Eudragit and its Pharmaceutical Significance

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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 their physiochemical properties.

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].

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 dimethylaminoethyl ester. Eudragit introduced in

USPNF, BP, PhEur, Hand book of pharmaceutical excipients[5]. The eudragit acrylic polymers have a long history of use, the individual types and grades being introduced in the following chronological order:

Table:1

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:2 Countries with regular imports of Eudragit

Western Europe	Eastern Europe	Near East	America	Africa	Asia/Pacific
Austria	Bulgaria	Cyprus	Argentina	Egypt	Australia
Belgium	Croatia	Iran	Bolivia	Kenya	Bangladesh
Denmark	Czech Republic	Israel	Brazil	Morocco	China, P.R.
Finland	Estonia	Jordan	Canada	Nigeria	China, Hong
France	Hungary	Kuwait	Chile	South Africa	Kong
Germany	Latvia	Lebanon	Colombia	Tunisia	India
Great Britain	Lithuania	Saudi Arabia	Costa-Rica		Indonesia
Greece	Mazedonia	Syria	Dominican		Japan
Ireland (Eire)	Poland	U.A.E.	Republic		Malaysia
Iceland	Romania		Ecuador		Nepal
Italy	Russia		Guatemala		New Zealand
Liechtenstein	Slovakia		Honduras		Pakistan
Luxembourg	Slovenia		Mexico		Philippines
Malta	Ukraine		Panama		Singapore
Netherlands			Paraguay		South Korea
Norway			Peru		Sri Lanka
Portugal			Uruguay		Taiwan
Sweden			USA		Thailand
Switzerland			Venezuela		Vietnam
Spain					
Turkey					

Glass transition temperature (Tg):

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: 3 Glass transition intervals of different grades

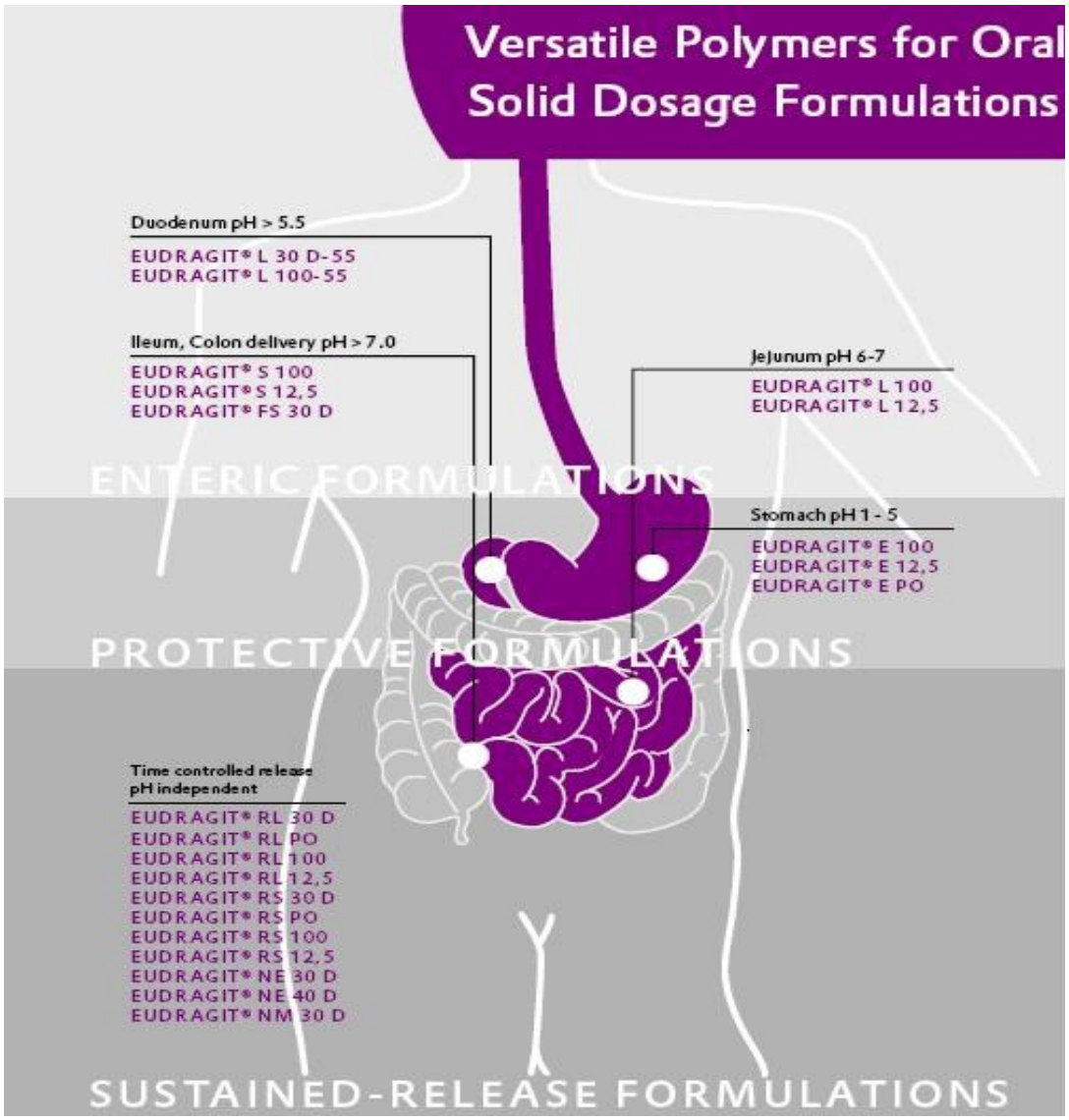
S. No.	Eudragit grade	$T_{g,m}$[iaC]
1.	Eudragit E 100 / E PO	48
2.	Eudragit L 100-55 / L 30 D-55	110
3.	Eudragit FS 30 D	48
4.	Eudragit RL 100 / RL PO	70
5.	Eudragit RS 100 / RS PO	65
6.	Eudragit NE 30 D	9
7.	Eudragit NM 30 D	11

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[5]	Film coating
Eudragit E 12.5	Soluble in gastric fluid- to pH 5	Cationic, Yellow in colour[5]	Film coating
Eudragit NE 30 D	Swellable, permeable	Cationic, Yellow in colour[5]	Sustained release
Eudragit L 100	Soluble in intestinal- fluid from pH 6	Anionic, white free-flowing powders[5]	Enteric coatings
Eudragit L 12.5	Soluble in intestinal- fluid from pH 6	Anionic, white free-flowing powders[5]	Enteric coatings
Eudragit L 12.5 P	Soluble in intestinal- fluid from pH 6	Anionic, white free-flowing powders[5]	Enteric coatings
Eudragit L 30 D-55	Soluble in intestinal- fluid from pH 5.5	Anionic, white free-flowing powders[5]	Enteric coatings

Eudragit L 100-55	Soluble in intestinal- fluid from pH 5.5	Anionic, white free-flowing powders[5]	Enteric coatings
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[6].	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 free-flowing powders[5]	Enteric coatings
Eudragit S 12.5	Soluble in intestinal-fluid from pH 7	Anionic, white free-flowing powders[5]	Enteric coatings
Eudragit S 12.5 P	Soluble in intestinal- fluid from pH 7	Anionic, white free-flowing powders[5]	Enteric coatings
Eudragit RL 100	High permeability	Cationic, non-biodegradable[7]	Sustained release
Eudragit RL PO	High permeability	Cationic, non-biodegradable[7]	Sustained release
Eudragit RL 30 D	High permeability	Cationic, non-biodegradable[7]	Sustained release
Eudragit RL 12.5	High permeability	Cationic, non-biodegradable	Sustained release
Eudragit RS 100	Low permeability	Cationic, non-biodegradable[7]	Sustained release
Eudragit RS PO	Low permeability	Cationic, non-biodegradable[7]	Sustained release
Eudragit RS 30 D	Low permeability	Cationic, non-biodegradable[7]	Sustained release
Eudragit RS 12.5	Low permeability	Cationic, non-biodegradable[7]	Sustained release

Fig: 1 Different grades of Eudragit in oral solid dosage formulation



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[8]

- **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[9].**
- **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[10].**
- **The release of propanolol HCL from a monolithic matrix (Eudragit NE 30 D) by a combination of diffusion through the polymer and pores or chanels[11].**
- 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 mechanism[12].
- Eudragit RS PO release the carbamazepine drug by complex mixture of diffusion and erosion mechanism[13]**.**
- 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 concentration[14].

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[15].

Duarte et. al. used Eudragit RS 100 and RL 100 as a drug carrier. The release behaviour of acetazolamide from the prepared microparticles was studied and most products exhibited a slower release than the single drug[16].

Pignatello et. al. were prepared from inert polymer resins (Eudragit RS100, RS, and RL100, RL). They were Successful to Avoid of any irritant effect on cornea, iris, and conjunctiva up to 24 h after application[17].

Khopade et. al. Eudragit RLPM and RSPM were used as carrier materials. Eudragit RSPM showed comparatively longer release than Eudragit RLPM nanosuspensions, excellent encapsulation efficiency of about 94-98%[18].

Bucolo et. al. The results indicated that the dispersion of cloricromene within Eudragit RL100 polymer nanoparticles increased its ocular bioavailability and enhanced the biopharmaceutical profile[19].

Buccal and Sublingual Drug Delivery:

The oral mucosae in general is a 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[20]. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal[21]. 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[22]. 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[23], 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[24], films[25], patches[26], disks[27],

strips [28], ointments[29], and gels[30], have recently been developed. Eudragit providing good drug release barier with good adhesive strength.

Ashwini Madgulkar et. al. Solid dispersion of itraconazole with Eudragit E100 prepared a tablet by spray-drying method in the ratio of 1:2 showed 100% drug release within 3 h[31]. **Gloria Ruiz et. al.** also used Eudragit RL PO to prepare mucoadhesive tablet[32]. **Mona Semalty et.al.** Were prepared mucoadhesive buccal films of glipizide with Eudragit RL-100[33].

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[34].

Kale et al. The microspheres of eudragit S100 were found to float continuously in the acidic solution and successfully release drug in a predetermined rate[35].

Gloria et al. Formulate bioadhesive two layers controlled release tablets with combination of Carrageenan 934 and Eudragit RL PO in 1:1 ratio. The drug release was 96.3% in phosphate buffer pH 7.4; 59.1% in 0.1 N HCl and 46.4% in distilled water[33].

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. Rahman et. al. prepared 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[36].

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[37].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[38].

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 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[39].

Vaginal Drug Delivery:

Eudragit RS100 vaginal suppositories containing sildenafil, and other excipients give adequate release[40]. 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[41].

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[42]. 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[43]. 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[44]. Antisense oligodeoxynucleotides were successfully delivered by nanoparticles prepared by Eudragit RL100, RS100[45].

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[46]. 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[47].

Table: 5 Taste Masking Drug Delivery System:

Sr. No.	Drug/Active Agent	Technique	Polymer	Reference
1	Ibuprofen	Air-suspension	Methacrylic acid copolymer	48

		coating	(Eudragit)	
2	Acetaminophen	Coating	Cellulose acetate, cellulose acetate butyrate, HPC/cellulose acetate, Eudragit E 100, PVP	49,50
3	Morphine HCl	Coating	Cellulose, Eudragit NE 30D	51
4	Roxithromycin	Granulation and coating	PEG, Eudragit L 100–55	52
5	Nizatidine	Spray drying	Eudragit E 100	53
6	Cetraxate HCl	Melt granulation and coating	Corn starch, Macrogol-6000, Eudragit S-100	54
7	Ciprofloxacin	Microencapsulation	Eudragit NE 30D, HPC	55
8	Ibuprofen	Spray coating	Eudragit L300, propylene glycol, mannitol, and flavor	56
9	Bifemelane HCl	Coating and spraying	Glycerin monostearate, Eudragit L30-D-55, PEG, sucrose	57
10	Cefuroxime axetil	Emulsion-solvent evaporation	Eudragit L-55 and RL	58
11	Pirenzepine and Oxybutynin	Dispersion coating	Eudragit E-100, MCC, HPC	59
12	Levofloxacin	Coating	Eudragit E100, cellulose acetate	60

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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