



International Journal of Chemistry and Pharmaceutical Sciences

IJCPS, 2013: Vol.1(4): 305-311

(Online at www.pharmaresearchlibrary.com/ijcps)

Eudragit a versatile Polymer: a Review

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Abstract

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 polymer in different drug delivery systems with special attention to used in its fabrication along with

Key words: Eudragit, Gastro resistance, Glass transition, Polymer, Sustained release.

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 manner¹. The development of NDDS has been made possible by the various compatible polymers to modify the release pattern of drug². 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 compliance⁴.

History

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, weiterstadt and worms sites⁵. Eudragit is trademark of rohm gmbh & co. Kg. Darmstadt in germany, first marketed in 1950s. Eudragit prepared by the polymerization of acrylic and methacrylic acids or their esters, e.g., butyl ester or dimethyl aminoethyl ester. Eudragit introduced in uspnf, bp, pheur, hand book of pharmaceutical excipients⁶. The eudragit acrylic polymers have a long history of use, the individual types and grades being introduced in the following chronological order.

Eudragit Polymers – Pharmaceutical Properties

The basis of our offerings is our poly (meth)acrylates for pharmaceutical applications, which are known worldwide in the industry under the trade name eudragi. 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. Eudragit polymers are available in a wide range of different physical forms. 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.

Table 1: Properties of Eudragit Polymer

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

Gastroresistance and GI Targeting

If you need to protect your active from the gastric fluid and would like to improve drug effectiveness—eudragit L and polymers are your 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. 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

Glass transition temperature (T_g)

The glass transition temperature is an important factor for describing the physical properties of polymers. On a macroscopic level it describes the solidification of an anisotropic polymer melt. The glass transition temperature has far-reaching consequences, e.g. For film formation, melt processing and storage of finished pharmaceutical dosage forms. Plasticizers, solvents or residual solvents (including water) that act as plasticizers usually cause a reduction in glass transition temperature, which is specifically exploited in application formulations. Most common plasticizer for eudragit polymers is triethyl citrate (TEC).

Table: 4 Physical and Chemical Properties

Trade Name ⁵	Solubility ⁵	Description	Applications ⁵
Eudragit E 100	Soluble in gastric fluid- to pH 5	Cationic, Yellow in Colour ⁶	Film coating
Eudragit E 12.5	Soluble in gastric fluid- to pH 5	Cationic, Yellow in Colour ⁶	Film coating

Eudragit NE 30 D	Swellable, permeable	Cationic, Yellow in Colour ⁶	Sustained release
Eudragit L 100	Soluble in intestinal- fluid from pH 6	Anionic, white freeflowing Powders ⁶	Enteric coatings
Eudragit L 12.5	Soluble in intestinal- fluid from pH 6	Anionic, white freeflowing Powders ⁶	Enteric coatings
Eudragit L 12.5 P	Soluble in intestinal- fluid from pH 6	Anionic, white freeflowing Powders ⁶	Enteric coatings
Eudragit L 30 D-55	Soluble in intestinal- fluid from pH 5.5	Anionic, white Free flowing Powders ⁶	Enteric coatings
Eudragit L 100-55	Soluble in intestinal- fluid from pH 5.5	Anionic, white Free flowing Powders ⁶	Enteric coating
Eastacryl 30D	Soluble in intestinal- fluid from pH 5.5	-	Enteric coatings
Kollicoat MAE 30 D	Soluble in intestinal- fluid from pH 5.5	Anionic, Milky White, Low Viscosity ⁷	Enteric coatings
Kollicoat MAE 30 DP	Soluble in intestinal- fluid from pH 5.5	-	Enteric coatings
Eudragit S 100	Soluble in intestinal-fluid from pH 7	Anionic, white freeflowing Powders ⁶	Enteric coatings
Eudragit S 12.5	Soluble in intestinal-fluid from pH 7	Anionic, white freeflowing Powders ⁶	Enteric coatings

Eudragit RL 100	High permeability	Cationic, nonbiodegradable ⁸	Sustained release
Eudragit RL PO	High permeability	Cationic, nonbiodegradable ⁸	Sustained release
Eudragit RL 30 D	High permeability	Cationic, nonbiodegradable ⁸	Sustained release
Eudragit RL 12.5	High permeability	Cationic, nonbiodegradable ⁸	Sustained release
Eudragit RS 100	Low permeability	Cationic, nonbiodegradable ⁸	Sustained release
Eudragit RS PO	Low permeability	Cationic, nonbiodegradable ⁸	Sustained release
Eudragit RS 30 D	Low permeability	Cationic, nonbiodegradable ⁸	Sustained release
Eudragit RS 12.5	Low permeability	Cationic, nonbiodegradable ⁸	Sustained release

Drug Release Mechanism

Oral preparation for controlled release can be sub divided in systems where drug release from the dosage form is governed by the following principles:

- ™ Dissolution
- ™ Diffusion
- ™ Osmotic Pressure
- ™ Ion-Exchange
- ™ Other Principle

Dissolution

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Dissolution is considered one of the most

important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability, and in some cases, replacing clinical studies to determine bioequivalence. Dissolution behaviour of drugs has a significant effect on their pharmacological activity. In fact, a direct relationship between in vitro dissolution rate of many drugs and their bioavailability has been demonstrated and is generally referred to as in vitro-in vivo correlation, IVIVC

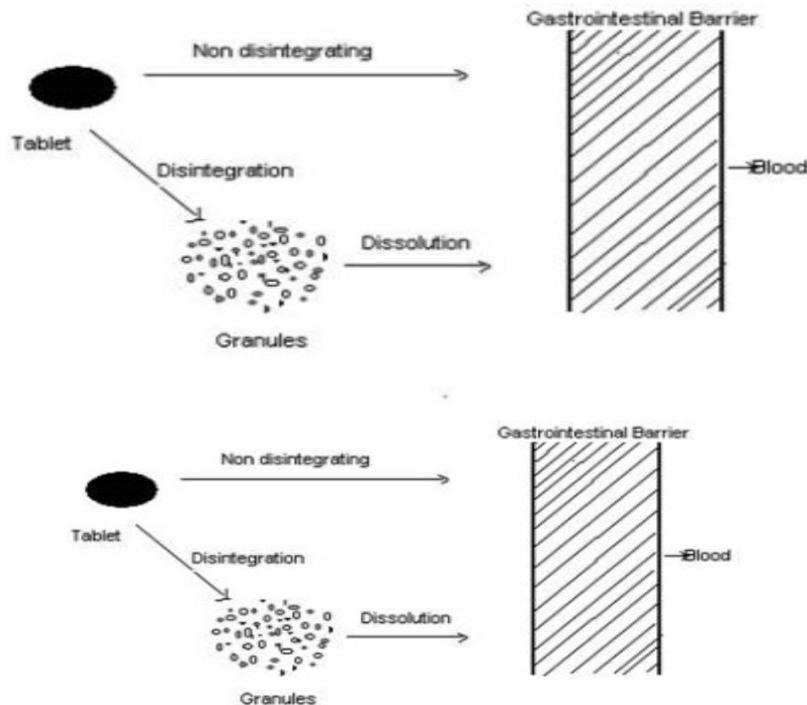


Fig 1: Dissolution

Diffusion

Diffusion is driving force where the movement of drug molecules occurs from high concentration in the tablet to lower concentration in gastro intestinal fluids. This movement depends on surface area exposed to gastric fluid, diffusion pathway, drug concentration gradient and diffusion coefficient of the system.

Osmosis

Osmosis is a phenomenon in which the flow of liquid occurs from lower concentration to higher concentration through a semi permeable membrane which allows transfer of liquid only. The whole drug is coated with a semi permeable membrane with a hole on one end of tablet made by a laser beam. The gastric fluid penetrates through the membrane, solubilizes the drug and increases the internal pressure which pumps the drug solution out of the aperture and releases the drug in gastric environment. The delivery rate is constant provided that the excess of drug present inside the tablet. But, it declines to zero once the concentration drops below saturation⁹.

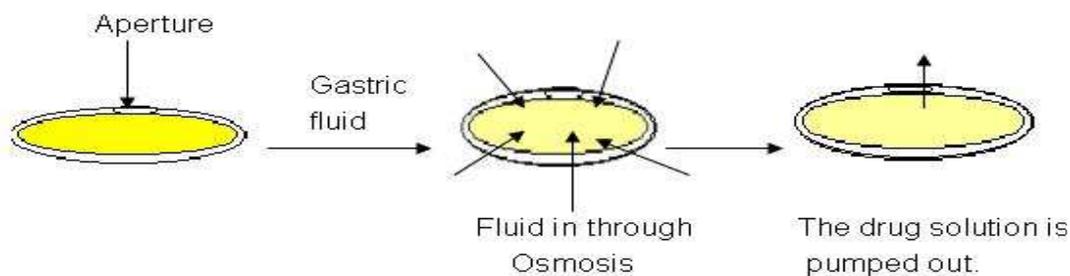


Fig. 2: Osmotic release pattern

In practice, we can follow either of the two methods, first the drug is formulated in an insoluble matrix; the gastric fluid penetrates the dosage form and dissolves the medicament and release the drug through diffusion and second the drug particles are coated with polymer of defined thickness so as the portion of drug slowly diffuse through the polymer to maintain constant drug level in blood.

Ion-Exchange

Ion exchangers are water insoluble resinous materials containing salt forming anionic or cationic groups. While manufacturing, the drug solution is mixed with resin and dried to form beads which are tableted. The drug release depends upon high concentration of charged ions in gastro intestinal tract where, the drug molecules are exchanged and diffused out of the resin into the surrounding fluid.

This mechanism relies upon the ionic environment of resin and not pH or enzyme on absorption site. Dissolution controlled dosage forms can be divided into reservoir and matrix system. Reservoir principle is given by a controlled release formulation comprising 400mg 5-ASA within an acrylic resin coat, eudragit S. Mechanism of drug release from pellets coated with polymer eudragit E 30 D, was governed by diffusion through water-filled pores in the film coat. The release of propranolol HCL from a monolithic matrix (Eudragit NE 30 D) by a combination of diffusion through the polymer and pores or channels¹². A desirable release profile of diphenhydramine was achieved by incorporating Eudragit L in a carnauba wax matrix. The drug release from these polymer-wax matrices is described by a combination diffusion/erosion mechanism¹³. Eudragit RS PO release the carbamazepine drug by complex mixture of diffusion and erosion mechanism¹⁴. Eudragit RS 30 D-coated theophylline beads proved ion exchange to be the responsible mechanism of controlling polymer permeability as a function of anionic species and concentration¹⁶

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 ophthalmic application¹⁵

Buccal and Sublingual Drug Delivery

The oral mucosae in general are some what 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 skin²⁰. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal. At physiological pH the mucus network carries a negative charge (due to the sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer. 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, and poly methacrylate derivatives. An ideal buccal film should be flexible, elastic, and soft yet strong enough to withstand breakage due to stress from activities in the mouth. Moreover, it must also possess good mucoadhesive strength so that it is retained in the mouth for the desired duration. To prevent discomfort, swelling of the film should not be too extensive. The mechanical, bioadhesive, and swelling properties of buccal films are critical and must be evaluated. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments, and gels, have recently been developed. Eudragit providing good drug release barrier with good adhesive strength.

Gastrointestinal Drug Delivery

The need for gastroretentive dosage forms has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in gastroretentive dosage forms that 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.

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 attack³⁶

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. 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

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. The prepared films were elastic, self-adhesive, transparent and pale yellow in colour. Eudragit E100 polymer was found to result in with 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. 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 able to 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. Nanoparticles prepared by blending PLGA with methacrylate copolymer (Eudragit E100) can efficiently and safely deliver plasmid DNA encoding mouse interleukin-10 leading to prevention of autoimmune diabetes. 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 immunization. Weight ratio of Noveon and Eudragit S-100 had a significant effect on adhesion time of bilayer films. Postloaded plasmid DNA and beta-gal remained stable after being released from bilayer films (release of -60-80% in 2 h for both). Buccal immunization using novel bilayer films (109 +/-6-microm thickness) containing plasmid DNA led to comparable antigen-specific IgG titer to that of subcutaneous protein injection. All rabbits immunized with plasmid DNA via the buccal route but none by the subcutaneous route with protein antigen demonstrated splenocyte proliferative immune responses.

Conclusion

The large variety of applications as well as the steadily increasing number of research workers engaged in studies of Eudragit polymers due to their unique properties, have made significant contributions to many types of formulations and suggest that the potential of Eudragit as novel and versatile polymer will be even more significant in future.

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