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"EUDRAGIT AND CHITOSAN – THE TWO MOST PROMISING POLYMER FOR COLON DRUG DILEVERY"

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Abstract

Polymers occupy a major portion of materials used for controlled release formulations and drug-targeting systems because this class of materials presents seemingly endless diversity in topology and chemistry. This is a crucial advantage over other classes of materials to meet the ever-increasing requirements of new designs of drug delivery formulations. The colonic region of the GIT has become an increasingly important site for drug delivery and absorption.Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzyme. With the advances in polymer synthesis chemistry and technology, more defined, controlled, and biocompatible polymers are becoming available, and such polymers will contribute to new generations of biomimetic nanostructures and vehicles for carrying diagnostic and imaging agents, therapeutic drugs, prognostic reagents, and multiagents in the future.

Introduction

A polymer, natural or synthetic is a substance that is combined with a drug or other active agent to release drug in a pre-designed manner[1]. The development of NDDS has been made possible by the various compatible polymers to modify the release pattern of drug [2, 3]. Choice of polymers always suffering from the problems of non-biocompatible, non-biodegradable and expensive and this problem can solve with a polymer of different properties. The basic objective of controlled drug release is to achieve more effective therapies by eliminating the potential for both under and overdosing. Other advantages are the maintenance of drug concentration within a desired range, fewer administrations, optimal drug use and increased patient compliance[4.]

The basic goal of drug therapy is to achieve a steady-state at blood or tissue level that is therapeutically effective and non toxic for an extended period of time. A basic objective in dosage form design is to optimize the delivery of the medication so as to achieve a measure of control of therapeutic effect in the place of uncertain fluctuations in the in-vivo environment in which drug release takes place. This is usually accomplished by maximizing drug availability, i.e., by attempting to attain a maximum rate and extent of drug action through formulation also implies controlling bioavailability to reduce drug absorption rates. An ideal controlled drug delivery system is one which delivers the drugs at a predetermined rate, locally or systematically, for a specified period of time.

Controlled Released Drug Delivery System interchangeable called as programmed release, sustained release, prolonged release, timed release and extended release. An ideal targeted drug delivery system is the one which delivers the drugs only to its sites of action and not to the non targeted organs or tissues. This targeted system is employed for the drugs that are destroy by the acidic environment of the stomach or metabolized by pancreatic enzymes are only slightly affected in the colon and this deliver system is used for the treatment of ulcerative colitis, crohn's disease, and colorectal cancer inflammatory bowel diseases. Colonic delivery mainly accomplished by rectal or oral administration. Rectal administration of colonic delivery is not effective widely, oral administration is preferred. Absorption or degradation of active constituent in the upper part of GIT is main obstacle and must be circumvented for successful colonic drug delivery.
In views of CDDS specifically delivering drug to the colon, a lot benefits would be acquired in terms of improving safety and reducing toxicity when treating local or systemic chronic diseases. First, as for treating localized colonic diseases, i.e. ulcerative colitis, Chron’s disease and constipation, etc. The optimal drug delivery system, such as CDDS, should selectively deliver drug to the colon, but not to the upper GI tract. Second, the Colon is referred to as the optimal absorption site for protein and polypeptide after oral administration, because of the existence of relatively low proteolytic enzyme activities and quite long transit time in the colon. Finally, CDDS would be advantageous when a delay in absorption is desirable from a therapeutically point of view, as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythms, such as nocturnal asthma, angina and rheumatoid arthritis.

The therapeutic advantages of targeting drug to the diseased organ include

1. Delivery of drug in its intact form as close as possible to the target site.
2. The ability to cut down the conventional dose and,
3. Reduce incidence of adverse side effects.

Why colon targeted drug delivery needed?

1. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.

2. Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.

3. Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.
4. The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).
5. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be
6. capable of being treated more effectively if drugs were targeted to the colon.

7. Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.[6]

Colon Anatomy[5]

1.The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts. These are the colon, the rectum and anal canal.

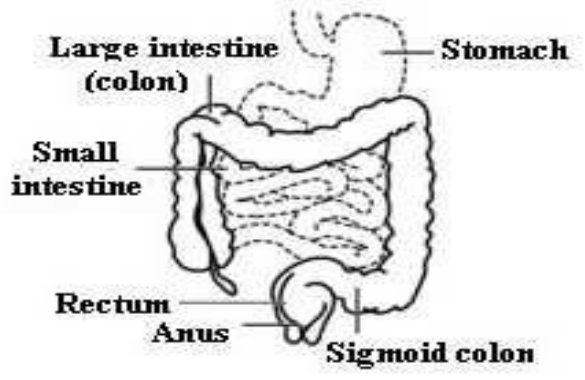

Figure 1: Structure of human intestine

The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus[6].

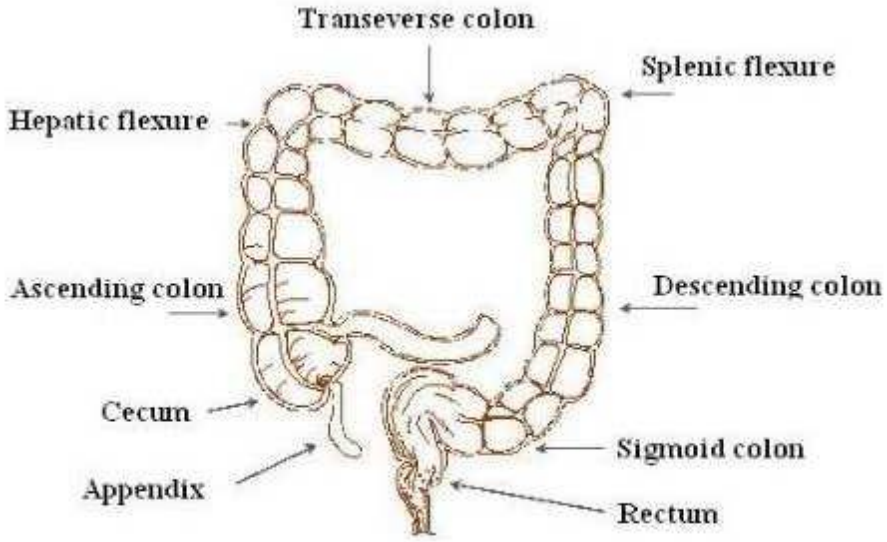

Figure 2: Structure of colon

The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of fecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen[7]. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileo cecal valve from which more than 90% of the fluid is absorbed. On average, it has been estimated that colon contains only about 220 gm of wet material equivalent to just 35 gm of dry matter. The majority of this dry matter is bacteria. The colon tissue containing the villi, lymph, muscle, nerves, and vessels.

Colonic micro flora

A large number of anaerobic and aerobic bacteria are present the entire length of the human GI tract. Over 400 distinct bacterial species have been found, 20- 30% of which are of the genus bacteroids[8]. The upper region of the GIT has a very small number of bacteria and predominantly consists of gram positive

facultative bacteria. The rate of microbial growth is greatest in the proximal areas because of high concentration of energy source.

1. The metabolic activity of microflora can be modified by various factors such as age, GI disease, and intake of drug and fermentation of dietary residues.
2. 1.5 pH differences in the colon
3. On entry in to the colon, the pH dropped to 6.4 ± 0.5. The pH in the mid colon was found to be 6.6 ± 1 and in the left colon, 7.0 ± 1 and the
4. 1.6 Gastrointestinal transit
5. Gastric emptying of dosage form is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and adensity. The transit times of dosage forms in tract.
6. Diseases affecting colonic transit have important implications for drug delivery, diarrhea increases colonic transit and constipation decreases it. The digestive motility pattern takes place when food is present in the stomach. It is said by regular, frequent contractions (about 4-5/min.) which effect the mixing intestinal contents and moving them towards the colon in short segments and lasts as long as food remains present in the stomach.The most frequent movements seen in the colon are very slow segmenting movements that typically occurs every 30 min.

Polymer for Colonic drug delivery

One would always like to have an ideal drug delivery system that will possess three main Properties:

(a) It will be a single dose for the whole duration of treatment.

(b) It will deliver the active drug directly at the site of action.

(c) It will possess possible fewer side effects.

Above approaches are achieved with the help of suitable choice of polymer. This review focuses on recent literature regarding use of Eudragit chitosan polymer in colon drug delivery systems with special attention to used in its fabrication along with their physiochemical properties.

Eudragit[9]

Methacrylic acid copolymers are the frequently used pH-dependent coating polymers, they are known commercially as Eudragit® (which is a registered trademark of Rohm Pharmaceuticals, Darmstadt, Germany). Eudragit® L and Eudragit® S are used in combination for meeting the effective pH-dependent

coating. Eudragit® L100 and S 100 are copolymers of methacrylic acid and methyl methacrylate in different ratios of carboxyl to ester groups which is about approximately 1:2 in Eudragit® S 100 and 1:1 in Eudragit® L100. These polymers after forming salts dissolve above pH 5.5 and disperse in water forming latex. Eudragit® L30D-55 is a ready to use aqueousdispersion of Eudragit® L100-55. The solubility of the Eudragit® S in water depends on the ratio of free carboxyl groups to the esterified groups. The factor, which is critical, is that influences the performance of these polymers, is the pH value at which dissolution happens. Polymers with an ionizable phthalic acid group dissolve much faster and at a lower pH than those with acrylic or methacrylic acid groups. The permutation of Eudragit® L100-55 and Eudragit® S100 could be effectively used from aqueous system to coat tablets for colon targeted drug delivery of drugs and can be adjusted to deliver drug at any other desirable site of the intestinal region of the GIT on the basis of pH unevenness. Lorenzo- Lamosa et al., (1998) demonstrated the efficacy of a system, which joins both the specific biodegradability and pH dependent release behavior. Various Eudragit coated oral dosage forms of Salsalazine® are presently in use for the treatment of ulcerative colitis and Crohn's disease (Dew et al., 1984). Morishita et al.,1993, compared the insulin delivery of two formulations containing Eudragit® L-100 and Eudragit® LS respectively. Formulation containing Eudragit® S showed optimal delivery of insulin in the ileum at pH 7.

History of eudragit

Until the 1950s, all oral medication, even the most modern, had one big disadvantage: It was not possible to control the time or the release location of the active substances. The development of EUDRAGIT by **Röhm & Haas GmbH** in **Darmstadt** was the solution to this problem. When the first drugs came onto the market in a EUDRAGIT coating, a new chapter in pharmaceutical history had begun. EUDRAGIT products are special polymers with varying degrees of solubility. The Research department at **Röhm** made use of this property. The first drug coatings developed in 1953 were alkaline soluble and therefore resistant to stomach acids. The active substances were therefore not released in the stomach, but in the intestine, where they were to be activated. Variants of this kind of EUDRAGIT are still used to coat solid drugs taken orally, such as tablets, capsules or granules. The first enhancement to EUDRAGIT came at the end of the 1950s, when a pill coating that dissolves in stomach acid came onto the market. In the meantime, other variants of EUDRAGIT have become available, which can also control the time at which substances are released. These are called retard preparations, are resistant to stomach acid and continue to work throughout the intestinal tract, increasing considerably the efficiency of certain therapies and applications EUDRAGIT research and manufacturing are today part of the Chemicals Business Area of Evonik Industries AG. Production takes place at Darmstadt, Weiterstadtand Worms's sites[10]. Eudragit is trademark of Rohm GmbH & Co. KG. Darmstadt in Germany, first marketed in1950s. Eudragit prepared by the polymerization of acrylic and

methacrylic acids or their esters, e.g., butyl ester or dimethylaminoethyl ester. Eudragit introduced in USPNF, BP, PhEur, Hand book of pharmaceutical excipients[11.] The eudragit acrylic polymers have a long history of use, the individual types and grades being introduced in the following chronological order.

Year of introduction	Eudragit grade
1954	Eudragit L 12.5 Eudragit s 12.5
1959	Eudragit E 12.5
1961	Eudragit E 100
1968	Eudragit RL 100 Eudragit RS 100
1972	Eudragit NE 30 D (formerly Eudragit E 30 D) Eudragit L 30 D-55 (formerly Eudragit L 30 D) Eudragit RS PO Eudragit RL PO
1977	Eudragit L 100
1983	Eudragit NE 40 D
1985	Eudragit L 100-55
1986	Eudragit RL 30 D Eudragit RS 30 D
1999	Eudragit E PO Eudragit FS 30 D

Table 1. Year of Introduction Eudragit Grade

PHARMACEUTICAL PROPERTIES OF EUDRAGIT[9]

Poly (meth) acrylates are known worldwide in the industry under the trade name EUDRAGIT®. These polymers allow the active in your solid dosage form to perform during the passage of the human body. The flexibility to combine the different polymers enables you to achieve the desired drug release profile by releasing the drug at the right place and at the right time and, if necessary, over a desired period of time.

Other important functions are protection from external influences (moisture) or taste/odor masking to increase patient compliance. The range of our product portfolio provides full flexibility for your targeted drug release profiles by offering best performance for enteric, protective or sustained-release properties. EUDRAGIT® polymers are copolymers derived from esters of acrylic and methacrylic acid, whose physicochemical properties are determined by functional groups (R). EUDRAGIT® polymers are available in a wide range of different physical forms (aqueous dispersion, organic solution granules and powders). A distinction is made between 1. Poly(meth)acrylates; soluble in digestive fluids by salt formation EUDRAGIT® L, S, FS and E polymers with acidic or alkaline groups enable pH-dependent release of the active ingredient.

EUDRAGIT® Polymer	**Availability**	**Dissolution Properties**
L 30 D-55	30 % Aqueous Dispersion	Dissolution above pH 5.5
L 100-55	Powder	Dissolution above pH 5.5
L 100	Powder	Dissolution above pH 6.0
L 12,5	12.5 % Organic Solution	Dissolution above pH 6.0
S 100	Powder	
S 12,5	12.5 % Organic Solution	Dissolution above pH 7.0
FS 30 D	30 % Aqueous Dispersion	Dissolution above pH 7.0

Table 2: Properties of Eudragit Polymer

Specifications and test methods of Eudragit RS100 and RL100[12]

a) Commercial form

Present in Solid substances

b) Chemical structure

EUDRAGIT® RL 100 and EUDRAGIT® RS 100 are copolymers of ethyl acrylate, methyl methacrylate and a low content of a methacrylic acid ester with quaternary ammonium groups (trimethylammonioethyl methacrylate chloride). The ammonium groups are present as salts and make the polymers permeable.

c) Characters Description

EUDRAGIT® RL 100 and EUDRAGIT ® RS 100: colourless, clear to cloudy granules with a faint amine-like odour.

EUDRAGIT® RL PO and EUDRAGIT® RS PO: white powders with a faint amine-like odour.

d) Solubility

1 g of the substances dissolves in 7 g aqueous methanol, ethanol and isopropyl alcohol (containing approx. 3 % water), as well as in acetone, ethyl acetate and methylene chloride to give clear to cloudy solutions. The substances are practically insoluble in petroleum ether, 1 N sodium hydroxide and water.

e) Tests

Test solution: A 12.5 % solution of the dry substance is used for the test solution: a quantity of the substance of corresponding to 12.5 g dry substance is dissolved in a mixture of 60 % (w/w) isopropyl alcohol and 40 % (w/w) acetone.

Particle size : EUDRAGIT® RL PO / RS PO: at least 90 % < 0.315 mm

Film formation: When the Test solution is poured onto a glass plate a clear film forms upon evaporation of the solvents.

Dry substance / Residue on evaporation: Not less than 97.0 %

1 g of the substances is dried in an oven for 5 hrs in vacuo at 80 °C.

Loss on drying: Max. 3.0 % according to "Dry substance / Residue on evaporation."

Assay:

EUDRAGIT® RL 100 / RL PO: 8.85 - 11.96 % ammonio methacrylate units on dry substance (DS). Alkali value: 23.9 - 32.3 mg KOH per g DS

EUDRAGIT® RS 100 / EUDRAGIT® RS PO: 4.48 - 6.77 % ammonio methacrylate units on DS. Alkali value: 12.1 - 18.3 mg KOH per g DS

The alkali value (AV) is defined similarly to the acid value. It states how many mg KOH are Equivalent to the basic groups contained in 1 g dry substance (DS). The assay is performed according to Ph. Eur. 2.2.20 "Potentiometric titration" or USP <541>. 1 g EUDRAGIT® RL 100 / RL PO or 2 g EUDRAGIT® RS 100 / RS PO are dissolved in 96 ml glacial acetic acid and 4 ml water. 0.1 N perchloric acid is used as the titrant after adding 5 ml mercury (II) acetate solution (5 % solution in glacial acetic acid). 1 ml 0.1 N perchloric acid corresponds to 20.772 mg ammonio methacrylate units.

$$\text{Ammonio methacrylate units (\%) on DS} = \frac{\text{ml 0.1 N HClO4. 207.72}}{\text{Sample weight (g). DS (\%)}}$$

AV (mg KOH / g DS) = ammonio methacrylate units (%). 2.701

Viscosity / Apparent viscosity: Max. 15 mPa. s

The viscosity of the Test solution is determined by means of a Brookfield viscometer (UL adapter / 30 rpm / 20 °C).

1.0 - 4.0 mm2 / s the test is performed according to the JPE monograph.

Refractive index: N_d^{20} : 1.380 - 1.385

The refractive index of the Test solution is determined according to Ph. Eur. 2.2.6.

Relative density: D_{20}^{20} : 0.816 - 0.836

The relative density of the Test solution is determined according to Ph. Eur. 2.2.5.

f) Purity

Sulphated ash / Residue on ignition**.** Max. 0.1 %. The test is performed according to Ph. Eur. 2.4.14 or USP <281>.1 g of the substances is used for the test.

g) Identity testing

First identification:

The material must comply with the tests for "Assay" and "Viscosity / Apparent viscosity."

Second identification:

IR spectroscopy on a dry film approx. 15 µm thick. To obtain the film, a few drops of the Test solution are placed on a crystal disc (KBr, NaCl) and dried in vacuo for about 2 hours at 70 °C.

The figures on page 4 show the characteristic bands of the ester groups at 1,150 - 1,190 and 1,240 - 1,270 cm-1, as well as the C = O ester vibration at 1,730 cm-1. In addition, CHX vibrations can be discerned at 1,385, 1,450, 1,475 and 2,950 - 3,000 cm-1.

h) Detection in dosage forms

The dosage forms are extracted using the solvents listed under "Solubility," if necessary after Crushing. Insoluble substances are isolated by filtration or centrifugation. The clear filtrate is boiled down and the residue identified by IR spectroscopy.

i) Storage

Store at controlled room temperature (USP, General Notices). Protect against moisture. Any storage between 8°C and 25°C fulfils this requirement. EUDRAGIT® RL 100 and EUDRAGIT® RS 100 tend to form lumps at warm temperatures. This has no influence on the quality. The lumps are easily broken up again.

j) Stability

Minimum stability dates are given on the product labels and batch-related Certificates of Analysis. Storage Stability data are available upon request.

How Eudragit works??

If you need to protect your active from the gastric fluid and would like to improve drug effectiveness – EUDRAGIT® L and S polymers are our preferred choice of coating polymers. They enable targeting specific areas of the intestine. Pharma Polymers offers a broad product portfolio of anionic EUDRAGIT® grades which dissolve at rising pH values. In addition, the different grades can be combined with each other, making it possible to adjust the dissolution pH, and thus to achieve the required GI targeting for the drug.

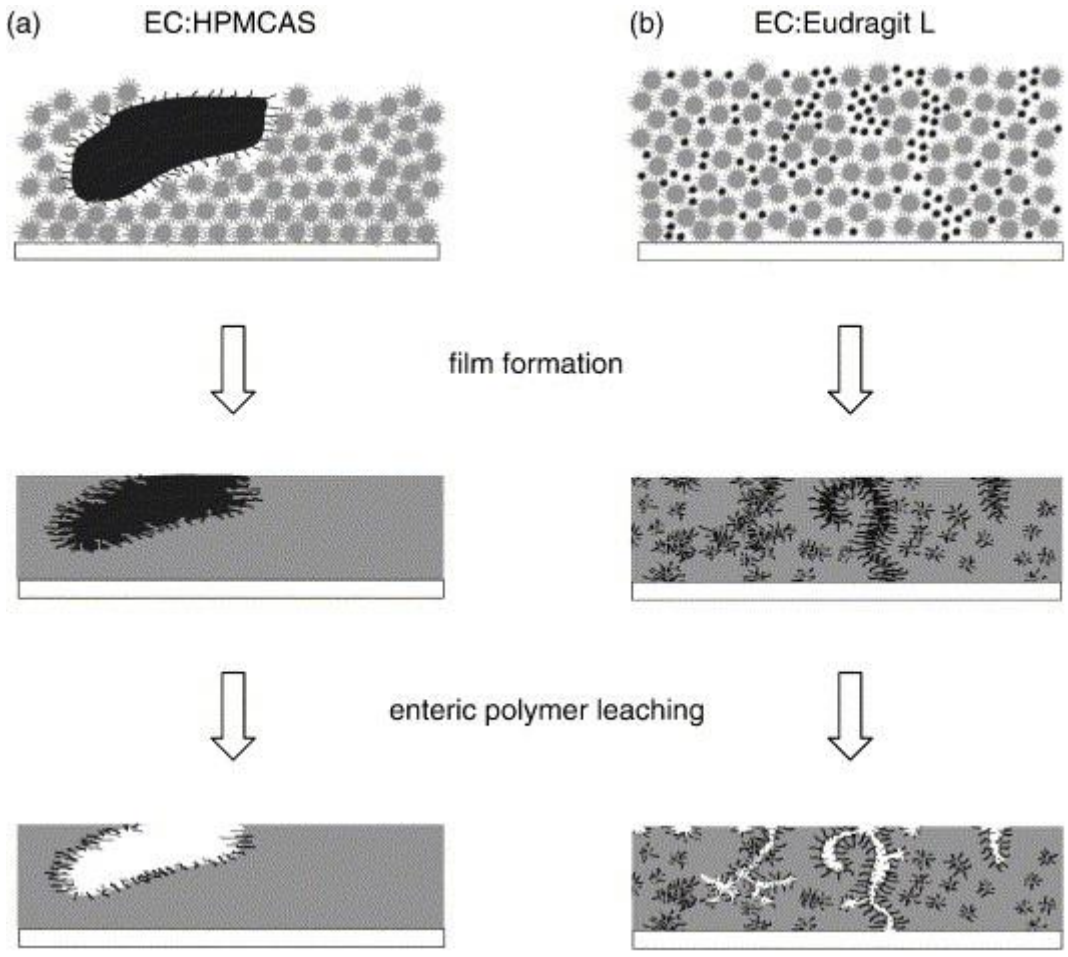

Figure 3. Degradation of Eudragit

Targeted drug release in the colon is required for local treatment of intestinal disorders such as Crohn's disease, ulcerative colitis or intestinal cancer. It is also required for drugs that are poorly soluble in the upper gastrointestinal tract. Moreover, the gastroresistance of the coating ensures that the oral dosage form is patient compliant. The preferred coating is EUDRAGIT® FS 30 D, which combines release in the colon with the following technical advantages:

• Aqueous processing

• Highly flexible coatings

• Suitable for multiparticulate tablet preparation

Table 3. Functional group present in Eudragits and their functions[13]

Functionality	Trade name
Anionic polymer of methacrylic acid and methacrylates with a -COOH group	Eudragit® L 100-55 - powder, spray dried L 30 D-55 which can be reconstituted for targeted delivery in the duodenum Eudragit® L 30 D-55 - aqueous dispersion, pH dependent polymer soluble above pH 5.5 for targeted delivery in the duodenumdelivery in the jejunum Eudragit® S 100 - powder, pH dependent polymer soluble above pH 7.0 for targeted delivery in the ileum. Eudragit® FS 30 D - aqueous dispersion, pH dependent polymer soluble above pH 7.0, requires no plasticizer
Cationic polymer with a dimethylaminoethyl ammonium group	Eudragit E 100 - granules, pH dependent, soluble in gastric fluid up to 5.0, swellable and permeable above pH 5.0. Eudragit® E PO - powder form of E-100

Copolymers of acrylate and methacrylates with quarternary ammonium group.	**Insoluble, High Permeability** Eudragit® RL 30D - aqueous dispersion, pH independent polymer for sustained release formulations Eudragit® RL PO - powder, pH independent polymer for matrix formulations Eudragit® RL 100 - granules, pH independent **Insoluble, Low Permeability** Eudragit® RS 30D - aqueous dispersion, pH independent polymer for sustained release formulations Eudragit® RS PO - powder, pH independent polymer for matrix formulations Eudragit® RS 100 - granules, pH independent
Copolymers of acrylate and methacrylates with quarternary ammonium group in combination with sodium carboxymethylcellulose	Eudragit RD 100 - powder, pH independent for fast disintegrating films

OTHER APPLICATIONS OF EUDRAGIT POLYMERS

• **Ophthalmic Drug Delivery**

A major problem being faced in ocular therapeutics is the attainment of an optimal concentration at the site of action. Poor bioavailability of drugs from ocular dosage forms is mainly due to the tear production, non-productive absorption, transient residence time, and impermeability of corneal epithelium. Eudragit exhibits favorable behavior, such as no toxicity, positive charge and controlled release profile this make them suitable for opthalic application[14-18].

• **Buccal and Sublingual Drug Delivery**

The oral mucosae in general are somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4 -4000 times greater than that of the skin[19, 20]. Major limitation of the buccal route of administration is the lack of dosage form retention at the site of absorption. Consequently, bioadhesive polymers have extensively been employed in buccal drug delivery systems. Polymers which can adhere to either hard or soft tissue have been used for many years in surgery and dentistry. Diverse classes of polymers have been investigated for their potential use as mucoadhesives. These include synthetic polymers such as monomeric a cyanoacrylate, polyacrylic acid[21] and poly methacrylate derivative.Eudragit providing good drug release
barier with good adhesive strength.

• Gastrointestinal Drug Delivery

Gastroretentive dosage forms were designed, in large part, based on the following approaches, Low density form of the dosage form that causes buoyancy in gastric fluid, High density dosage form that is retained in the bottom of the stomach, Bioadhesion to stomach mucosa, Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients, Expansion by swelling or unfolding to a large size which limits emptying of the dosage form through the pyloric sphincter . All these techniques we can achieved with different grades of eudragit[22].

• Intestinal Drug Delivery

Sustained intestine delivery of drugs was developed that could bypass the stomach and release the loaded drug for long periods into the intestine by coating of eudragit polymer. Eudragit L & Eudragit S are two forms of commercially available enteric acrylic resins. Both of them produce films resistant to gastric fluid. Eudragit L & S are soluble in intestinal fluid at pH 6 & 7 respectively. Eudragit L is available as an organic solution (Isopropanol), solid or aqueous dispersion. Eudragit S is available only as an organic solution (Isopropanol) and solid. Sodium para aminosalicylate Pellets were coated with Eudragit L 30 D-55 using fluidized bed processor and evaluated for in vitro dissolution behavior in 0.1 N HCl for two hours and then media was changed to phosphate buffer pH 6.8. A 60% w/w coating level of Eudragit L30 D 55 has produced the most acceptable results against the gastric attack [23.]

• Colon Drug Delivery

Colonic drug delivery is a relatively recent approach for the treatment of diseases like ulcerative colitis, Crohn's disease, and irritable bowel syndrome. PH-sensitive polymers that dissolve, or above pH 7 used for colonic drug delivery [24.] Tegaserod maleate was used as a drug for irritable bowel syndrome, whereas Eudragit L 100 and S100 mixture (1:1, 1:2, and 1:3) were used [25].

• Transdermal Drug Delivery

The mechanical properties of casted Eudragit E-100 films were tested for the combined effect of two cohesion promoters (succinic or citric acid) and triacetin as a plasticizer [26.] The prepared films were elastic, self-adhesive, transparent and pale yellow in colour. Eudragit E100 polymer was found to result in wrinkle-free transparent films with good adhesion to skin. Release kinetics from transdermal therapeutic system was observed due to erosion of hydrophilic Eudragit E100 polymer, and 100% release was observed within 20 minutes.

• Vaginal Drug Delivery

Eudragit RS100 vaginal suppositories containing sildenafil, and other excipients give adequate release [27]. Intravaginal tablet were prepared with 1:1 ratio of lactic acid to Eudragit E-100, tablets disintegrating into a

gelform at physiological range of 3.8-4.4 pH. These gels possess an acid reserve that might be ableto neutralise the excess of alkali present in severe vaginal infections

• Gene Delivery

The course of many hereditary diseases could be reversed by gene delivery. In addition, many acquired diseases such as multigenetic disorders and those diseases caused by viral genes could be treated by genetic therapy[28]

Nanoparticles prepared by blending PLGA with methacrylate copolymer (Eudragit(R) E100) can efficiently and safely deliver plasmid DNA encoding mouse interleukin-10 leading to prevention of autoimmune diabetes[29].New Anionic nanoparticles were prepared by Eudragit L100/55 provide a versatile platform for protein surface adsorption and a promising delivery system particularly when the maintenance of the biologically active conformation is required for vaccine efficacy. Antisense oligodeoxynucleotides were successfully delivered by nanoparticles prepared by Eudragit RL100, RS100.

• Vaccine Delivery

Anionic surfactant-free polymeric core-shell nanospheres and microspheres were prepared by Eudragit L100-55. Vaccines were administered by different routes, including intramuscular, subcutaneous or intranasal and the results were compared to immunization with Tat alone or with Tat delivered with the alum adjuvant. The data demonstrate that the nano and microspheres/Tat formulations are safe and induce robust and long-lasting cellular and humoral responses in mice after systemic and/or mucosal immunization45. Weight ratio of Noveon and Eudragit S-100 had a significant effect on adhesion time of bilayer films.

CHITOSAN

One of the most famous polysaccharide is chitosan, which has universal using. Chitosan is a natural, cationic aminopolysaccharide (pKa 6.5) copolymer of glucosamine and N-acetylglucosamine obtained by the alkaline, partial deacetylation of chitin. It is the second most abundant natural polysaccharide and originates from **shells of crustaceans**. Chitosan is a biodegradable, biocompatible, positively charged nontoxic mucoadhesive biopolymer. Since chitosan contains primary amino groups in the main backbone that make the surfaces positively charged in biological fluids, biodegradable nano/microparticles can be readily prepared by treating chitosan with a variety of biocompatible polyanionic substances such as sulfate, citrate, and tripolyphosphate[30]. It is linear polysaccharide composed of randomly distributed β-(1-4)-linked Dglucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). It has a number of commercial and possible biomedical use Chitosan is a natural polymer obtained by deacetylation of chitin. It is a biologically safe, non-toxic, biocompatible, and biodegradable polysaccharide. Chitosan (poly [-(1,4)-2-

amino-2-deoxy-D-glucopiranose]) is obtained by the alkaline deacetylation of chitin. Chitin is the second most abundant polysaccharides in nature after cellulose. Chitosan is a high molecular weight cationic polysaccharide derived from naturally occurring chitin in crab excipient in oral drug formulation to improve the dissolution of poorly soluble drugs or for the sustained release of drugs by a process of slow erosion from a hydrated compressed matrix . This biopolymer is considered to be non-toxic, with an oral LD50 in mice of >16 g/kg. It was reported that this compound is completely degraded by microflora, which are richly distributed in the colon.

Chitosan Sources and Chemical Structure[31]

Chitin is found in the exoskeleton of some anthropods, insects, and some fungi.Commercial sources of chitin are the shell wastes of crab, shrimp, lobster, etc. Chitosan is usually prepared by the deacetylation of chitin. The conditions used for deacetylation will determine the average molecular weight (Mw) and degree of deacetylation (DD). The structure of chitosan is very similar to that of cellulose [made up of b (1-4)-linked D-glucose units], in which there are hydroxyl groups at C-2 positions of glucose rings. Chitosan is a linear copolymer polysaccharide
consisting of b (1-4)-linked 2-amino-2-deoxy-D-glucose (D-glucosamine) and 2-acetamido-2-deoxy-D-glucose (N-acetyl-D-glucosamine) units .

Figure 4. Different sources of chitosan

The properties, biodegradability, and biological role of chitosan is frequently dependent on the relative proportions of N-acetyl-D-glucosamine and D-glucosamine residues. The term chitosan is used to describe a series of polymers of different Mw and DD, defined in terms of the percentage of primary amino groups in the polymer backbone. The DD of typical commercial chitosan isusually between 70 and 95%, and the Mw between 10 and 1,000 kDa.

Chemical Methodology for the Preparation of Chitosan

Preparation of chitosan involves four steps: deproteinization, demineralization, decoloration, and deacetylation. Deproteinization is carried out by alkaline treatment using 3–5% NaOH (w/v) aqueous solution at room temperature overnight. Other inorganic constituents remaining are removed by treatment with 3–5% aqueous HCl (w/v) solution at room temperature for 5 h. The product is again reacted with 40–45% NaOH solution at 120_C for 4–5 h. This treatment gives the crude sample of chitosan. The crude sample is purified by precipitating the chitosan. from its aqueous acetic acid solution to NaOH and washing with distilled water until neutralized[32].

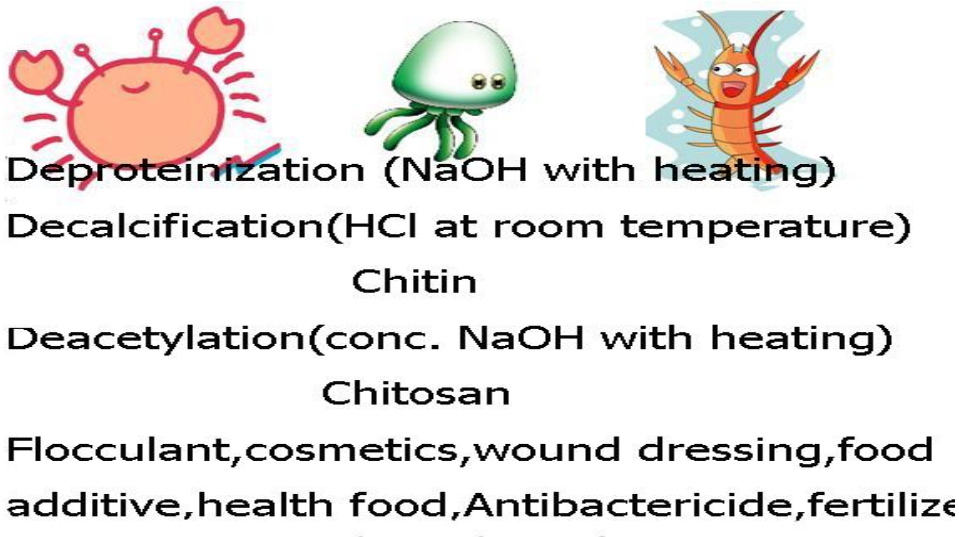

Figure 5. Various ways to get chitosan

Physicochemical and Biological Properties of Chitosan

- Chitosan is a **semicrystalline** polymer that exhibits polymorphism.
- Chitosan belongs to a series of polymers with different DD and Mw which are the two important physicochemical properties of chitosan[33]. DD is defined as of the **percentage of primary amino groups in the polymer backbone**. The DD and Mw of chitosan can be altered by changing the reaction conditions during the manufacture of chitosan from chitin *(typical commercial chitosan has a DD of 66–95%).*
- Chitosan appears as colorless, odorless flakes.
- It is readily soluble in aqueous **acidic** solution. The solubilization occurs through protonation of amino groups on the C-2 position of D-glucosamine residues, whereby polysaccharide is converted into polycation in acidic media. Chitosan has a low solubility at physiological pH of 7.4 as it is a weak base (pKa 6.2–7). Adjusting solution pH to approximately 7.5 induces flocculation due to deprotonation and insolubility of the polymer[34].
- Higher Mw chitosan of approximately 1,400 kDa demonstrates a stronger level of mucoadhesion than low Mw chitosan of 500–800 kDa, because the former has a higher level of viscosity. The viscosity of chitosan solution increases with an increase in chitosan concentration and DD but with a decrease in solution temperature and pH.
- It is known to possess a **good complexing capacity**. Chitosan can also complex with an oppositely charged polymer such as poly (acrylic acid), sodium salt of poly(acrylic acid), carboxymethyl cellulose, xanthan, carrageenan, alginate, pectin etc.

Limitations:

- Chitosan suffers from low solubility at a physiological pH of 7.4, limiting its use as absorption enhancer in, for example, nasal or peroral delivery systems[35].
- Another limitation of chitosan for the preparation of sustained release systems arises from its rapidly adsorbing water and higher swelling degree in aqueous environments, leading to fast drug release . In order to overcome these problems, a numberof chemically modified chitosan derivatives have been synthesized[36].

Modification of Chitosan

Most chemical modifications of chitosan are performed at the free amino groups of the glucosamine units. There are also reports on modifications of chitosan hydroxyl group[37]. Modification does not change the fundamental skeleton of chitosan but brings new or improved properties for, e.g., mucoadhesion and

permeation enhancement. The advantage of chitosan over other polysaccharides is that its chemical structure allows specific modifications without too many difficulties at C-2 position. Specific groups can be introduced to design polymers for selected applications. The main reaction easily performed involving the C-2 position is the quaternization of the amino group or a reaction in which an aldehydic function reacts with –NH2 by reductive amination[38]. This latter reaction can be performed in aqueous solution under very mild conditions to obtain randomly distributed substituents in a controlled amount along the chitosan chain.

a) Covalent Modifications

Covalent modification of chitosan includes thiolation and hydrophobic modifications like acylation and quaternization.

b) Polyelectrolyte Complexes

Polyelectrolyte complex formation occurs when two oppositely charged polymers (polycations and polyanions) in solution phase separate to form a dense polymer phase, known as the coacervate, and a supernatant, which typically has very low concentrations of polymer.

Applications in Drug Delivery

Chitosan is widely used for **dental, buccal, gastrointestinal, colon-specific**, and **gene delivery** applications due to its favorable biological properties. It is used in the form of tablets, gels etc.

Colon-Specific Drug Delivery

Due to its high solubility in gastric fluids, chitosan is widely used for colon-specific drug delivery. Similarly to other polysaccharides, it shows degradation in the colon. Although chitosan can be insoluble in acidic fluids through chemical crosslinking of the microsphere with aldehydes, it is not effective in preventing the release of the encapsulated drugs. To overcome this problem, microencapsulated chitosan microspheres coated with enteric coating materials were developed[39]. The potential of this microsphere was evaluated using sodium diclofenac, an anti-inflammatory drug. Sodium diclofenac was entrapped into the chitosan cores by the spray drying method, after which the chitosan cores were microencapsulated into Eudragit L-100 and Eudragit S-100 using an oil-in-oil solvent evaporation method. The in vitro release studies revealed that no sodium diclofenac was released at gastric pH; however, when the microspheres reached the colonic environment, a continuous release was observed for a variable time (8–12 h). Eudragit S-100-coated chitosan beads developed by Jain et al. exhibited pH-sensitive properties and specific biodegradability for colon-targeted delivery of satranidazole. Eudragit S-100 coating

on the chitosan beads prevented premature drug release in simulated upper gastrointestinal conditions and most of the loaded drugs was released in the colon, an environment rich in bacterial enzymes that degrade

the chitosan[40]. Chourasia et al. prepared a similar multiparticulate system, by coating crosslinked chitosan microspheres with Eudragit L-100 and S-100 as pH-sensitive polymers, for targeted delivery of the broad-spectrum antibacterial agent metronidazole [41]. The results showed a pH-dependent release of the drug that was attributable to the presence of Eudragit coating. Moreover, the release of drug was found to be higher in the presence of rat caecal contents, indicating the susceptibility of the chitosan matrix to colonic enzymes. Similar nanoparticular systems for colon-specific delivery of metronidazole were reported by Elzatahry and Eldin [42]. For the treatment of 2,4,6-trinitrobenzene sulfonic acid sodium salt (TNBS)-induced colitis in rats, 5-aminosaliycylic acid (5-ASA) was orally administered using chitosan capsules or a carboxymethyl cellulose (CMC) suspension. Better therapeutic effects were obtained with chitosan capsules than with the CMC suspension. The release of 5-ASA from the chitosan capsule was markedly increased in the presence of rat cecal contents [43]. Degradation of chitosan–tripolyphosphate hydrogel beads in the presence of rat cecal and colonic enzymes indicated the potential of this microparticulate system for colon targeting. The ability of rat cecal and colonic enzymes to degrade chitosan hydrogel beads was independent of pretreatment conditions[44]. Chitosan salts mixed with anti-inflammatory drugs, such as sodium diclofenac, were evaluated for their in vitro release behavior. Chitosan salts, such as glutamic and aspartic salts, provided good controlled release of sodium diclofenac. Slower drug release was obtained with physical mixtures compared to the pure drug both in acidic and alkaline pHs. Interaction with b-glucosidase at pH 7.0 enhanced the release rate[45].

Conclusion

With the advances in polymer synthesis chemistry and technology, more defined, controlled, and biocompatible polymers are becoming available, and such polymers will contribute to new generations of biomimetic nanostructures and vehicles for carrying diagnostic and imaging agents, therapeutic drugs, prognostic reagents, and multiagents in the future. Thus, controlling polymer architecture will be one of the most crucial technologies for future drug delivery. The

new polymers and nanocarriers definitely require extensive consideration of toxicological and immunological issues, which are often ignored during the research phase.

a) Thus Chitosan was used in oral drug formulations to provide sustained release of drugs. Accordingly, chitosan could be promising for colonspecific drug delivery. Number of approaches have been employed in designing chitosan based colonic delivery system such as the use of chitosan capsule. The main drawback of chitosan in per- oral delivery is its acid solubility. The use of enteric coating was commonly used to overcome this problem. A semi synthetic polymer was prepared by reacting

chitosan with phthalic and succinic anhydride to produce chitosan esters which have been successfully a potential matrices for colon drug delivery.

b) Coating for controlled release needs special types of polymer that have selective solubility in the GIT. One of the commonly used polymers is **Eudragit®,** which is registered trademark of Rohm Pharmaceuticals, Darmstadt,Germany. In 1953, the first drug came onto the market in a Eudragit coating. By that, a new chapter in pharmaceutical history has begun.

REFERENCE

1. Sintze M.B., Bernatchez S. F., Tabatabay C. and Gurny R, Eur. J. Pharm. Biopharm, 1996, 42: 358–374.
2. Nagai, T., Machida, Y., Pharm. Int. 1985, 6:196-200.
3. Bodde, H.E., De Vries, M.E., and Junginger, H.E., J. Control. Rel, 1990, 13:225-231.
4. Le Bourlais C. A., Treupel-Acar L., Rhodes C.T., Sado P. T., Leverge R., Drug Dev. Ind. Pharm, 1995, 21: 19– 59.
5. Sarasija S, Hota A. Colon-specific drug delivery systems, Indian journal of pharmaceutical sciences, 62(1), 2000, 1-8.
6. Colonic Delivery Formulations, Recent Patents on Drug Delivery and Formulation, 1(1),2007, 55.
7. Bajpai S K, Bajpai M, Dengree R. Chemically treated gelatin capsules for colontargeted drug delivery: a novel approach, J.Appl. Polym.Sci., 2003, 89, 2277–2282.
8. Colonic Delivery Formulations, Recent Patents on Drug Delivery and Formulation, 1(1), 2007, 55.
9. Nikam V .K , Kotade K, Gaware V, Dolas R,Dhamak K, Somwanshi S, Khadse A, Kashid V . EUDRAGIT A VERSATILE POLYMER : A REVIEW Pharmacologyonline 1: 152-164 (2011) Newsletter.
10. Ray C. Rowe., Paul J. Sheskey., Paul J. Weller., Hand Book of Pharmaceutical excipients, 3rd ed., American Pharmaceutical Association Washington DC, USA & Pharmaceutical press, London U.K.
11. http://www.scribd.com/doc/5682786/Kollicoat-MAE-grades.
12. EVONIK Röhm GmbH Pharma Polymers Kirschenallee INFO 7.9/E 2007-11.
13. Eudragit technical bulletin, Rohm America, Pformulate 08/03/2002.

14. Duarte A.R ., Roy C., Vega-Gonzalez A, Duarte C.M., Subra-Paternault P., Int J Pharm. 2007, 332:132-9.

15. Pignatello R , Bucolo C, Puglisi G., J Pharm Sci. 2002, 91: 2636-41

16. Khopade AJ , Jain NK., Pharmazie. 1995, 50: 812-4.

17. Bucolo C., Maltese A., Maugeri F., Busa B., Puglisi G., Pignatello R., J. Pharm. Pharmacol., 2004, 56: 841-846.

18. Galey, W.R., Lonsdale, H.K., Nacht S., J. Invest. Dermat. 1976, 67: 713-717.

19. Harris D., Robinson J.R., J. Pharm. Sci., 1992, 81:1-10

20. Gandhi, R.E. and Robinson, J.R.., Ind. J. Pharm. Sci., 1988, 50:145-152.

21. Kohda Y, Kobayashi H, Baba Y, et al., Int J. Pharm.1983,15:147-155.

22. Md A Rahman, J Ali., Ind. J. Pharm. Sci., 2008; 70: 477-481.

23. Jain SK, Chourasia MK, Dengre R.,Ind. J. Pharm. Sci. 2005; 67:43-50.

24. D Nagasamy Venkatesh, Ajay Kumar Reddy, MK Samanta, B Suresh., Asian J. Pharm., 2009; 3: 50-53.

25. . Degim IT , Tugcu-Demiroz F, Tamer-Ilbasmis S, Acarturk F., Drug Deliv. 2008 4:259-65.

26. Dnyanesh Tipre, Dr. Pradeep Vavia., Drug del. Tech. 2002, 2:44.

27. RC. Mulligan, Science.1993; 260:926-932.

28. Basarkar A, Singh J., Pharm Res. 2009 ; 26(1):72-81. Epub 2008 Sep 9.

29. Voltan R , Castaldello A, Brocca-Cofano E, Altavilla G, Caputo A, Laus M, Sparnacci K, Ensoli B, Spaccasassi S, Ballestri M, Tondelli L., Pharm Res. 2007 ;24: 10:1870-82.

30. Wang WX , Chen HL, Liang WQ., Yao Xue Xue Bao. 2003 ;38:4:298-301.

31. Rinaudo M (2006) Prog Polym Sci 31:603.

32. Felt O, Buri P, Gurny R (1998) Drug Dev Ind Pharm 24:979

33. Jayakumar R, Deepthy M, Manzoor K, Nair SV, Tamura H (2010) Carbohydr Polym 82:227

34. Jayakumar R, Nair SV, Tamura H (2009) Asian Chitin J 5:1

35. Bhattarai N, Gunn JJ, Zhang M (2010) Adv Drug Deliv Rev 62:83

36. Park JH, Saravanakumar G, Kim K, Kwon IC (2010) Adv Drug Deliv Rev 62:28

37. Esmaeili F, Heuking S, Junginger HE, Borchard GJ (2010) Drug Deliv Sci Technol 20:53

38. Aranaz I, Harris R, Heras A (2010) Curr Org Chem 14:308

39. Thakral NK, Ray AR, Majumdar DK (2010) J Mater Sci Mater Med 21:2691

40. Tozaki H, Komoike J, Tada C, Maruyama T, Terabe A, Suzuki T, Yamamoto A, Muranishi S (1997) J Pharm Sci 86:1016

41. Tozaki H, Fujita T, Odoriba T, Terabe A, Suzuki T, Tanaka C, Okabe S, Shoo Muranishi S.Yamamoto A (1999) Life Sci 64:1155

42. Tozaki H, Odoriba T, Okada N, Fujita T, Terabe A, Suzuki T, Okabe S, Muranishi S, Yamamoto A (2002) J Control Release 82:51 .

43. Chourasia MK, Jain SK (2004) Drug Deliv 11:12

44. Jain SK, Jain A (2008) Expert Opin Drug Deliv 5:483

45. Hejazi R, Amiji M (2003) J Control Release 89:151