IJPSR (2020), Volume 11, Issue 6 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 September 2019; received in revised form, 20 December 2019; accepted, 29 February 2020; published 01 June 2020

EUDRAGIT: A VERSATILE AND ROBUST PLATFORM

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Keywords:

Eudragit, Polymer, Excipients, Polymethacrylates

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ABSTRACT: In many aspects, polymeric materials have a pre-eminent position among excipients as they form the backbone of modern pharmaceutical formulations and drug delivery technologies in particular. A polymer is a natural, semi-synthetic or synthetic substance that is combined with a drug or other active pharmaceutical ingredient or excipient to release the drug in a pre-programmed manner. The drug delivery system focuses particularly on the enhancement of bioavailability, site-specific release, mucoadhesive release, sustained release, controlled release, targeted release. For achieving different release patterns as mentioned above different types of polymers are needed. Though there are various natural semi-synthetic and synthetic polymers available Eudragit polymers always have special consideration during polymer selection as it can offer a variety of grades which are useful during product development for any of the above-mentioned purpose. This article reviews Eudragit polymers in terms of usefulness during pharmaceutical applications. Eudragit polymers that are chemically Polymethacrylates are synthetic cationic, anionic and non-ionicpolymers of dimethyl-aminoethyl methacrylates, methacrylic acid and methacrylic acid esters in varying ratios. Eudragit polymers play a pivotal role in the formulation and development of different types of dosage forms with versatile applications.

INTRODUCTION: Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety and are intentionally included in a drug delivery system. Excipients are responsible for the release stability and effectiveness of a drug product. Polymers constitute major part of excipients in a formulation.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(6).2626-35

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(6).2626-35

A polymer is a natural, semi-synthetic or synthetic substance that is combined with a drug or other active pharmaceutical ingredient or excipient to release the drug in a pre-programmed manner. The development of a novel drug delivery system has been made possible by the various compatible polymers to modify the release pattern of drug [1].

The basic objective of controlled and sustained release drug delivery system 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. The choice of polymers always suffers from the problem of

bioavailability or formulation incompatibilities [2]. A clever solution to these bioavailability and formulation incompatibilities is Eudragit polymer. Eudragit is a trading name given by Evonik industries. The word Eudragit is derived from the word Oi´ drăgĭt n, which means Eu meaning good, Dragee meaning coated tablet and GIT meaning gastrointestinal tract [3].

History: Until the 1950s, all oral medications even the most modern, had one big disadvantage that is, it was not possible to control the time or release location of the active pharmaceutical ingredient. The development of Eudragit by Rohm & Haas Gmbh in Darmstadt was the solution to this problem. When the first drugs came into 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 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 that are 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 which are resistant to stomach acid and continue to work throughout the intestinal tract and considerably increase 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' sites [4]. Eudragit is a trademark of Rohm Gmbh & Co. KG. Darmstadt in Germany, first marketed in the 1950s. Eudragits are official in USP/NF, BP, PhEur, and 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 are as shown in **Table 11**.

TABLE 1: YEAR OF INTRODUCTION OF EUDRAGIT GRADE

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

Chemistry: Eudragit polymers that are chemically Polymethacrylates are synthetic cationic, anionic and non-ionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several types are commercially available and may be obtained as the dry powder, aqueous dispersion, and organic solution. The most common organic phase used is (60:40) mixture of acetone and Propan-2-ol.

Polymethacrylates are primarily used as film-coating agents in tablet and capsule dosage forms. Films of different solubility can be produced by using different polymer grades.

Apart from the above applications, recent studies revealed that polymethacrylates have got broad applications in formulation vis-à-vis taste masking, better permeation across the skin, intestinal epithelium and corneal permeation, dissolution enhancement, bioavailability enhancement, enteric coating, sustained release, radioprotection, pH-dependent release, colon targeting, *etc*. Polymethacrylates play a pivotal role in the formulation and development of a different type of dosage form with versatile applications [6].

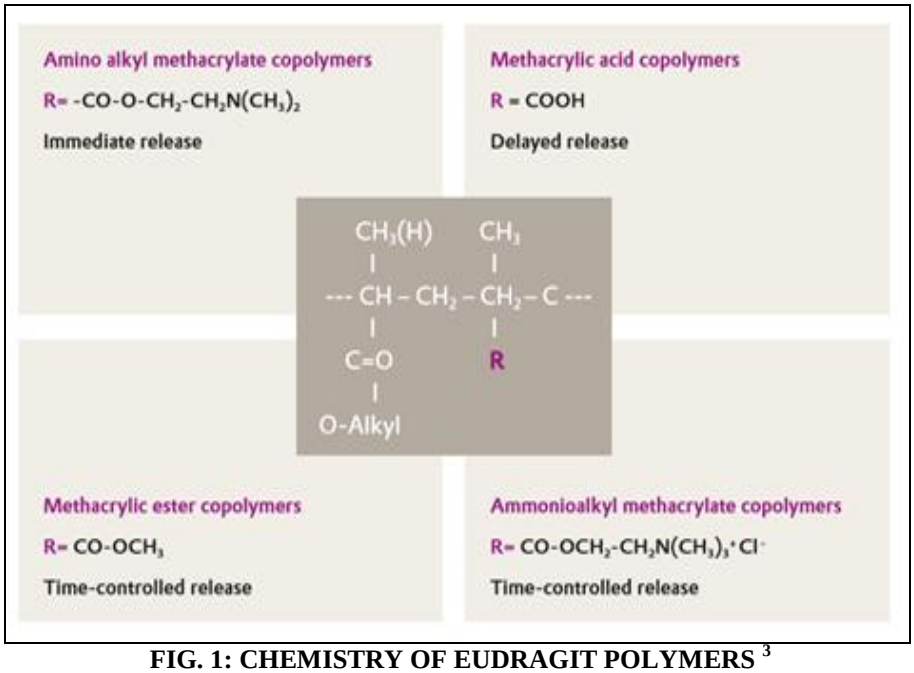

FIG. 1: CHEMISTRY OF EUDRAGIT POLYMERS [3]

Advantages of Eudragit Polymers: Eudragit offers valuable advantages as follows: [7]

- pH-dependent drug release.
- Protection of sensitive active pharmaceutical ingredients from the gastric fluid.
- Protection of gastric mucosa from aggressive active pharmaceutical ingredients.
- Enhancement in drug effectiveness.
- Good storage stability.
- Gastrointestinal and colon targeting.
- Moisture protection.
- Improved passage of the dosage form.
- Smooth and glossy coating surfaces with good color coating.
- Time-controlled release of active ingredients.
- Therapeutically customized release profiles.
- Higher patient compliance due to the reduced number of doses to be taken.
- Cost-effective processing.
- High pigment binding capacity.
- Reliable functionality also at very low coating levels.
- Good compressibility.
- Superb logo definition.
- High yield.
- High thermal stability.
- Polymer combination is feasible.
- Multiple layer coatings.
- Excellent adhesion.
- Wide formulation versatility.
- Safe taste-masking through insolubility in saliva.
- Available as customized ready to use powder blend.

Classification of Eudragit Polymers: Eudragit polymers are classified based on chemistry, based on solubility and based on use or types of formulations that can be developed.

➢ **Based on Chemistry:**

- Anionic.
- Cationic.
- Non-ionic.

➢ **Based on Solubility:**

- Soluble.
- Insoluble.

- **Based on use or Types of Formulations that can be Developed:**

- Moisture protection & odor or taste masking by protective formulations.
- Gastro resistance and gastrointestinal targeting by enteric formulations
- Time controlled drug release by sustained-release formulations.

Anionic Polymers: Anionic polymethacrylate polymers contain methacrylic acid functional groups, which dissociate and render the polymer soluble at the higher pH of the small intestine and colon. Anionic polymers containing methacrylic acid–ethyl acrylate copolymer (1:1) in coating products (*e.g*, Eudragit L 30-D) are soluble from a pH 5.5 but insoluble at the low pH in the stomach. Anionic copolymers of methacrylic acid and methyl methacrylate at a ratio of approximately 1:1 (type A; *e.g*, Eudragit L) and approximately 1:2 (type B; *e.g*, in Eudragit S). Both polymers are readily soluble in neutral to weakly alkaline conditions (from pH 6 for type A and from pH 7 for type B); the latter enables drug delivery to the colon since the polymers become soluble at pH >7.0.8.

Cationic Polymers: Cationic polymethacrylate polymers typically consist of copolymers of ethyl acrylate, methyl methacrylate and low content of methacrylic acid ester with quaternary ammonium groups. Cationic polymethacrylate containing more quaternary ammonium groups (*e.g*, Eudragit RL 100) is, therefore, more permeable than the one containing less quaternary ammonium groups (*e.g*, Eudragit RS 100). Another available cationic polymethacrylate is a copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate (*e.g*, Eudragit E 100). It is soluble in gastric fluid below pH 5 but becomes swellable and permeable, but not soluble, above pH 5.8.

Non-ionic Polymers (Neutral): Neutral polymethacrylates are copolymers of ethyl acrylate and methyl methacrylate (2:1) they do not contain ionic groups and therefore, only swell in aqueous media independent of pH without dissolving. These are generally available as aqueous dispersions with solid content at 30% and 40% respectively (*e.g*, Eudragit NE 30 D and Eudragit NE 40 D). Films prepared from these are insoluble in water but will swell and become permeable when they are in contact with water and exhibit pH-independent drug permeability. Such neutral polymethacrylate aqueous dispersions can be used for controlled-release coatings and wet-granulation binders [8].

TABLE 2: EXAMPLES OF POLYMETHACRYLATES

Type of polymer	Examples
Anionic	Eudragit L
	Eudragit S
	Eudragit L 30 D
Cationic	Eudragit RL100
	Eudragit RS 100
	Eudragit E
Non-ionic	Eudragit NE 30 D
	Eudragit NE 40 D

Based on Solubility: The polymethacrylates are classified as soluble and insoluble.

Soluble Polymethacrylates: They are soluble in digestive fluids by salt formation. Examples are- Eudragit L, S, FS, and E polymers. These polymers with acidic or alkaline groups enable the pH-dependent release of the active ingredient. Applications include simple taste-masking through gastric resistance to controlled drug release in all sections of the intestine.

Insoluble Polymethacrylates: These are insoluble but permeable in digestive fluids. Some of the examples are- Eudragit RL and RS polymers with alkaline and Eudragit NE polymers with neutral groups enable controlled time release of the active ingredient by pH-independent swelling.

Based on use or Types of Formulations that can be Developed:

Moisture Protection and Odour or Taste Masking by Protective Formulations: Eudragit E polymers encapsulate sensitive actives, masking drug taste and odor and thus neutralizing the patient's reticence to take the medicine. They further enhance patient compliance by ensuring a smooth and glossy surface that facilitates swallowing. In addition, excellent color coating means the drug is always clearly identifiable. The desired functionality can be delivered with a coating thickness of just 10 to 20 micrometers, and that makes Eudragit E polymers extremely cost-effective to use [3, 9].

Gastro Resistance and Gastrointestinal Targeting by Enteric Formulations: When a drug must be protected from the gastric fluids in the stomach's acidic environment until it reaches the intestine for delivering maximum efficacy, Eudragit L and S polymers are the preferred choices of coating polymers. Part of a broad family of anionic Eudragit grades that only dissolve above a specific trigger pH, these polymers enable formulators to target specific areas of the intestine. They can also be combined with each other to dial in a specific dissolution pH for additional precision in gastrointestinal targeting. This is especially helpful for therapies that rely on targeted drug release in the high-pH colon area, *i.e.,* for the local treatment of intestinal disorders such as Crohn's disease, ulcerative colitis or intestinal cancer [3, 7].

Time Controlled Drug Release by Sustained Release Formulations: Drug delivery can be controlled throughout the entire GI tract to increase the therapeutic effect and patient compliance. Various polymer combinations of Eugradit RL and RS grades with other ingredients variations enable custom-tailored release profiles to achieve the desired drug delivery performance. Eudragit NE and NM grades are neutral ester dispersions, which do not require additional plasticizer [3, 7].

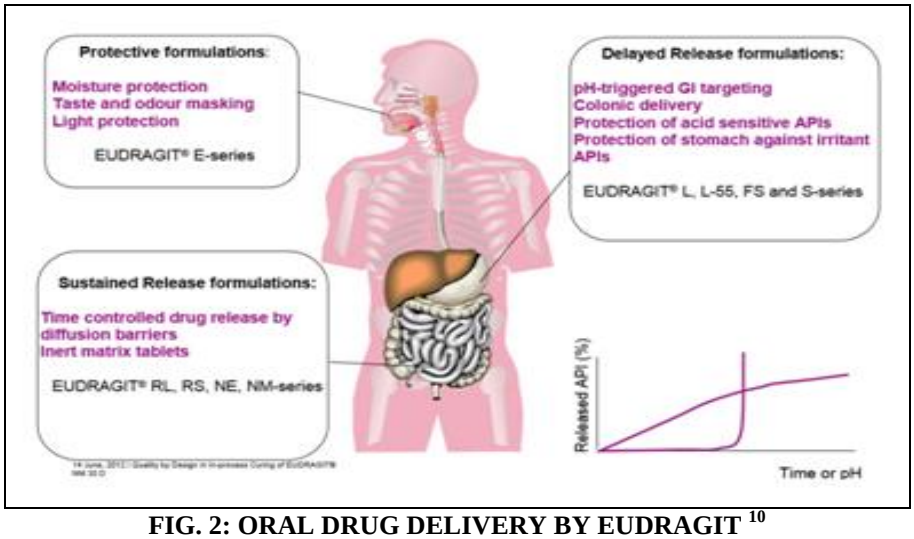

FIG. 2: ORAL DRUG DELIVERY BY EUDRAGIT [10]

Trade Name Codes: The trade name codes as specified by Evonik industries is as given in **Table 3**.

Name Codes: Eudragit polymers are coded on the basis of its chemistry as follows: Eudragit E is cationic polymer based on dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters. Eudragit L and S are anionic copolymers of methacrylic acid and methyl methacrylate. The ratio of the free carboxylic group to ester group is approximately 1:1 in Eudragit L and 1:2 in Eudragit S. Eudragit FS is anionic copolymer based on methyl acrylate, methyl methacrylate ad methacrylic acid. The ratio of free carboxylic group to ester group is approximately 1:10. Eudragit RL and RS are copolymers synthesized from acrylic and methacrylic acid esters, with Eudragit RL having 10% of functional quaternary ammonium groups and Eudragit RS having 5%. These ammonium groups are present as salts and give rise to pH-independent permeability of polymers. Eudragit NE is neutral copolymers based on ethyl acrylate and methyl methacrylate [4].

TABLE 3: TRADE NAME CODES OF VARIOUS EUDRAGIT POLYMERS [7]

Code	Availability	Eudragit grade
100	Solid	Eudragit L 100
		Eudragit S 100
		Eudragit L 100-55
		Eudragit RL 100
		Eudragit RS 100
		Eudragit E 100
PO	Powder	Eudragit RL PO
		Eudragit RS PO
		Eudragit E PO
30D	Aqueous dispersion	Eudragit L 30 D-55
		Eudragit RL 30 D
		Eudragit RS 30 D
		Eudragit NE 30 D
		Eudragit NM 30 D
12.5	Organic solution	Eudragit L 12.5
		Eudragit S 12.5
		Eudragit RL 12.5
		Eudragit RS 12.5
		Eudragit E 12.5

Properties of Various Eudragit Polymers:

TABLE 4: PROPERTIES OF VARIOUS GRADES OF EUDRAGIT POLYMERS [4]

Polymer grade	Recommended solvents or diluents	Glass transition interval T_gm[iaC]	Solubility/ Permeability	Applications
Eudragit E 12.5	Acetone, alcohols	-	Soluble in gastric fluid pH 5	Film coating
Eudragit E 100	Acetone, alcohols	48	Soluble in gastric fluid pH 5	Film coating
Eudragit E PO	Acetone, alcohols	48	Soluble in gastric fluid pH 5	Film coating
Eudragit L 12.5	Acetone, alcohols	-	Soluble in intestinal fluid from pH 6	Enteric coating
Eudragit L 100	Acetone, alcohols	-	Soluble in intestinal fluid from pH 6	Enteric coating
Eudragit L 100-55	Water	110	Soluble in intestinal fluid from pH 5.5	Enteric coating
Eudragit S 12.5	Water	-	Soluble in intestinal fluid from pH 7	Enteric coating
Eudragit S 100	Acetone, alcohols	-	Soluble in intestinal fluid from pH 7	Enteric coating
Eudragit FS 30 D	Water	48	Soluble in intestinal fluid from pH 7	Enteric coating
Eudragit RL 12.5	Acetone, alcohols	-	High permeability	Enteric coating
Eudragit RL 100	Water	70	High permeability	Enteric coating
Eudragit RL PO	Acetone, alcohols	70	High permeability	Sustained release
Eudragit RL 30 D	Water	-	High permeability	Sustained release
Eudragit RS 12.5	Acetone, alcohols	-	Low permeability	Sustained release
Eudragit RS 100	Water	65	Low permeability	Sustained release
Eudragit RS PO	Acetone, alcohols	65	Low permeability	Sustained release
Eudragit RS 30 D	Water	-	Low permeability	Sustained release
Eudragit NE 30 D	Water	9	Low permeability	Sustained release
Eudragit NE 40 D	Water	-	Low permeability	Sustained release
Eudragit NM 30 D	Water	11	Swellable, permeable	Sustained-release, tablet matrix

Formulation Methods:

1. Matrix Formulation
2. Multiparticulate Formulation

Matrix Formulation: Eudragit serves as a matrix within which the active ingredient is embedded. The matrix structure is obtained by direct compression, granulation, or melt extrusion. Eudragit NM 30 D is particularly suitable for granulation processes in the manufacture of matrix tablets [7].

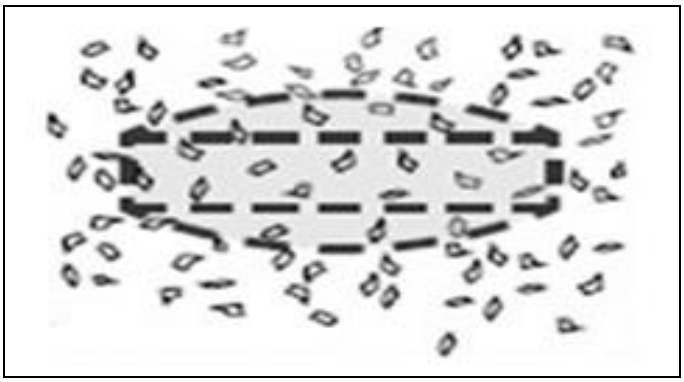

FIG. 3: STRUCTURE OF MATRIX TABLET 7

Multiparticulate Formulations: Eudragit is used as a coating material, usually for the coating of pellets or particles that are filled into capsules or compressed into tablets. These pellets or particles act as diffusion cells in the digestive tract and release a constant drug quantity per unit of time (multi-unit dosage forms) [7].

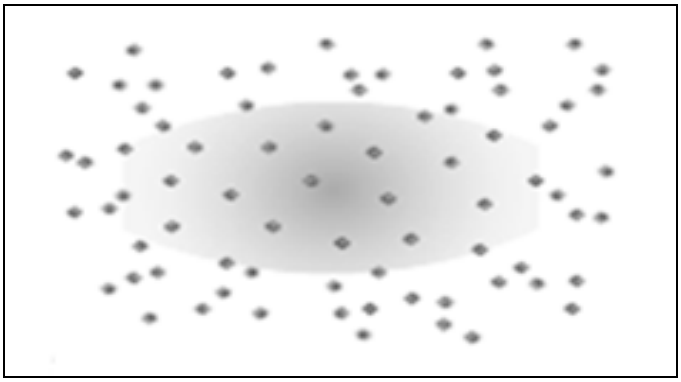

FIG. 4: STRUCTURE OF MULTIPARTICULATE TABLETS [7]

Drug Release Mechanism: The drug release from the dosage form is governed by the following principles [11].

1. Dissolution.
2. Diffusion.
3. Osmosis.
4. Ion-exchange.

Dissolution: The rate-limiting step in the absorption of most of the drugs from the dosage form from the gastrointestinal tract is dissolution. Dissolution is a process in which a solid substance solubilizes in a given solvent *i.e.* mass transfer from the solid surface to the liquid phase. Dissolution rate is defined as the amount of solid substance that goes into solution under standard conditions of temperature, pH, solvent composition and constant solid surface area [12]. Eudragit S coated 5-ASA has dissolution to be the responsible mechanism of controlling drug release. The dissolution release pattern is shown in **Fig. 5**.

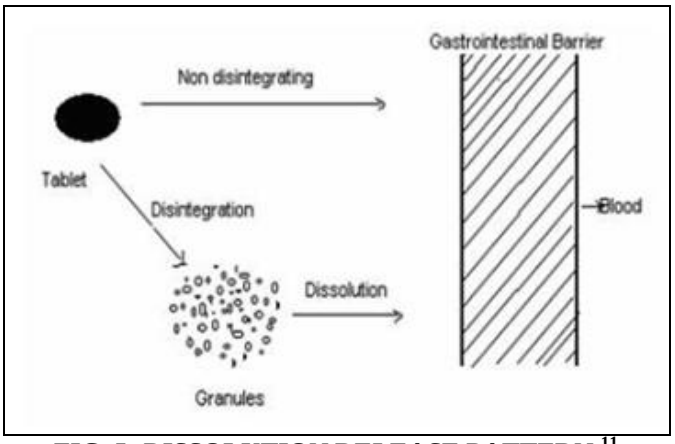

FIG. 5: DISSOLUTION RELEASE PATTERN [11]

Diffusion: Diffusion is the movement of a substance down to concentration gradient *i.e.* drug molecules diffuse from higher concentration to lower concentration in gastrointestinal fluids [12]. Several factors that affect the rate of diffusion include temperature, density of the diffusing substance, medium of diffusion and concentration gradient. The release of propranolol HCL from a monolithic matrix of eudragit NE 30 D by a combination of diffusion through polymer and pores is an example of diffusion. A desirable release profile of diphenhydramine was achieved by incorporating Eudragit L in a carnauba wax matrix.

The drug release from polymer-wax matrices is described by a combination diffusion/erosion mechanism [11]. The diffusion release pattern is shown in **Fig. 6**.

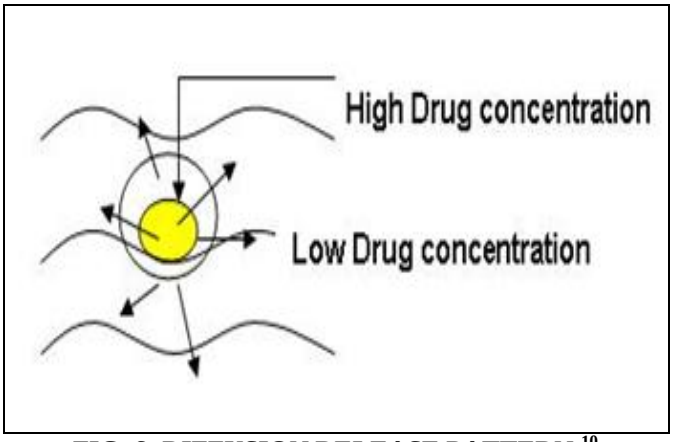

FIG. 6: DIFFUSION RELEASE PATTERN [10]

Osmosis: Osmosis is a natural movement of a solvent from lower concentration into a solution of higher concentration through a semipermeable leading to an equal concentration of solute on either side of the membrane. Osmotic systems imbibe water from the body through a semipermeable membrane into an osmotic material which dissolves in it and increase in volume and generate osmotic pressure that results in slow and even delivery of drug through an orifice [12]. The release rate of drugs from the osmotic dispensing device is dependent on solubility, molecular weight and partition coefficient of solute. The whole drug is coated with a semi-permeable membrane with a hole at the tip of a 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 [12]. The osmotic release pattern is shown in **Fig. 7**.

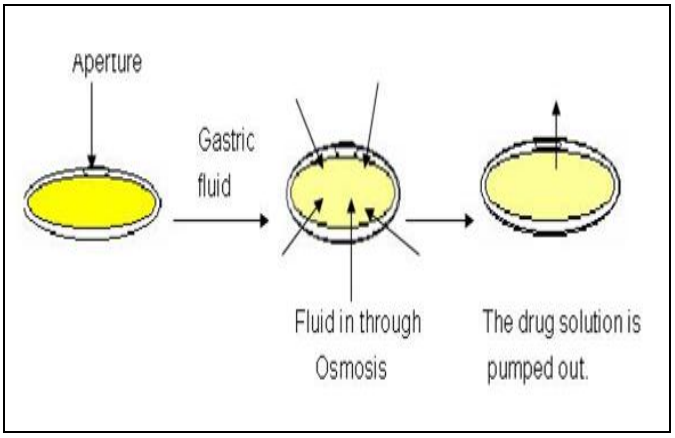

FIG. 7: OSMOTIC RELEASE PATTERN 11

Ion-exchange: Ion exchange resins are water-insoluble resinous materials containing salt-forming anionic or cationic groups. The use of ion-

exchange resins into drug delivery systems has been encouraged because of their physicochemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in the ionic environment. Ion-exchange resins are cross-linked; water-insoluble, polymer-carrying, ionizable functional groups. The drug is released from the drug-resin complex by exchanging with ions in the GI fluid, followed by drug diffusion. Eudragit RS 30 D-coated theophylline beads proved ion exchange to be a response mechanism of controlling polymer permeability as a function of anionic species and concentration. 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 [11].

Applications of Eudragit Polymers:

- Ophthalmic drug delivery.
- Buccal drug delivery.
- Sublingual drug delivery.
- Gastrointestinal drug delivery.
- Intestinal drug delivery.
- Colon drug delivery.
- Transdermal drug delivery.
- Vaginal drug delivery.
- Gene delivery.

Ophthalmic Drug Delivery: A major problem usually faced in the ophthalmic drug delivery system is the attainment of an optimal concentration at the site of action. The reason for poor bioavailability of drugs from ocular dosage forms is mainly tearing 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 application [7, 11].

Buccal Drug Delivery: The permeability of the buccal mucosa is 4-4000 times greater than that of the skin. At physiological pH, the mucus network carries a negative charge (due to the silica acid and sulfate residues), which 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.

A 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 that 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.

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. Ideal polymers for such buccal drug delivery systems are Eudragit polymers. Eudragit provides a good drug release barrier with good adhesive strength. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments, and gels, have recently been developed [7, 11].

Sublingual Drug Delivery System: The permeability of the oral mucosa decreases in the order of sublingual greater than the buccal greater than palatal. Sublingual delivery provides rapid absorption and good bioavailability for some small molecules.

Sublingual mucosa is more permeable, thinner and richer in blood supply compared to the buccal mucosa and produces a rapid onset of action which makes it appropriate for drugs with a short delivery period. Eudragit polymers have found to be ideal for such drug delivery systems [13].

Gastrointestinal Drug Delivery System: The need for gastroretentive dosage forms has led to extensive efforts in academics and industry towards the development of such drug delivery systems. These efforts resulted in gastroretentive dosage forms that were designed for a low-density form of the dosage form that causes buoyancy in gastric fluid, a 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. All these techniques can be achieved with different grades of Eudragit polymers [7, 11].

Intestinal Drug Delivery: Intestine delivery of drugs was developed that could bypass the stomach and release the loaded drug into the intestine. This was enabled by coating the drug with Eudragit polymers. Eudragit L & Eudragit S are two forms of commercially available enteric acrylic resins. Both of them produce films resistant to gastric fluid and some are soluble in an intestinal fluid at pH 6 & 7 respectively. Eudragit L30 D 55 has produced the most acceptable results against the gastric attack [7, 11].

Colon Drug Delivery: Colonic drug delivery is a relatively recent approach for the treatment of diseases like ulcerative colitis, Crohn's disease, irritable bowel syndrome, and arthritis. pH-sensitive polymers that dissolve or above pH 7 used for colonic drug delivery. Eudragit L 100 and S100 are used for colon targeting [7, 11].

Transdermal Drug Delivery: Eudragit polymers find extensive use in transdermal drug delivery systems. The films produced by Eudragit polymers are elastic, self-adhesive, transparent, and pale yellow in color. Eudragit E100 polymer results in wrinkle-free transparent films with good adhesion to skin. Release kinetics from the transdermal therapeutic system was observed due to erosion of hydrophilic Eudragit E100 polymer, and a 100% release was observed within 20 min [7, 11].

Vaginal Drug Delivery: Eudragit RS 100 vaginal suppositories containing active pharmaceutical ingredients other excipients give adequate release. Intravaginal tablet prepared with a 1:1 ratio of lactic acid to Eudragit E-100, tablets are disintegrating into a gel form at a physiological range of 3.8-4.4 pH. These gels possess an acid reserve that might be able to neutralize the excess of alkali present in severe vaginal infections [7, 11].

Gene Drug Delivery: Many hereditary diseases could be treated or controlled by gene delivery. In addition, many acquired diseases and those diseases caused by viral genes could be treated by genetic therapy. Nanoparticles prepared by blending PLGA with Eudragit RE 100 can efficiently and safely deliver plasmid DNA encoding mouse interleukin-10 leading to the prevention of autoimmune diabetes. New Anionic nanoparticles 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 EudragitRL100, RS100 [7, 11].

CONCLUSION: Eudragit polymers can produce sustained release formulations for time-controlled drug release, enteric formulations for GI targeting and protective formulations for moisture protection and odor/taste masking. These multifaceted applications of eudragit polymers in novel drug delivery systems have made significant contributions to novel drug delivery systems. It can thus be concluded that Eudragit polymers can significantly be utilized as a novel and versatile tool for release modification.

ACKNOWLEDGEMENT: I acknowledge the support of my college P.E.S's Rajaram and Tarabai Bandekar College of Pharmacy Farmagudi Ponda-Goa for providing the necessary facilities for carrying out the review.

CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

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How to cite this article:
Bhilegaonkar S and Parvatkar A: Eudragit: a versatile and robust platform. Int J Pharm Sci & Res 2020; 11(6): 2626-35. doi: 10.13040/IJPSR.0975-8232.11(6).2626-35.

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