, hydroxypropyl cellulose, polyethylene oxides, etc.) may enhance drug release properties.

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Detailed product information and samples of Noveon's high performance specialty chemicals for the pharmaceutical industry can be obtained through our web site at www.pharma.noveon.com or contact your sales representative or nearest Noveon office.

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