STUDY ON THE POLYMER CHITOSAN, PECTIN, EUDRAGIT - USED IN THE COLON SPECIFIC TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

A current topic of research is colon-targeted drug delivery system, which is to precisely releases the medication in a colon to improve oral administration of active pharmacological moiety, that is sensitive to acidic condition of the upper gastro intestinal tract. This review focuses much more on polymers used in colon-specific drug delivery. Herein, the emphasis is basically on the physicochemical characteristics of polymers and their effects on colon-specific drug delivery. Chitosan is a widely used biopolymer in the colon. Probably, pectin is recognized as among the most promising components for colon-targeted drug delivery, even though it is stable in changing the Gastrointestinal environment and got quickly reduced its concentration by pectinases generated by colonic microflora. Eudragit is also known for polymethacrylate based copolymers. It is composed of cationic, anionic and neutral copolymers which are derived from methacrylic/acrylic esters and methacrylic acid. We anticipate future advances and new research fields encircling chitosan, pectin and eudragit based methods of delivery, which can increase the polymers' usability in novel medication modalities.

KEY WORDS: Polymer, Chitosan, Pectin, Eudragit

1.INTRODUCTION

The term "Drug Delivery System" (DDS) means a bio system-based preparation or a technology that enhances therapeutic drug transport in the body by controlling the time, region, rate and route of drug delivery to the intended site [1]. To treat any ailment with medication, a patient must follow a prescribed dosage schedule. This is accomplished through "specific drug dose at specific interval" in conventional drug therapy, which exclusively depends on the drug's therapeutic index and half-life. A specific drug release kinetics must be followed to sustain the dosage and achieve an appropriate therapeutic drug concentration, hence permitting controlled drug release [2]. The route of administration is probably based on the bioavailability of drugs within the host. The bioavailability of medications is through various administration systems following, enteral (oral; nasal; ocular; transmucosal) or parenteral (intra-venous, intra-muscular and sub-cutaneous). By altering the number of biological membranes, a medication should pass through or altering the contact of the medication [3,4]. Drugs are to be given in the form of capsules, and tablets in the conventional drug delivery system which are formulated by compression, coating and encapsulation of bio-active drug molecules. The advent of an improved DDS revolutionized the medical practice and promotes several technological advancements.

Colon-targeted DDS is highly indicative of localized colonic pathology treatment, amoebiasis, colonic cancer, Crohn’s disease and ulcerative colitis [5]. The absorption targeted DDS directly occurs in the colon without involving the stomach or small intestine [6]. Peptides and protein medicines are thought to be well absorbed in the colon. The oral route is more convenient and preferred as especially in comparison to various other administrative routes. Even though, targeting the colon rectal administration is the shortest but it could be uncomfortable for some patients [7].

The polymer is made up of several structural components which they have high molecular mass. Polymerization reaction deals with small molecules (monomers) are joined together to form a polymer [8]. Polymers are extracted from microorganisms, plants and animals [9]. Biopolymers act as capsule binders, tablet film coating agents and viscosity enhancing agent. Therapeutic advantages are sustained and controlled delivery of single and multiple doses of formulations [1]. There are numerous categories of polymers used in biomedical and pharmaceutical applications in the following,[8]

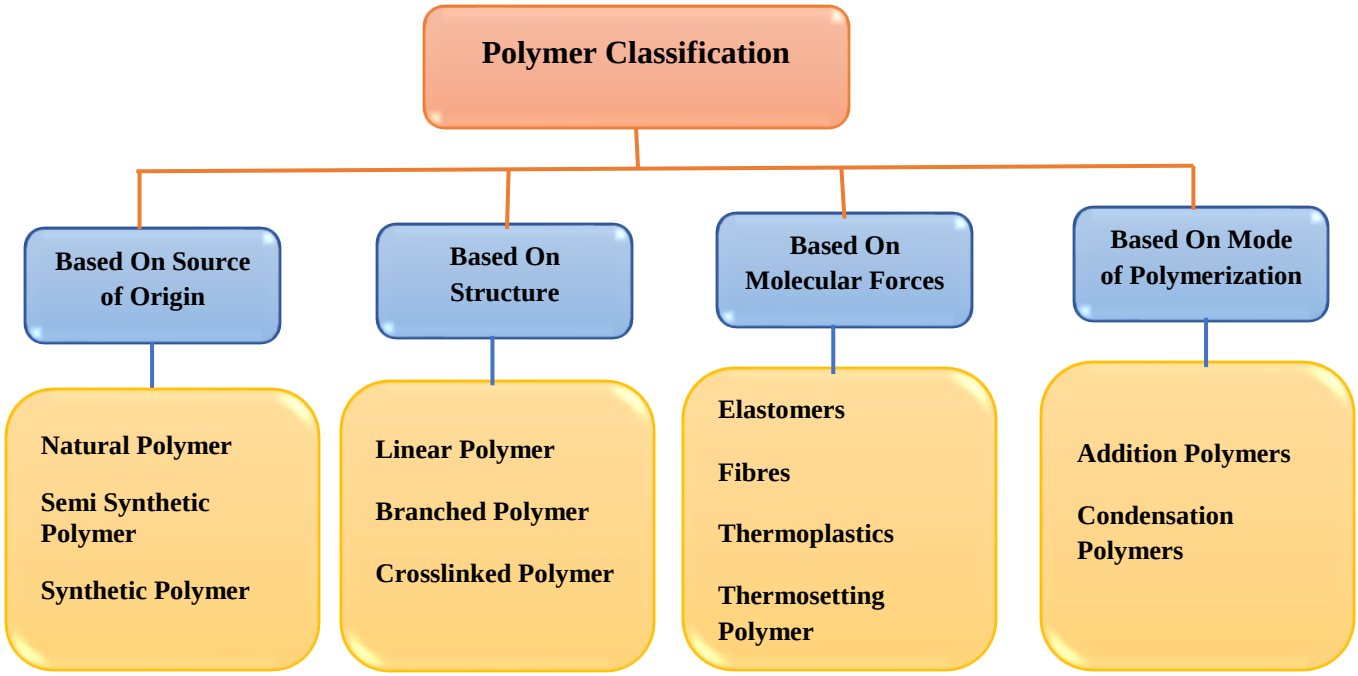

Fig. 1: classification of polymer

2. ORAL ROUTE OF DRUG DELIVERY

The oral route is more convenient and preferred among other administration routes. In recent years there are many oral cargo delivery systems have been developed [10]. Previous studies have shown that more than half of the drugs are administered orally. Due to their comfort and non-invasive nature, oral drug delivery system is an efficient strategy for treating intestinal diseases [11].

2.1. gastro-intestinal pH

Gastrointestinal pH varies from the upper tract to the lower tract. Gastric pH in the empty stomach is around 1 to 2 on intake conditions it may increase to pH 5[12]. Under normal physiological conditions**,** the pH varies largely from stomach to lower GIT. Probably, stomach has acid pH 1.5 - 3.5, pH valve in duodenum is 6, terminal ileum is pH 7.4, terminal cecum is pH 6 and colon has pH 6.7[13].

2.2. GI transit time

Gastrointestinal transit duration changes from person to person, it is based on the differences in upper and lower GIT fluids and peristalsis movement, the intestinal length and the gut bacteria composition [14]. Due to age, physical exercise, sexuality, fluid volume, food consumption, etc., plays a major role regarding difference in transit time [12]. The small intestine's transit time is likely to be 4hrs. Colon transit time probably differs, from 6-7hrs. There are considerable variances in GI emptying time also seen in Intestinal Bowel Disease (IBD) patients, this may enhance the

unpredictability of the time the drug enters the colon [13]. Thus, physiological body function is accompanied by transit time changes in varied sections of the GIT. According to this, polymers and drug delivery system is being selected [12].

2.3. mucus in gastro-intestinal tract

The double-layered mucus membrane in the Gastrointestinal tract protects against stomach acid and provides a conducive environment for normal microbial flora. The mucus membrane slows down the medication absorption because a medicine should pass through it to reach the absorption site [15].

3. ORAL COLON SPECIFIC DRUG DELIVERY

The oral colon DDS is the distal portion of the GIT and is considered to be the drug that needs to travel through the entire Gastrointestinal tract. To develop such carriers, complete knowledge of Gastrointestinal tract physiology is mandatory [16]. Physiological variations can be categorized as transit time and pH, as well as the specific index in the colon, which involves enzymes\ microbes and pressure. Therefore, mucus in the colon has dual uses, and ligands or drugs that respond to colon illness increase specificity [17]. The major delivery designs targeting the colon are pH-dependent delivery, time-dependent delivery, ligand/receptor-mediated Delivery, and enzyme-sensitive delivery [16,17]. Biopolymers that are employed in colon cargo delivery are Dextran, Chitosan, Pectin, Gaur Gum, Alginate and Starch.

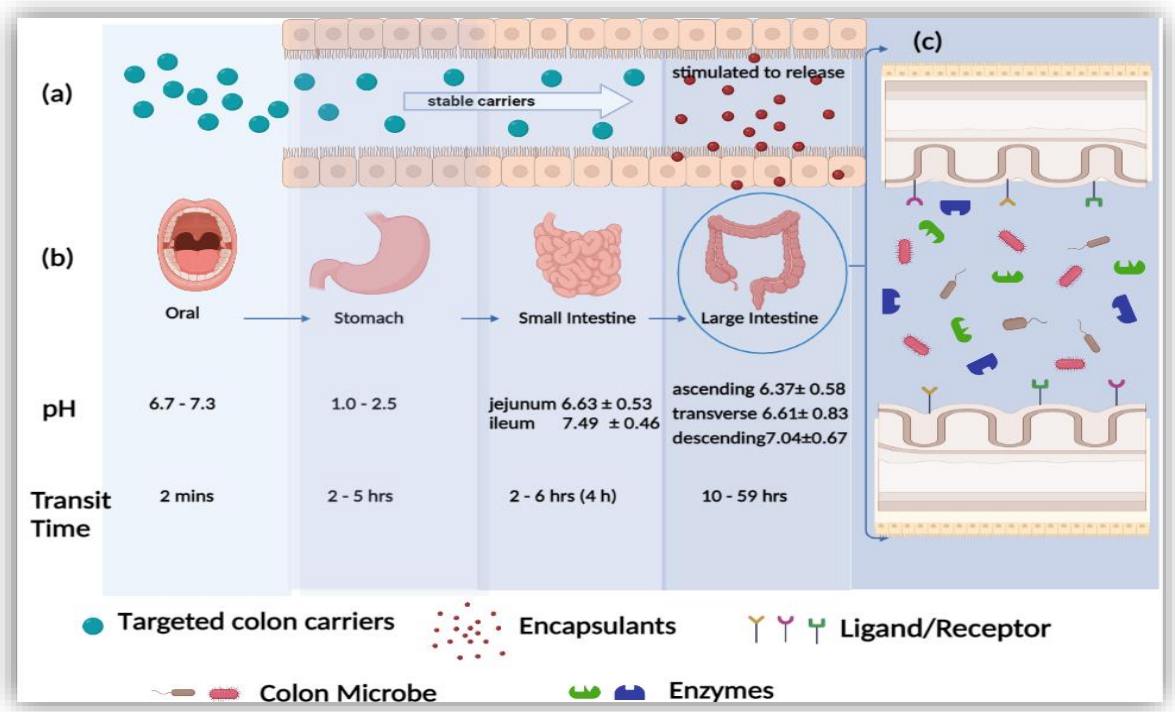

Fig. 2: oral colon dds (a) git physiological factors that influencing the colon dds (b and c) fig. created using bio-render (https://bio_render.com/).

4. CHITOSAN

Among natural biopolymers, Polysaccharides have received great attention due to ease of availability, non-toxicity, biocompatibility, renewability and biodegradability these are unique aspects of physicochemical and biomedical features of polysaccharides. Chitosan is an extraordinary and multifunctional polymer excipient [18]. Since chitin and chitosan has a wide range of uses in many areas [19].

4.1 physicochemical characteristics of chitosan

Probably, chitin can be present in two major polymeric forms β-chitin and α-chitin, both combined to form γ-chitin. Intermolecular hydrogen bonding, crystalline sheet structure and degree of hydration varies slightly across all these three forms. [20]. Chitosan includes hydroxyl and amino groups, that are bonded with polysaccharide chains. It gives chitosan the desired adaptability and flexibility for structural changes, in addition the ability to reinforce with other polymers. Chitosan has a unit formula of C6H11O4N and one 1^{o} amine and two free hydroxyl groups [21]. Chitosan is not soluble at basic and neutral pH level, but dissolves at acidic pH level (around pH less than 6). This occurs because an amino group with a pKa of 6.3 & low no of N-acetylated groups get protonated at acidic pH, raising net $+^{ve}$ charge and acting as a strong base [21]. Because of its aggregation with polyanionic compounds, among known polysaccharides, chitosan has been proven to be a good gel-forming agent [22]. According to the study, increasing the molecular weight of chitosan has been shown to enhance permeation and muco-adhesion[23]. The viscosity is affected by environmental factors and it gets increases as the degree of deacetylation rises owing to enhanced charge repulsion at high levels of deacetylation [12]. Similarly, increasing concentration increases solution viscosity, while decreasing temperature decreases it. It is employed in various formulations as a viscosity altering agent [24]. It is generally known that the GI mucus layer contains anionic elements like sulfonic acid and sialic acid. Mucosal adhesion takes place between anions and numerous cations, they are between the gel-like mucus layer and amino groups in chitosan [25]. Chitosan and derivatives of chitosan extend the duration of dose form at desirable targeted regions such as the gastrointestinal buccal region, stomach, portions of the small intestine, large intestine and other body regions having a muco layer like the vaginal and nasal mucosa [12].

4.2 chitosan for colon specific drug delivery

For the construction of mucosal and transmucosal cargo delivery systems, chitosan plays a favorable biomaterial [26]. Chitosan has been broadly utilized in the fabrication of oral colon-specific delivery to supply bioactive components with increased bioactivity because Chitosan's biodegradability might be used to produce a microbe/enzyme-dependent oral colon-specific delivery system, while its muco-adhesion is excellent. Yet, Chitosan is dissolved in aqueous environments with pH less than its pKa (approx6.3), indicating that it is easily soluble in gastric juice [27]. In an oral colon cargo delivery system, chitosan-based carriers can often fail to tackle the

challenging condition of the upper Gastrointestinal tract for compound delivery to the colon. To improve chitosan characteristics such as swelling ability, mechanical strength, and so on, it is required to combine two or more process of preparations.

5. PECTIN

Natural macromolecules are getting more popular because of their biodegradability, biocompatibility and low toxicity. Pectin is one of just a few polysaccharides exhibiting biomedical activity [28]. Pectin is a non-toxic polysaccharide that indigested by stomach or intestine enzymes but is virtually fully dissolved by pectinolytic enzymes secreted by gut the colon's bacteria [29]. Pectin is not absorbed into the circulation; it cannot have direct impacts on physiological systems so they are proven to be safe in oral intake. The FDA has named pectin a GRAS (Generally Recognized as Safe) substance, which may be ingested in any amount by people without concern of toxicity.

TABLE I: List of colon-specific drug delivery using modified chitosan formulations

Polymer	Formulation	Function	Comments
Chitosan succinate and chitosan phthalate matrix	Matrix tablet	Drug release	Drug release is decreased in an acidic environment, while dissolution is facilitated in a basic environment.
Succinyl chitosan-encapsulated liposome	Liposomes	Stability	Better Stability
N-Succinyl-chitosan microparticle	Microparticles (Spray-dried)	Drug efficacy	Colitis *in-vivo* study healing is more effective.
γ-poly (glutamic acid) crosslinked chitosan	Hydrogel (pH-responsive)	Drug release	Hydrogel swelling was seen for 72 hours at colonic pH
Chitosan-Tripolyphosphate cross-linking for encapsulation	Encapsulation & glutaraldehyde cross lining	Drug delivery	Consistent insulin delivery to the colon
Chitosan zinc pectin composite	-	Drug release	Significantly increased colon-specific drug release with 1% chitosan at pH 1.5 and a pectin/drug ratio of 3:1.

5.1 physicochemical characteristics of pectin

The Physical and chemical characteristics of pectin and related function in plant physiological, physical characteristics of biopolymer constituents and merits for human body system functioning deals with the beginning point of research. All terrestrial plants and seagrass have a lot of pectin in their cell walls [31]. Pectin is composed of galacturonate molecules that are covalently bonded to one another. Pectin has a chemical structure composed of (1 → 4)-α-D-galacturonic acid (Gal A) residues branched with various neutral sugars. Due to its significant unpredictability, the precise chemical structure is currently being investigated [28,29]. Natural pectin and readily available polysaccharides have a high MW (100-400 kDa).

According to the Mark-Houwink equation; MW is directly proportional to the inherent viscosity. Pectin from any source has a high degree of esterification, which means in the addition of water and sucrose; it may generate gels. In positively charged cation-containing media, low-esterified pectin exhibits gelling properties [32]. The mechanisms determining the binding activity of pectin polymers are assumed to be the degrees of polymerization and esterification. In the acidic medium, pectin gels are more stable whereas in alkaline shift often leads to de-stabilization with resultant viscosity reduction [33].

5.2 pectin for colon specific drug delivery system

Pectin are more potential components in colon-targeted cargo delivery because they are stable in altering GI conditions and pectinases produced by intestinal bacteria quickly breakdown it. There are several pectin-containing delivery methods have been established, resulting in increased concentrations of active drug in specific regions inside the colon and lower blood levels, lowering the chance of severe adverse effects [29]. Pectin is entirely destroyed in the colon by bacterial enzymes, resulting in the synthesis of short-chain fatty acids, which serve as the principal source of energy for colonocytes. Although, any the colon's natural microbial balance ultimately led to altering in the pectin fermentation process [34]. Moreover, epidemiological data show that the occurrence of colon cancer is substantially greater in people with a pH of intestinal media of 7.0, whereas the pH in the colon of healthy individuals is 6.5[35]. There is numerous recent research have demonstrated that regular Pectin ingestion with meals has shown to be protective against the risk of colon cancer development because these acids trigger an acidic pH shift [36]. Pectin polysaccharides are mean to be excellent choice because they are not destroyed in stomach or the small intestine until they reach part of the colon, where enzymes generated by colon bacteria ferment them, leads to rapid cargo release [37]. Enzyme sensitive colon cargo delivery systems rely on certain enzyme activity in bacteria and are made up of biopolymers that can be degraded by colonic microflora. Chitosan, Pectin, guar gums and alginates are non-starch polysaccharides that have been used for colon targeted drug delivery, since they are present in the upper part of GIT and small intestine in a stable gel state, but are swiftly destroyed by intestinal microflora agents, leading in efficient release of drug [29].

6. POLYMETHACRYLATES (EUDRAGIT®)

Eudragit was initially introduced in 1953, it is a medication coating constituent that is alkaline soluble that was impervious to gastric acid. Eudragit are synthetic polymers synthesized from the acrylic acid polymerization and methacrylic acids or their esters. Unlike cellulosic derivatives, whose physicochemical properties fluctuate based on the raw material source, Eudragit is delivered in highly reproducible forms because they are synthetic polymers [38].

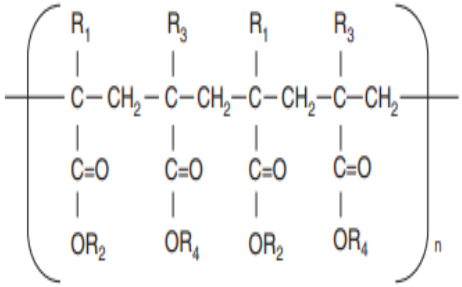

Fig. 3: basic chemical structure of eudragit.

Fig.3 and Tab II depicts the basic chemical structure of polymer & its various grades. Commercially available Eudragit grades come in a wide range of forms. The chemical structure, distinguishing characteristics and application of many forms of polymer have been gathered in four broad classes. (A) Cationic Eudragit E (dissolve below pH5.5) is used in masking the taste. (B) Anionic Eudragit L & S (soluble above pH 6 & 7) are used in colon cargo delivery/enteric coating. (C) Neutral types Eudragit RL & RS (pH-independent solubility). (D) Eudragit NE & NM are employed in sustained release cargo delivery [38].

TABLE II: Different grade of eudragit

Eudragit Grade	R_1	R_2	R_3	R_4
E	CH_3	$CH_2CH_2N(CH_3)_2$	CH_3	CH_3, C_4H_9
L & S	CH_3	H	CH_3	CH_3
RL & RS	H, CH_3	CH_3, C_2H_5	CH_3	$CH_2CH_2N(CH_3)_3^+Cl^-$
NE 30D	H, CH_3	CH_3, C_2H_5	H, CH_3	CH_3, C_2H_5
L 30 D-55 & L 100-55	H, CH_3	H	H, CH_3	CH_3, C_2H_5

6.1 physicochemical characteristics of eudragit

TABLE III: Physical properties of different eudragit grades

Eudragit grade	Density (g/cm^3)	Min film forming temperature (°C)	Water vapor transmission rate (g/m^2.day)
Eudragit E	0.811 - 0.821	-	~ 350 (organic)
Eudragit L 100, S 100	0.831 - 0.852	> 85#	~ 150 (redispersed)
Eudragit L 30 D-55	1.062 - 1.072	~ 25	~ 100 (10% TEC)
Eudragit L 100-55	0.821 - 0.841		
Eudragit RL PO	0.816 - 0.836	~ 40#	~ 450
Eudragit RS PO	0.816 - 0.836	~ 45#	~ 250
Eudragit NE 30 D	1.037 - 1.047	~ 5	~ 300
Eudragit FS 30 D	1.058 - 1.068	~ 27	~ 100 (3% TEC)

#Includes aqueous dispersion's minimum film forming temperature.
TEC: Triethyl Citrate.

TABLE IV: Some of different eudragit grades, properties with applications

Eudragit Grade	Available as polymer dry content	Solubility	Application
Cationic (Amino alkyl methacrylate copolymers)			
Eudragit **E 100**	Granules/98%	Soluble in gastric fluid to pH 5	Film coating
Eudragit E 12.5	Organic solution/12.5%	Soluble in gastric fluid to pH 5	Film coating
Anionic (Methacrylic copolymers)			
Eudragit L 100	Powder/95%	Soluble in intestinal fluid from pH 6	Enteric coating
Eudragit L 30 D-55	Aqueous dispersion/30%	Soluble in intestinal fluid from pH 5.5	Enteric coating
Eudragit S 100	Powder/95%	Soluble in intestinal fluid from pH 7	Enteric coating
Eudragit FS 30 D	Aqueous dispersion/30%	Soluble above pH 6.8	Enteric coating
Neutral (Amino alkyl methacrylate copolymers)			
Eudragit RL 100 (Type A)	Granules/97%	High permeability	Sustained release
Eudragit RS 100 (Type B)	Granules/97%	Low permeability	Sustained release
Neutral (Methacrylate copolymer)			
Eudragit NE 30 D (formerly Eudragit E 30 D)	Aqueous dispersion/30%	Swellable, permeable	Sustained release
Eudragit NM 30 D	Aqueous dispersion/30%	Swellable, permeable	Sustained release

6.2 eudragit for colon specific drug delivery system

Polymers can produce a strand of constant layer across the surface of the formulation, forming a bias between the tablet core and the fluid media. To avoid early drug release/absorption before the tablet hits the colon, colonic encapsulation agents must endure the small intestine environment [39]. In addition to natural polymers in the pharmaceutical industry, synthetic coating agents are commonly utilized as film-coating materials for colon-targeted delivery. Polymethacrylate-based coating agents have been widely employed. These filming polymers, are also known commercially as Eudragit®, are synthetic both cationic and anionic polymers of dimethyl amino ethyl methacrylate, methacrylic acid, and methacrylic acid esters in different ratios [40]. Eudragit are widely used as pH-sensitive coating polymers that can provide either an enteric effect or colon targeting of drugs. Polymer utilized as a coating material for targeting colon should be capable of surviving lower pH values of the stomach & disintegration a slightly alkaline or neutral pH at the terminal ileum, especially at the ileocecal junction [41]. Eudragit L 100 and S 100 are the most frequently used Eudragit grades. Eudragit L dissolves at a pH greater than 6 and is employed for enteric coating, while Eudragit S soluble at a pH greater than 7 and is suitable for colon targeting [38]. In buffer solution at pH 7.2, pellets with Eudragit® FS30 D coating exhibited fast drug release. Since there was no drug content in plasma before the first 3-4 hours following delivery of the tested coated pellets., however in vivo investigations showed the capacity of coated pellets for medication release in the colon [42]. In association with Eudragit® RS-PO, Eudragit® FS30D has been investigated as a coating polymer for shielding and delivering nanoparticles to the colon. At pH6.8, the rate of nanoparticle release in a combination of FS-RSPO at a ratio of 0.73-05 ranged between 27.11 and89.24%, with practically the complete drug release occurring within 24 hours [43]. In some circumstances, to increase colonic medication distribution, combo of both natural and synthetic coating agents can be utilized. The polyvinyl acetate aqueous dispersion, marketed widely as Kollicoat®, was mixed with chitosan in varying proportions and then applied to pellets [44]. When a chitosan/Kollicoat® film was applied to pressure-controlled tablets, colon targeting was improved, with < 2% of the medication content expelled from the small intestines, although burst release was observed when colonic peristaltic pressure was applied [45].

7. CONCLUSION

Colon Targeted Drug Delivery System has emerged as prominent field of research in recent years. Many polymers, whereas a vast array of pharmaceutical formulations, have been explored in an attempt to withstand the harsh physic-chemical conditions of the upper GIT. Recent advances in biopolymer sciences led to the creation of several novel and efficient DDS capable of delivering better therapeutics. In terms of safety, effectiveness and patient compliance, it may provide significant advantages over conventional dosage forms. Colon Drug Delivery System is getting more popular as an effective formulation technique for improving oral bioavailability. The review shows that the use of chitosan in a Colon targeted cargo delivery system is owing to its Physical

and chemical characteristics & there is ongoing effort/research to enhance the intrinsic physical and chemical properties of chitosan to increase its applicability for more better drug delivery system. We foresee future studies into physical and chemical modifications of chitosan to facilitate macromolecule transport to the targeted area. Pectin has unique characteristics such as proteolytic enzymes, less toxic and resistance to acid medium in stomach, and the potential to successfully bind diverse molecules and complex pharmaceutical substances. As a result, they are ideal for colon targeted cargo delivery. Pectin-based drug carriers' future prospects will be homogeneous oligosaccharides with a low molecular weight that facilitate site-specific administration with rapid and entire release of medicinal substances. Eudragit is a category of synthetic polymethacrylate co-polymers that are used as a functional excipient in a wide range of dosage forms. Commercially available as powders, granules, organic solution or aqueous dispersions. These compounds are extensively employed as coating agents to achieve drug release behavior changes or taste masking. Eudragit is nontoxic synthetic polymers that provide the scope of manipulation of release profiles through the use of various grades in combination.

8. REFERENCES

1] Gopi, S., Amalraj, A., Sukumaran, N.P., Haponiuk, J.T. and Thomas, S., 2018, August. Biopolymers and their composites for drug delivery: a brief review. In *Macromolecular Symposia* (Vol. 380, No. 1, p. 1800114).

2] D. Suvakanta, N. M. Padala, N. Lilakanta, C. Prasanta, Acta. Pol. Pharm. [dnlm] 2010, 67, 217

3] S. K. Bardal, J. E. Waechter, D. S. Martin, Applied Pharm. 2011, 17.

4] J. D. Spahn, S. J. Szefler, Pediatric Respiratory Med. (2nd ed.) 2008, 219.

5] Philip AK, Dabas S, Pathak K. Optimized prodrug approach: A means for achieving enhanced anti-inflammatory potential in experimentally induced colitis. J Drug Target 2009; 17:235-241

6] Patel Parul, K., Satwara Rohan, S. and Pandya, S., 2012. Bacteria aided biopolymers as carriers for colon specific drug delivery system: A Review. *International Journal of Pharm Tech Research*, *4*, pp.1192-214.

7] Philip, A.K. and Philip, B., 2010. Colon targeted drug delivery systems: a review on primary and novel approaches. *Oman medical journal*, *25*(2), p.79.

8] Prajapati, S.K., Jain, A., Jain, A. and Jain, S., 2019. Biodegradable polymers and constructs: A novel approach in drug delivery. *European polymer journal*, *120*, p.109191.

9] Hasnain, M.S., Ahmed, S.A., Alkahtani, S., Milivojevic, M., Kandar, C.C., Dhara, A.K. and et al., 2020. Biopolymers for drug delivery. In *Advanced biopolymeric systems for drug delivery* (pp. 1-29). Springer, Cham.

10] Raza, M., Jayswal, M.G., Ahmed, A., Majaz, Q. and Khan, G.J., 2022. REVIEW ON GASTRO RETENTIVE DRUG DELIVERY SYSTEM.

11] Li, S., Zhang, H., Chen, K., Jin, M., Vu, S.H., Jung, S., and et al., 2022. Application of chitosan/alginate nanoparticle in oral drug delivery systems: prospects and challenges. *Drug Delivery*, *29*(1), pp.1142-1149.

12] Kurakula, M., Gorityala, S. and Moharir, K., 2021. Recent trends in design and evaluation of chitosan-based colon targeted drug delivery systems: Update 2020. *Journal of Drug Delivery Science and Technology*, *64*, p.102579.
13] Cui, M., Zhang, M. and Liu, K., 2021. Colon-targeted drug delivery of polysaccharide-based nanocarriers for synergistic treatment of inflammatory bowel disease: A review. *Carbohydrate Polymers*, *272*, p.118530.
14] Feng, K., Wei, Y.S., Hu, T.G., Linhardt, R.J., Zong, M.H. and Wu, H., 2020. Colon-targeted delivery systems for nutraceuticals: A review of current vehicles, evaluation methods and future prospects. *Trends in Food Science & Technology*, *102*, pp.203-222.
15] Johansson, M.E., 2013. Sjövall H.., Hansson GC. The gastrointestinal mucus system in health and disease. *Nat Rev Gastroenterol Hepatol*, *10*(6), pp.352-361.
16] Chen, S., Zhu, H. and Luo, Y., 2022. Chitosan-based oral colon-specific delivery systems for polyphenols: Recent advances and emerging trends. *Journal of Materials Chemistry B*.
17] Lee, S.H., Bajracharya, R., Min, J.Y., Han, J.W., Park, B.J. and Han, H.K., 2020. Strategic approaches for colon targeted drug delivery: an overview of recent advancements. *Pharmaceutics*, *12*(1), p.68.
18] Casadidio, C., Peregrina, D.V., Gigliobianco, M.R., Deng, S., Censi, R. and Di Martino, P., 2019. Chitin and chitosans: Characteristics, eco-friendly processes, and applications in cosmetic science. *Marine drugs*, *17*(6), p.369.
19] S.M. Ahsan, M. Thomas, K.K. Reddy, S.G. Sooraparaju, A. Asthana, I. Bhatnagar, Chitosan as biomaterial in drug delivery and tissue engineering, Int. J. Biol. Macromol. 110 (2018) 97–109.
20] Birolli, W.G., de Moura Delezuk, J.A. and Campana-Filho, S.P., 2016. Ultrasound-assisted conversion of alpha-chitin into chitosan. *Applied Acoustics*, *103*, pp.239-242.
21] Bakshi, P.S., Selvakumar, D., Kadirvelu, K. and Kumar, N.S., 2020. Chitosan as an environment friendly biomaterial–a review on recent modifications and applications. *International journal of biological macromolecules*, *150*, pp.1072-1083.
22] Nilsen-Nygaard, J., Strand, S., Vårum, K. and Draget, K., 2015. et Nordgård, C. *Chitosan: Gels and Interfacial Properties. Polymers*, *7*(3), pp.552-579.
23] Park, J.K., Chung, M.J., Choi, H.N. and Park, Y.I., 2011. Effects of the molecular weight and the degree of deacetylation of chitosan oligosaccharides on antitumor activity. *International journal of molecular sciences*, *12*(1), pp.266-277.
24] Yaneva, Z., Ivanova, D., Nikolova, N. and Tzanova, M., 2020. The 21st century revival of chitosan in service to bio-organic chemistry. *Biotechnology & Biotechnological Equipment*, *34*(1), pp.221-237.
25] Sandri, S.R.G., Bonferoni, M.C., Ferrari, F., Mori, M. and Caramella, C., 2012. The role of chitosan as a mucoadhesive agent in mucosal drug delivery. *Journal of drug delivery science and technology*, *22*(4), pp.275-284.
26] Collado-González, M., González Espinosa, Y. and Goycoolea, F.M., 2019. Interaction between chitosan and mucin: Fundamentals and applications. *Biomimetics*, *4*(2), p.32.

27] Szymańska, E. and Winnicka, K., 2015. Stability of chitosan—a challenge for pharmaceutical and biomedical applications. *Marine drugs*, *13*(4), pp.1819-1846.
28] Bratovcic, A., 2022. Application of Natural Biopolymers and its Derivatives as Nano-Drug Delivery Systems in Cancer Treatment: https://doi. org/10.54037/WJPS. 2022.100209. *World Journal of Pharmaceutical Sciences*, pp.232-242.
29] Khotimchenko, M., 2020. Pectin polymers for colon-targeted antitumor drug delivery. *International journal of biological macromolecules*, *158*, pp.1110-1124.
30] 21CFR184.1588. CFR - Code of Federal Regulations Title 21
31] J. Wisniak, Rev. CENIC Cienc. Quím. 38 (2007) 345–355
32] Jakóbik-Kolon, A., Mitko, K. and Bok-Badura, J., 2017. Zinc sorption studies on pectin-based biosorbents. *Materials*, *10*(7), p.844.
33] Khotimchenko, M.Y., Kolenchenko, E.A. and Khotimchenko, Y.S., 2008. Zinc-binding activity of different pectin compounds in aqueous solutions. *Journal of Colloid and Interface Science*, *323*(2), pp.216-222.
34] Jin, M., Kalainy, S., Baskota, N., Chiang, D., Deehan, E.C., McDougall, C., and et al., 2019. Faecal microbiota from patients with cirrhosis has a low capacity to ferment non-digestible carbohydrates into short-chain fatty acids. *Liver International*, *39*(8), pp.1437-1447.
35] Juloski, J.T., Rakic, A., Ćuk, V.V., Ćuk, V.M., Stefanović, S., Nikolić, D., and et al., 2020. Colorectal cancer and trace elements alteration. *Journal of Trace Elements in Medicine and Biology*, *59*, p.126451.
36] Dahm, C.C., Keogh, R.H., Lentjes, M.A., Spencer, E.A., Key, T.J., Greenwood, D.C., and et al., 2010. Intake of dietary fats and colorectal cancer risk: prospective findings from the UK Dietary Cohort Consortium. *Cancer epidemiology*, *34*(5), pp.562-567.
37] Sardou, H.S., Akhgari, A., Garekani, H.A. and Sadeghi, F., 2019. Screening of different polysaccharides in a composite film based on Eudragit RS for subsequent use as a coating for delivery of 5-ASA to colon. *International Journal of Pharmaceutics*, *568*, p.118527.
38] Thakral, S., Thakral, N.K. and Majumdar, D.K., 2013. Eudragit®: a technology evaluation. *Expert opinion on drug delivery*, *10*(1), pp.131-149.
39] Sharma, S., Jyoti, K., Sinha, R., Katyal, A., Jain, U.K. and Madan, J., 2016. Protamine coated proliposomes of recombinant human insulin encased in Eudragit S100 coated capsule offered improved peptide delivery and permeation across Caco-2 cells. *Materials science and engineering: c*, *67*, pp.378-385.
40] Patra, C.N., Priya, R., Swain, S., Jena, G.K., Panigrahi, K.C. and Ghose, D., 2017. Pharmaceutical significance of Eudragit: A review. *Future Journal of Pharmaceutical Sciences*, *3*(1), pp.33-45.
41] Basit, A.W., 2005. Advances in colonic drug delivery. *Drugs*, *65*(14), pp.1991-2007.
42] Gao, C., Huang, J., Jiao, Y., Shan, L., Liu, Y., Li, Y. and Mei, X., 2006. In vitro release and in vivo absorption in beagle dogs of meloxicam from Eudragit® FS 30 D-coated pellets. *International journal of pharmaceutics*, *322*(1-2), pp.104-112.

43] Hales, D., Vlase, L., Porav, S.A., Bodoki, A., Barbu-Tudoran, L., Achim, M. and et al., 2017. A quality by design (QbD) study on enoxaparin sodium loaded polymeric microspheres for colon-specific delivery. *European Journal of pharmaceutical sciences*, *100*, pp.249-261.
44] Maroni, A., Del Curto, M.D., Zema, L., Foppoli, A. and Gazzaniga, A., 2013. Film coatings for oral colon delivery. *International journal of pharmaceutics*, *457*(2), pp.372-394.
45] Drechsler, M., Garbacz, G., Thomann, R. and Schubert, R., 2014. Development and evaluation of chitosan and chitosan/Kollicoat® Smartseal 30 D film-coated tablets for colon targeting. *European.*