New Reverse Enteric Polymer for Oral Dosage Forms

Excipient Development at NCL

Complete Solution for

Taste Masking
Moisture Barrier
Sustained Release
Immediate Release
Polymorphism Inhibition
NREP
New Reverse Enteric Polymer

Product Description

NREP is a cationic ter-polymer, responsive to changes in pH. It dissolves at acidic pH < 3.5 and is insoluble and impervious at pH > 4. It is hydrophobic and insoluble in water. The polymer can be used for taste masking where the drug leaching is prevented at pH of saliva and also in aqueous media in case of liquid orals. The polymer can also be used as functional film coating for moisture barrier/sealant properties, immediate release applications and blends of NREP can be used for custom release profiles.

Advantages of Self association

- NREP has high T_g (121.2°C). This avoids tack during pharmaceutical processing like drying and heat sealing. No change in release pattern on curing.
- Rigid polymer structure inhibits adherence to biological membranes, enhances biocompatibility.
- The association of pyridine nitrogen inhibits its interactions with acidic drugs thereby avoiding the adverse drug-polymer interactions normally seen in acidic drugs and cationic polymers.
- Polyacid-polybase blends result in complexation and cannot be used for film coating applications. The self associations in NREP result in controlled hydrogen bonding with polyacids and other nonionic polymers. This provides a new set of miscible film forming blends of polyacids and NREP which can be used to custom sustained release of drugs.

Structure of NREP

NREP is a random terpolymer based on methyl methacrylate, 2-hydroxy ethyl methacrylate and 4-vinylpyridine. It is a self-associated acid soluble polymer.
Pharmaceutical Applications

1) Coatings for Immediate Release: NREP film coatings can be used for rapid release at gastric pH < 3.
2) Taste Masking Applications: NREP can be used for coating conventional, orally disintegrating tablets and granules for reconstitution, with rapid release in stomach and inhibition of drug release at salivary pH.
3) Moisture Barrier Coatings: NREP coatings provide moisture barriers for anhydrous drugs or drugs exhibiting polymorphic transformations in presence of moisture.
4) Alternative to the existing cationic polymers. NREP is an ideal hydrophobic coating agent which offers rapid release in stomach.
5) Coatings for Sustained Release: The blends of NREP with polyacids like Eudragit L, Eudragit S, Cellulose acetate phthalate, Hydroxy propyl methyl cellulose phthalate can be tailored to ensure sustained release of drugs along the entire length of GI tract.

NREP vs. Commercially Available Cationic Polymer

<table>
<thead>
<tr>
<th>Properties</th>
<th>Eudragit E</th>
<th>NREP</th>
<th>NREP Merits</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_g$ Storage Temperature</td>
<td>45-50 °C</td>
<td>121.2 °C</td>
<td>No tack during storage and processing</td>
</tr>
<tr>
<td>pH Response</td>
<td>25°C and below</td>
<td>No Stringent requirements</td>
<td>Polymer and product performance not affected by storage and processing history</td>
</tr>
<tr>
<td></td>
<td>Soluble &lt; pH 5</td>
<td>Soluble &lt; pH 3.5</td>
<td>Ideal for Taste Masking of Solid Dosage Forms and Liquid Orals, Granules for Reconstitution</td>
</tr>
<tr>
<td></td>
<td>Permeable above pH 5.0</td>
<td>Impermeable above pH 4.0</td>
<td>Rapid release at gastric pH</td>
</tr>
<tr>
<td>Interactions With Drugs</td>
<td>Interacts with acidic drugs</td>
<td>Inert to acidic drugs</td>
<td>More stable dosage forms</td>
</tr>
<tr>
<td>Interactions with other excipients</td>
<td>Strong Interactions Polyelectrolyte complex formation</td>
<td>Weak Interactions No Complexation Film Forming ability</td>
<td>Provides New Set of Film coatings for sustained release applications</td>
</tr>
</tbody>
</table>
Taste Masking

The highly bitter drugs Cefuroxime axetil, Ciprofloxacin HCL and Clarithromycin were encapsulated by NREP coatings. NREP ensures immediate release in the gastric region by dissolution of polymer. Taste masking with immediate release of Clarithromycin is especially useful to treat H. Pylori infections in children. Cefuroxime axetil and Ciprofloxacin HCl is better absorbed from upper gastric region and hence rapid release in stomach is especially desirable to ensure bioavailability and NREP coating also provides taste masking. Further, NREP coatings can be used for other drugs to achieve taste masking and enhancing patient compliance.

NREP dissolves rapidly at acidic pH ensuring immediate release of drug Cefuroxime axetil at gastric pH.

NREP is impervious to moisture at salivary and reconstitution pH and inhibits drug release enhancing palatability.
NREP Blends for Sustained Drug Release

The self-associations in NREP result in controlled hydrogen bonding with anionic polymers. This provides a new set of miscible film forming blends of polyacids and polybase without complexation. NREP forms film forming blends with polyacids like Cellulose acetate phthalate, hydroxyl propyl methyl cellulose phthalate, Eudragit L and Eudragit S. The blend compositions can be optimized to provide sustained gastric and intestinal release of drugs. Yet another advantage of using blends is that the amount of each component is reduced such that it falls within the permissible safe limits prescribed by FDA.

NREP forms miscible blends with HPMCP, CAP, Ethylcellulose and Eudragit L useful to modulate drug release at acidic pH

Blends of NREP with HPMCP and CAP effectively sustain the release of highly water soluble drug at pH 1.2 and 5.8
NREP for Polymorphism Inhibition of Drugs

Solid dispersions are used for enhancing dissolution of drugs. The residual solvent always induces devitrification of drugs. High Molecular Weight NREP inhibits conversion of metastable / amorphous form of polymorphic drug to stable crystalline form. The retention of amorphous form of polymorphic drugs enhances dissolution and bioavailability.

Blends of NREP-Fatty Acids for Taste Masking

NREP forms miscible blends with Fatty acids. Since Fatty acids are hydrophobic they are used to provide moisture protection and taste masking of granules for reconstitution. The major limitation of fatty acids is they result in slow release of drugs. The NREP-Fatty acid blend can be used for taste masking applications and as hydrophobic coatings with rapid release in stomach. These coatings can be applied by spray drying, hotmelt granulation and by wurster coating.
Adaptability to Processing

NREP is obtained as white odorless fine powder. NREP solutions can be prepared easily in most of the solvents used in pharmaceutical processing like methanol, ethanol, isopropanol, chloroform and methylene chloride. NREP forms clear and transparent films. NREP solutions can be used for film coating using the common coating equipments. It can withstand the heat during coating, drying and heat sealing process. NREP solutions can be spray dried easily. NREP is compatible with most of the pharmaceutical excipients.

NREP Characteristics

NREP can be synthesized in molecular weight ranges from 50 kD to 250 kD onwards for coating applications polymorphism inhibition. The $T_g$ of NREP is 121.2°C (determined by MDSC).

Dissolution pH of NREP

NREP film dissolves completely in the buffer pH 1.2 in 30-45 min but does not solubilize at pH 4.5 and 5.8. Figure shows equilibrium swelling at pH 4.5 and 5.8 and in distilled water. The dissolution characteristics of NREP make it ideal for the gastric delivery of drugs and for the formulation of taste-masked products, especially liquid oral preparations like dry syrup.

Minimum swelling of NREP at different pH and water

Moisture Barrier Properties

NREP is insoluble in water. It is completely impervious to water and these impart moisture barrier/ sealant properties to film coatings of NREP. The SEM evaluation of NREP coatings exposed to water for seven days does not show any morphological changes in the film. The TGA analysis showed a total moisture uptake of less than 2% on immersion of film in water for seven days. However the coatings are soluble in gastric pH rapidly unlike the hydrophobic cellulosic polymers which effectively protect from moisture but cause delayed release. These properties can be exploited for
providing moisture barrier during storage and yet ensuring rapid release in stomach.

**Biocompatibility of NREP**

**In-vitro Biological Response**

The response of NREP extracts on mouse fibroblast cells is shown below. The morphological examination of cell cultures treated with 25, 50 and 100% NREP extract, showed that the L929 mouse fibroblast cells were confluent and showed discrete intracytoplasmic granules with no cell lysis. These results indicate NREP is noncytotoxic as per in-vitro biological reactivity tests (USP).

**In-vivo Biological Response**

NREP extract in sodium chloride injection and cottonseed oil was used for intravenous and intraperitoneal injection test respectively. None of the animals injected showed any abnormalities or loss in body weight during the observation period. The results showed that NREP extracts in both media meet the requirements of the systemic injection test for intravenous and intraperitoneal application as per USP. The in vitro and in vivo biological reactivity tests show that NREP is non toxic.
Selected References and Patents

The detailed scientific understanding of the structure of NREP and its implications on properties and pharmaceutical applications can be found in following references.

- Miscible blends of Reverse Enteric Polymer with Enteric and pH independent Polymers: Mechanistic Investigations for Tailoring Drug Release,
  *Biomacromolecules*, 8, 240-251, 2007

- Designing a Self Associated Cationic Polymer for Enhanced Compatibility, Palatability and Gastric Release of Cefuroxime axetil
  *Biomacromolecules*, 8, 532-542, 2007

- Mechanistic Investigations of Phase Behavior in Eudragit® E Blends

- **US 20050137372**, pH Sensitive Polymer And Process For Preparation Thereof

- **US 20050136114**, Taste Masked Pharmaceutical Compositions Comprising Bitter Drug And pH Sensitive Polymer

- **US 20050136115**, Taste Masked Pharmaceutical Composition Comprising pH Sensitive Polymer

- **US 20050281874**, Coating Compositions For Bitterness Inhibition

- **US 20060141053**, Pharmaceutical Composition For Improving Palatability Drugs And Process For Preparation Thereof
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