# Comprehensive review of the role of acrylic acid derivative polymers in floating drug delivery system

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## Abstract

In the development of drug delivery systems, an oral drug delivery system is the preferred route of drug administration. Many components play an important role in developing a drug delivery system. Amongst those components, polymers have evolved with these systems. Macromolecule compounds consisting of many monomer units which are joined to each other by different bonds are known as polymers. For drugs that are absorbed primarily in the upper gastrointestinal tract, floating drug delivery systems offer an additional advantage. The purpose behind this review was to focus on different types of floating drug delivery systems and different types of polymers used in floating drug delivery systems, focusing on acrylic acid derivatives and their applications. In this review, the main emphasis is on acrylic acid derivative polymers, their formulation and grades, and various patents on these types of polymers. Based on the literature survey, mainly 2 types of polymers are used in this drug delivery system; i.e., natural and synthetic. Examples of natural polymers are xanthan gum, guar gum or chitosan, and synthetic polymers include acrylic acid derivatives and hydroxylpropyl methylcellulose (HPMC). Eudragit and Carbopol are the most widely used acrylic acid derivatives.

**Key words:** acrylic polymers, Eudragit, floating drug delivery system, acrylic acid derivatives, carbomer

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## Introduction

A gastro-retentive drug delivery system (floating), which is less dense than gastric fluids, thus remaining buoyant in the stomach for a prolonged period, and which does not affect the gastric emptying rate is known as a floating drug delivery system (FDDS).[1] Floating drug delivery systems are also known as hydrodynamically balanced systems (HBS). The system floats within the gastric contents and the drug is released at the desired rate from the system.[2,3] The remainder of the system is emptied from the stomach after the release of the drug; as a result, an increased gastric residence time (GRT) and a better control of fluctuations in plasma drug concentration can be achieved. The differences between zero-order controlled release and sustained release are shown in Fig. 1.

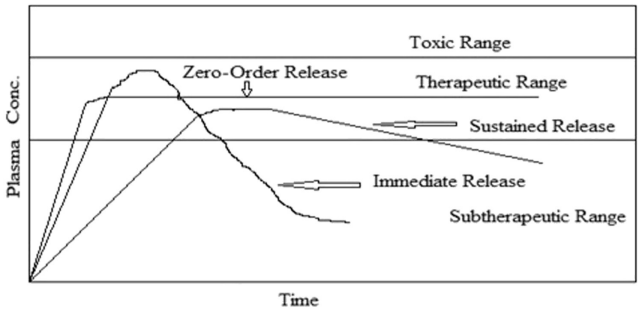
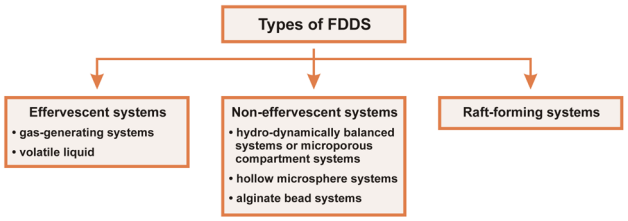



Fig. 1. Drug release profile, showing the differences between zero-order controlled and sustained release

## Types of floating drug delivery systems

There are various types of commercially available FDDSs[4,5] through which drugs are administered to the body and the effective controlled release of a drug is achieved. Some of these formulations are described in Table 1.[6]




## Polymers used in floating drug delivery systems

In a floating drug delivery system, many polymers are used to target drug delivery at a specific region within the stomach. Both types of polymers, i.e., synthetic and natural, are used in such a system. Natural polymers like chitosan, xanthan gum and sodium alginate are used in a floating system, while synthetic polymers, such as hydroxylpropyl methylcellulose (HPMC), ethyl cellulose and acrylic acid derivatives, are used for the floating drug delivery.[7] Different natural and synthetic polymers and their properties are listed in Table 2.

Natural polymers have some inherent disadvantages, such as microbial contamination, variation between batches, uncontrolled hydration rate, and loss of viscosity in storage.[8]

## Synthetic polymers

Synthetic polymers are macromolecules with very large chains containing a variety of functional groups. They have a very wide range of uses, and are thus becoming more and more important in pharmaceuticals. The uses of synthetic polymers, e.g., as a binder or film coating agent for targeted drug delivery, are very common. Synthetic polymers are either purely synthetic or semi-synthetic, the latter being a modified form of natural polymers.[9]

Some examples of synthetic polymers are Eudragit or Carbopol, which are acrylic acid derivatives, and HPMC.

Table 1. Commercially available floating formulations

| Name of the product | Active ingredient | Category | Remarks |
|---|---|---|---|
| Madopar | levodopa and benserazide | anti-parkinsonian | floating, controlled-release (cr) |
| Valrelease | diazepam | anti-anxiety | floating capsule |
| Gaviscon | Al hydroxide<br>Mg carbonate | antacid (in reflux esophagitis) | effervescent floating liquid<br>alginate preparation |
| Cytotec | misoprostol | antiulcer | floating dosage form |
| Topalkan | alginic acid,<br>aluminium and magnesium salts | antacid | floating liquid<br>alginate preparation |
| Almagate flowcoat | Al-Mg antacid | antacid | floating dosage form |

Table 2. List of polymers and their properties

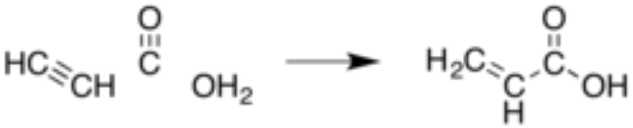
| No. | Polymer (type) | Source | Properties |
|---|---|---|---|
| 1. | guar gum (natural) | endosperm of seed of cynopsis tetragonolobus | insoluble in organic solvents, strong hydrogen bond |
| 2. | chitosan (natural) | shell of marine invertebrates | nontoxic, biodegrable, biocompatible |
| 3. | xanthan gum (natural) | fermentation of glucose by *Xanthomonas campestris* | excellent solubility and stability under acidic and alkaline conditions |
| 4. | gellan gum (natural) | *Pseudomonas elodea* | high gel strength, an excellent stability, process flexibility, high clarity |
| 5. | sodium alginate (natural) | *Laminaria hyperboria* | acidity/alkalinity ph-7.2 (1% w/v aqueous solution) |
| 6. | Eudragit (synthetic) | acrylamide monomer | Eudragit S and FS are soluble at pH above 7 while Eudragit L is soluble at pH above 6. Eudragit RL, NE 40D, RS, NE 30D, and NM 30D are used to form water-insoluble film coats. |
| 7. | ethyl cellulose (synthetic) | prepared from cellulose, it is a partly O-ethylated cellulose, its ethoxy content (-$OC_2H_5$) is 44–51% | water-insoluble cellulose ether |

## Acrylic acid

Byproduct of the production of ethylene and gasoline, acrylic acid is produced by the oxidation of propylene:

$$CH_2{=}CHCH_3 + {}^3\!/_2O_2 \rightarrow CH_2{=}CHCO_2H + H_2O$$

The IUPAC name of acrylic acid is propenoic acid. It is an organic compound with the formula $CH_2$=CHCOOH. It has good solubility with water, ethers, chloroform, and alcohols.[10]




## Acrylic acid derivatives

There are many derivatives for the preparation of floating microspheres to be used as polymers. Of these numerous polymers, Eudragit and Carbopol are the most commonly used derivatives. A derivative of acrylic and methacrylic acids, such as Eudragit and its various grades – RL, E and RS – are used in the preparation of floating microspheres.[10] The grades RL 100 and RS 100 are both granular in nature and are the most widely used forms of any pH-independent swelling polymer with muco/adhesive properties.[11]

For sustained-release products and to form water-insoluble film coatings, Eudragit RL, NM 30D, NE 30D, RS, and NE 40D are used. Varying permeability films can be obtained by mixing any 2 polymers, but Eudragit RL films are more permeable than Eudragit RS. In aqueous as well as organic wet-granulation processes, polymethacrylates are also used as binders. To control the release of a drug from a tablet matrix, more (5–20%) dry polymer is used; solid polymers (10–50%) may be used in direct compression processes. To prepare novel gel formulations for rectal delivery and the matrix layers of transdermal delivery systems, polymethacrylate polymers are also used.[12]

## History of Eudragit

Before the 19th century, the control of drug release time and its release site was impossible. In order to remove this main drawback, scientists can use polymers to plan and modulate the release of drug. The discovery of Eudragit by Rohm and Haas played a major role in finding the solution to this problem. Over time, various grades of Eudragit have been discovered, with varying degrees of solubility. To coat solid drugs, as with tablets, capsules or granular formulations, Eudragit is used as an excipient. Then, in the 1950s, the use of Eudragit in drug release was first discovered when a coated pill that dissolves in stomach acid was released. Since then, many other variants of Eudragit which control the drug release time have become available, but these are called retard preparations because they release their drugs at intestinal pH due to their resistance to stomach pH.[13] Eudragit is a trademark of Rohm GmbH and Co. KG. Eudragit is produced through the polymerization of acrylic and methacrylic acids or their esters, such as butyl ester.[14] The different grades of Eudragit are introduced in chronological order in Table 3.

## Glass transition temperature

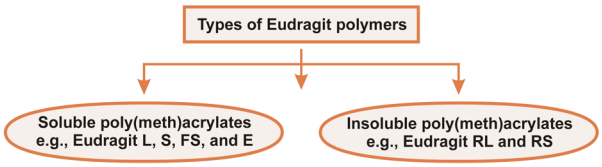
In the description of the physical properties of polymers, glass transition temperature is an important factor. The solidification of an anisotropic polymer melt is

Table 3. Specifications and applications of different grades of Eudragit

| Grade of Eudragit | Year of introduction | Available form | Glass transition temperatures (Tg) | Dissolution properties | Applications |
|---|---|---|---|---|---|
| RL 100 | 1968 | granules | 63 | insoluble | sustained release |
| RL 30 D | 1986 | 30% aqueous dispersion | 55 | pH-independent | sustained release |
| RS 100 | 1968 | granules | 65 | insoluble | sustained release |
| RL 12.5 | 1954 | 12.5% organic solution | 130 (±5) | – | sustained release |
| RL PO | 1972 | powder | 63 | high permeability | sustained release |
| RS 12.5 | 1954 | 12.5% organic solution | 130 (±5) | – | sustained release |
| RS PO | 1972 | powder | 65 | low permeability | film coating |
| NE 40 D | 1983 | 40% aqueous dispersion | –8 | pH-independent swelling | film coating |
| RS 30 D | 1986 | 30% aqueous dispersion | 55 | pH-independent swelling | sustained release |
| NE 30 D 30 % | 1972 | aqueous dispersion | –8 | Insoluble, low permeability | film coating |

described on a macroscopic level. In short, as the temperature is increased, the glass transition or glass–liquid transition is the reversible change in an amorphous product from a solid and moderately brittle "glassy" state into a rubbery or viscous state.[15] The glass transition temperature of different grades of Eudragit is presented in Table 3.

# Types of Eudragit polymers




## 1. Soluble poly(meth)acrylates

Soluble poly(meth)acrylates will dissolve in digestive fluids by forming salt and are able to release a drug at certain pH levels with acidic or alkaline groups.

### Applications

Through simple masking and gastric resistance, the drug is delivered to all sections of the intestine for controlled drug release.

## 2. Insoluble poly(meth)acrylates

Insoluble poly(meth)acrylates are permeable in digestive fluids but insoluble in nature. For example, by pH-independent swelling Eudragit RL and RS polymers are able to control the drug release time in alkaline conditions, while Eudragit NE polymers are able to do so with neutral groups.

### Advantages of Eudragit polymers

The advantages of the acrylic acid derivative[16] Eudragit are listed in Fig. 2.

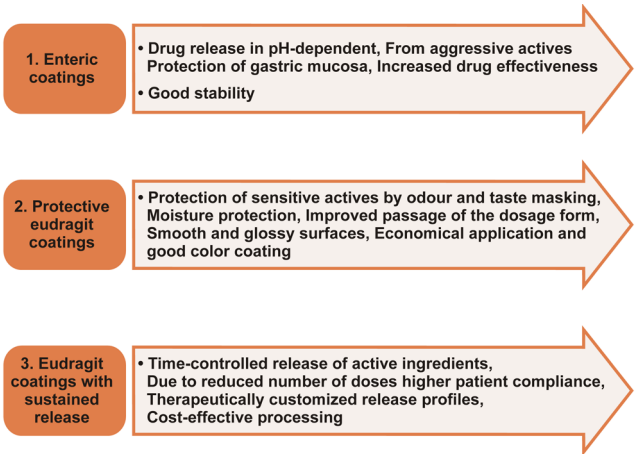



Fig. 2. Advantages of Eudragit polymers

# Carbopol

Another acrylic acid derivative with a high mucoadhesive property and a high swelling property is Carbopol; it is very often used in FDDSs. Carbopol is used alone and in combination with other polymers, such as Eudragit or natural polymers, in preparations of floating formulations.[17–19] By using the emulsification solvent evaporation method, floating microspheres can also be prepared with different grades of Carbopol: Carbopol 934, Carbopol 910, Carbopol 940, and Carbopol 941. The different grades of carbomer and their uses, viscosities and properties are described in Table 4. This floating system has been accepted as a process to accomplish controlled drug delivery by delaying the residence time of the dosage form at the site of absorption, thereby enhancing the bioavailability of the active ingredient.[20–22] The advantages of this polymer are summarized in Fig. 3.

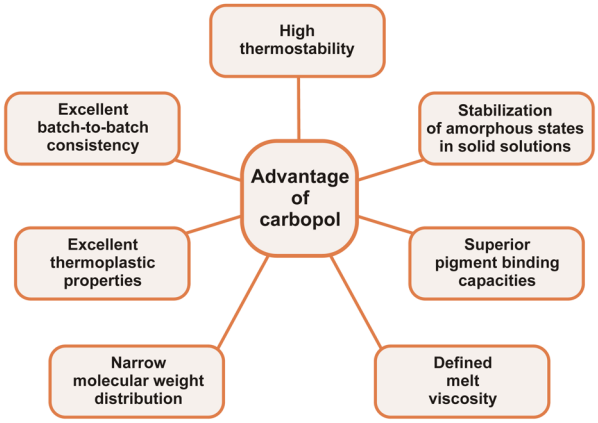



Fig. 3. Advantages of Carbopol polymers


Fig. 4. The role of acrylic acid derivatives in drug delivery

## Pharmaceutical applications of acrylic acid derivatives

There are numerous applications of acrylic acid derivatives; they are primarily used as tablet coatings, film forming agents, tablet binders, etc. Eudragit E12.5 is a 12.5% solution in propanol acetone (60:40) with a molecular weight of 32,000 g/mol. It is available as an organic solution and is mainly used as a film coating agent. It appears light yellowish in color and is soluble at a pH of less than 5. It is miscible in ethyl acetate, acetone, alcohols, 1N HCl, dichloromethane, and petroleum ether.

Eudragit E100 is used for a targeted area such as the stomach. It is accessible as tinged granules which are colorless or yellow in color with an amine-like odor. Its properties include great pigment binding capacity, low polymer weight, low viscosity, and good adhesion. The solubility characteristics of Eudragit E100 are similar to Eudragit 12.5. Eudragit grade RSPO is available as a white powder and has a faint amine-like odor, while Eudragit RS 100 is available as a colorless granule with an odor similar to Eudragit RSPO.[15] The description and uses of Carbopol derivatives are presented in Table 4. The role of these polymers is depicted in Fig. 4.

Eudragit E PO is available as a free-flowing white powder which is used as a film coating agent. It is soluble in acetone and alcohols and in a pH of less than 5. Eudragit RS 100, RS 30D, RS 12.5, and RSPO are copolymers with quaternary ammonium groups of methyl methacrylate, ethyl acrylate and a small amount of methacrylic acid ester. The ammonium groups exist as salts and this permeability is an asset. Eudragit grade RS 30 D is available in liquid form. It has squat viscosity, a faint, characteristic odor, and a milky white color.[15] The widespread applications of different acrylic acid derivatives as single polymers or in combination with other natural or synthetic polymers are summarized in Table 5 along with their dosage form and method of preparation.

Different grades of Eudragit, such as RSPO, are available in powder form, while RS 30D, RS 100, and RS 12.5 are accessible in granular form, 30% aqueous dispersion and organic solution (12.5%), respectively; all grades are insoluble. They show pH-independent swelling with low permeability. Different grades of Eudragit are used in various ratios for the controlled and modified release profile.[59] Out of the many grades of Eudragit, a brief outline on RS 30D, RS 100 and RSPO is provided in Table 6.

Table 4. Different grades of carbomers and their properties

| Name of polymer | Viscosity [Pa·s] | Used in dosage forms | Properties |
|---|---|---|---|
| Carbopol 910 | 3,000–7,000 | emulgel, liposomal gel | Effective in low fixations and give a low consistency formulation. |
| Carbopol 940 | 40,000–60,000 | emulgel | Effective in thick formulations and very great clarity in water or hydroalcoholic topical gels. Forms clear gels with hydroalcoholic frameworks. |
| Carbopol 941 | 4,000–11,000 | emulgel | Produces low consistency gels and great clarity. |
| Carbopol 934 | 30,500–39,400 | jojoba oil-based emulgel | Effective in thick details, for example, emulsions, suspensions, sustained release formulations, transdermals, and topicals. Forms clear gels with water. |
| Carbopol 934P | 29,400–39,400 | emulgel, liposomal gel | Same properties as 934; however, expected for pharmaceutical plans. "P" = exceptionally purified product |

Table 5. List of drugs with their dosage form for gastric retention

| Drug | Polymer | Dosage form | Method used | Reference |
|---|---|---|---|---|
| Ofloxacin | ethyl cellulose, sodium bicarbonate, Eudragit RL 30D | pellets | extrusion–spheronization | 25 |
| Itraconazole | chitosan | microspheres | ionotropic gelation | 26 |
| Norfloxacin | Eudragit®L100, Eudragit®RS 100 | microballoons | emulsion solvent diffusion | 27 |
| Nifedipine | ethyl cellulose | microspheres | solvent evaporation | 28 |
| Bumetanide | Eudragit RS 100, sodium chloride, triethyl citrate | pellets | fluid bed layering and coating | 29 |
| Famotidine | Eudragit S 100 | microspheres | solvent evaporation | 30 |
| Levodopa | gelatin, ethyl cellulose, carbidopa, L-polylactic acid, Eudragit S 100 | novel unfolded CR-GRDF | solvent evaporation | 31 |
| Acacia catechu | Carbapol, HPMC and sodium CMC | microspheres | solvent evaporation | 32 |
| Pantaprazole | Eudragit L 100 and RS 100 | microballoons | emulsion solvent diffusion | 33 |
| Piroxicam | alginate, pectin and HPMC | beads | ionotropic gelation method | 34 |
| Diclofenac potassium | Kollicoat SR 30D, Eudragit NE 30D and RS 30D | pellets | extrusion–spheronization | 35 |
| Carvedilol | chitosan | beads | ionotropic gelation method | 36 |
| Metformin hydrochloride | polyethylene oxide and Eudragit®L100 | matrix tablets | direct compression | 37 |
| 5- Fluorouracil | ethyl cellulose | microspheres | emulsion solvent diffusion | 38 |
| Levodopa | Eudragit®RL 30D, acetyl, triethyl citrate | floating coated mini-tabs | melt granulation and compression | 39 |
| Procynanidins | chitosan | capsules containing beads | ionotropic gelation method | 40 |
| Riboflavin | Eudragit L and Eudragit S plasticized with triethyl citrate | unfolding dosage form | accordion pill technology | 41 |
| Anthocyanin | calcium alginate, calcium carbonate, sodium acetate anhydrous and calcium chloride | microspheres | ionotropic gelation method | 42 |
| Diltiazem hydrochloride | sodium alginate, $CaCO_3$, $CaCl_2$, Eudragit RS 30D, and chitosan | floating microspheres | ionotropic gelation method | 43 |
| Clarithromycin | ethyl cellulose and HPMC E5 | microspheres | solvent evaporation | 44 |
| Rabeprazole sodium | MC, Mannitol SD 200, Colorcoat EC4S, Kollidon CL | enteric coated tablet | wet granulation and direct compression | 45 |
| Nizatidine | Eudragit S 100 and HPMC | microballoons | emulsion solvent diffusion | 46 |
| Riboflavin | Eudragit RS 100 and HPMC | microballoons | emulsion solvent diffusion | 47 |
| Metformin | HPMC K4M, ethyl cellulose | microballoons | solvent evaporation | 48 |
| Ketoprofen floating | Eudragit S 100 and RL 100 | microparticles | emulsion solvent diffusion | 49 |
| Meclizide HCL | HPMC K 15M, Eudragit S 100 and RS 100 | microspheres | solvent evaporation | 50 |
| Riboflavin | Eudragit S 100, PVA, dichloromethane, HPMC, and ethanol | microballoons | emulsion solvent diffusion | 51 |
| Repaglinide | PC, PPG | microspheres | solvent evaporation | 52 |
| Verapamil | Povidone K 30, talc, Eudragit NE 30 D and L 30 D, triethyl citrate | floating pellets | wet granulation and spheronization | 53 |
| Curcumin | ethyl cellulose | microspheres | emulsion solvent diffusion | 54 |
| Felodipine | ethyl cellulose | hollow microspheres | emulsion solvent diffusion | 55 |
| Riboflavin | Eudragit RS 100 and HPMC | microballoons | emulsion solvent diffusion | 56 |
| Fluconazole | Carbopol 934 | liposomal gel | simple gelation method | 57 |
| Ketoconazole | Carbopol 934 and 940 | emulgel | simple gelation method | 58 |

Recently, Carbopol- and Eudragit-based formulations were collected for various patents and it was observed that formulations prepared using both of these polymers have been patented for diversified uses. Some of the patented applications are listed in Table 7, e.g., for colonic drug delivery, enhanced stability, improved bioavailability, improved hardness, oral drug delivery, reaction of carbomers, prolonged drug release, etc.[59]

## Conclusions

Acrylic acid derivative polymers have made significant contributions to various formulations due to their unique properties. In this article, the role of Carbopol and Eudragit was observed as novel and useful polymers, which can become more important in the future. This comprehensive review of 78 references signi-

**Table 6.** Specifications of Eudragit RS 30D, RS 100 and RSPO

| Drug name | Grade of Eudragit | Method of preparation | Dosage form | Significance | Reference |
|---|---|---|---|---|---|
| Oxymatrine | Eudragit RS 30D | extrusion/spheronization | pellets | sustained release of drug for 12 h | 60 |
| Stavudine | Eudragit RSPO | solvent evaporation method | microspheres | sustained release | 61 |
| Ketoprofen | Eudragit RS 30D | same as in reference 60 | pellets | The initial drug release is minimized but the terminal drug release increased more significantly. | 62 |
| Lobenzarit disodium | Eudragit RSPO | direct compression | tablet | slow drug release | 63 |
| Ambroxol hydrochloride | Eudragit RS 30D | same as in reference 60 | pellets | stable as well as sustained release formulation | 64 |
| Verapamil hydrochloride | Eudragit RS 100 | wet granulation method | matrix tablets | Coating with Eudragit RS 100 polymer reduced initial drug release. | 65 |
| Diclofenac sodium | Eudragit RS 30D | roto agglomeration | pellets | extended drug release for 24 h | 66 |
| Terbinafine hydrochloride | Eudragit RS 100 | nano preciptation method | nanoparticles as eye drop | improved ocular bioavailability | 67 |
| Alfuzosin hydrochloride | Eudragit RSPO | same as in reference 63 | tablets | The drug release was prolonged for 20 h. | 68 |
| Clotrimazole | Eudragit RS 100 | spray drying technique | tablets containing microspheres | controlled intravaginal drug release | 69 |
| Theophylline | Eudragit RSPO | rotary tablet press | microtablets | sustained release | 70 |
| Genistein | Eudragit RS 100 | melt-emulsification technique | nanostructured lipid carrier | Corneal penetration increases 3.3-fold. | 71 |

**Table 7.** Patents on applications for acrylic acid derivatives

| Title of the patent | Invention | Patent No. | Reference |
|---|---|---|---|
| Zinc/pectin beads with a Eudragit coating for colonic delivery | The systems comprise pectin beads which are cross-linked with any divalent cation or zinc which are coated with Eudragit polymers. | US 20080124279 | 73 |
| With enhanced mechanical properties modified release tablet formulations | For said pharmaceutical formulation Eudragit L00-55 is used which achieves a desired hardness. | US 2007010 | 74 |
| Enhanced stabilization of misoprostol | Misoprostol was complexed with several grades of Eudragit, such as RS series, RL series, Eudragit S and L; the solid dispersions were stable and showed sustain release. | EP0896823 | 75 |
| Preparation method for the carbomer | Reaction in a mixed solvent of ethyl acetate and n-hexane and cyclohexane. | 201310453464.3 | - |
| Ursodeoxycholic acid-synthetic hydrotalcite-eudragit hybrid, pharmaceutical composition and method for preparing the same | The ursodeoxycholic acidsynthetic hydrotalcite-eudragit hybrid was used for bitter-taste-blocking effect and with high solubility improved body absorption rate. | US 2012015 6263 | 76 |
| Oral drug delivery formulations | One active substance and minimum 1 coat containing Eudragit E in order to manage pain the preparation may be used for releasing loading dose up to about 55% of a total dose. | US 20150250733 | 77 |
| Preparation of carbomers | Carbomer portion of the reaction medium is water instead of organic solvent such that the process toward the preparation of non-toxic carbomer, development of green direction. | 201410010540.8 | - |
| Coated senna extract granules | With 20% sennosides obtained from Senna extract are granulated with Eudragit grade L 100 and then covered with Eudragit grade L 30 D 55. | Wo/2011/014976 | 78 |

fies the uses of various grades of Eudragit and Carbopol polymers, which are the most widely used acrylic acid derivatives. The various drugs, dosage forms, and methods used to prepare formulations based on them have been described with all necessary details. These details are sufficient for the reader to understand the basic role of acrylic acid derivatives in different formulations. Some patents are also discussed in order to describe the current status of these polymers. Therefore, researchers can use this review as a guide to develop drug delivery systems based on acrylic acid derivatives, i.e., using Eudragit or Carbopol.

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