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COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT:

The colon drug delivery system is a type it is classified under the sustain or controlled drug delivery system. CDDS is defined as the wanted pharmacological (or) therapeutical action at the required site of colon in case of disease like chron's disease, IBS (Inflammatory Bowel Syndrome) etc.

Colon Targeted drug delivery system is utilized for the therapeutical, action at the site. In the review, mentioned the total anatomy of colon and physiological functions of colon. The following contents consist of the colon diseases and disorders in detail. This review project, consist of different types of drug carriers of the colon targeted drug delivery system. In this review project we are studied about the different approaches and different types of evaluated studies. In this review, mentioned different types of the marketed colon targeted drug delivery dosage forms.

In this review project, we discussed about the limitations, need, advantages and disadvantages of the colon targeted delivery system. Colon targeted delivery system is evaluated by using different evaluated in-vitro studies. There are two different types of marketed drug formulations of CDDS; it is a type of controlled drug delivery system.

INTRODUCTION:

Colon is the largest segment of the large intestine it is a one of the long Tube of the large intestine. The entire colon length is about 5 Feet (150 cm) long and divided into 5 major segments [1]. The colon contains the highest microbial density of the human body between 300 to 1000 different species [2], and 99 % of gut bacteria are come from about 30 or 40 key species [3]. In that up to 60 % of dry mass of feces is bacteria and 99 % of the bacteria in the gut are anaerobes. But in cecum aerobic bacteria reaches high densities. Colon is divided into four parts (proximal to distal) [4][5][6].

- Ascending Colon
- Transverse Colon
- Descending Colon
- Sigmoid Colon

ANATOMY:

S.NO	MAIN PART	SUB PART	PH(18-20)
1	Stomach		1to2
2.1	Small intestine	Proximal small intestine	6.5
2.2		Distal small intestine	7.5
3	Large intestine		
3.1		Ascending colon	5.7
3.2		Transverse colon	6.6
3.3		Descending colon	7.0

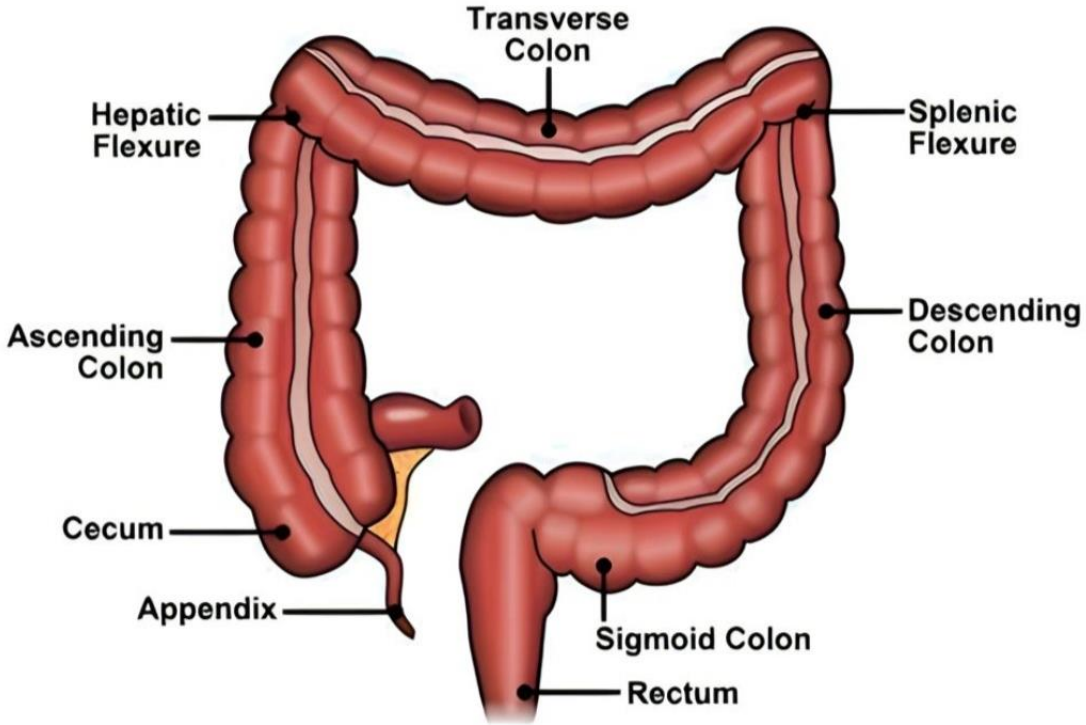


Fig: 1

ANATOMY OF COLON

ASCENDING COLON:

The colon begins as the ascending colon a retroperitoneal structure meets the right lobe of the liver. The ascending colon is around 15 cm long. It rises from the hepatic flexure level, running beside the psoas muscle and in front of the iliacus, quadratus lumborum, and the lower pole of the right kidney. The ascending colon is devoid of peritoneum which is instead replaced by areolar tissue resulting from an embryologic process of fusion of the mesentery to the posterior parietal peritoneum. In the lateral peritoneal reflection this process is represented by the white line of which is more evident at the descending sigmoid junction. This line serves as a guide for the surgeon when the ascending, descending colon is mobilized [7].

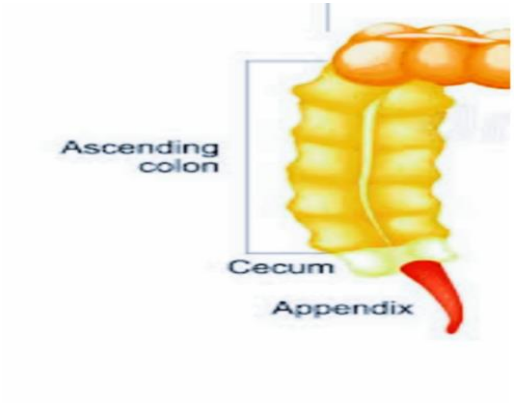


Fig: 2 ASCENDING COLON

TRANSVERSE COLON:

Transverse colon extends from the right colic flexure to the spleen It turns another 90 degrees to point inferiorly. Transverse colon has its own mesentery known as the transverse mesocolon.

It is approximately 45 cm long which is the longest segment at the largest bowel. It crosses the abdomen with an inferior curve immediately caudad to the greater curvature of stomach. The transverse colony is relatively fixed as each flexure and in between it is suspended by a 10 to 15 cm wide area which provides variable motility.

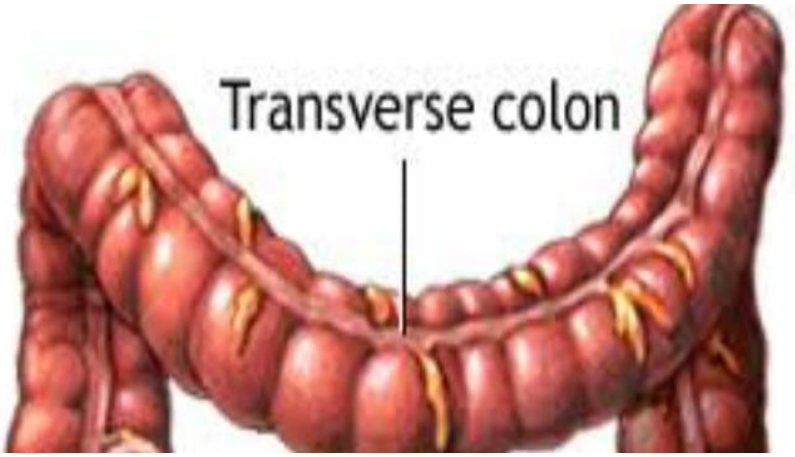


Fig: 3 TRANSVERSE COLON

DESCENDING COLON:

Begins at the left colic flexure and ends by becoming continues with sigmoid colon at the pelvic brim. The descending colon travels from the bend near the spleen to the lower edge of the true pelvis, spanning about 25 centimeters. The descending colon is covered by peritoneum only on its lateral and anterior aspects. Posteriorly it Rest directly against the left kidney and quadratus, lumtorum and transvers abdomen is muscle. However the descending colon is narrower and more dorsally situated than ascending colon.

Fig: 4 DESCENDING COLON

SIGMOID COLON:

Begins where descending colon passes inform of the pelvic brim it hangs down into the pelvic cavity in the form of a loop it is attached to the posterior wall of the pelvis by a fan shaped fold of peritoneum known as sigmoid mesocolon. The sigmoid colon is commonly a 35- to 45-cm-long, mobile, omega -shaped loop completely invested by peritoneum; however, it varies greatly in length and configuration. The mesosigmoid connects to the pelvic walls in a shape resembling an inverted V, situated within a depression called the intersigmoid fossa. The fossa directly overlies the left ureter and is crossed on its front side by the spermatic, left colic and sigmoid vessels [8].

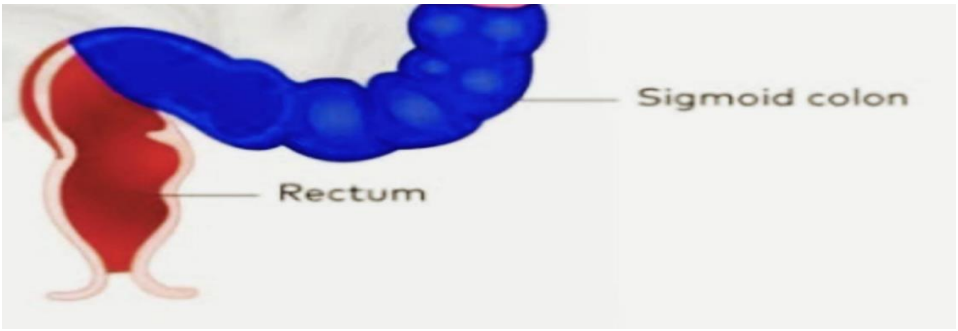


Fig: 5 SIGMOID COLON

TYPES OF DISEASES:

TARGEGT SITE	DISEASE CONDITIONS	DRUG AND ACTIVE AGENT
Topical action	Inflammatory Bowel diseases, Irritable bowel disease. Chronic pancreatitis.	Hydrocortisone Prednisolone, Olsalazine, Mesalazine
Local action	Pancreatactomy and Cystic fibrosis, colorectal cancer	Digestive enzymes supplements 5-flurouracil.
Systemic action	To prevent gastric irritation to prevent first pass metabolism of orally ingested drugs oral delivery of vaccines	NSAIDS Steroids Insulin Typhoid

TARGATED DRUG DELIVERY SYSTEM:

Targeted Drug Delivery System is also known as smart delivery system. It means if the positive medication is administered to a patient, the concentration of medication in some portions of the body is higher than others. This method of delivery is mostly based on nano medications. This nano medicine contains nanoparticles.

This would be drug loaded of the body with diseased tissues and avoiding interactions with healthy tissues. The purpose of targeted drug delivery system is to extent localize, target and have safe medication contact with sick tissues [9].

To maximize the effectiveness of regeneration methods, targeted drug delivery system have been developed. The technology is based on to technique that delivers a specific amount of a therapeutic art to specific portions of the targeted diseased areas. This helps in maintain the proper plasma and tissue drug levels in the body. The drug delivery system is highly inter connected and requires various disciplines, such as chemist biologist and engineers.

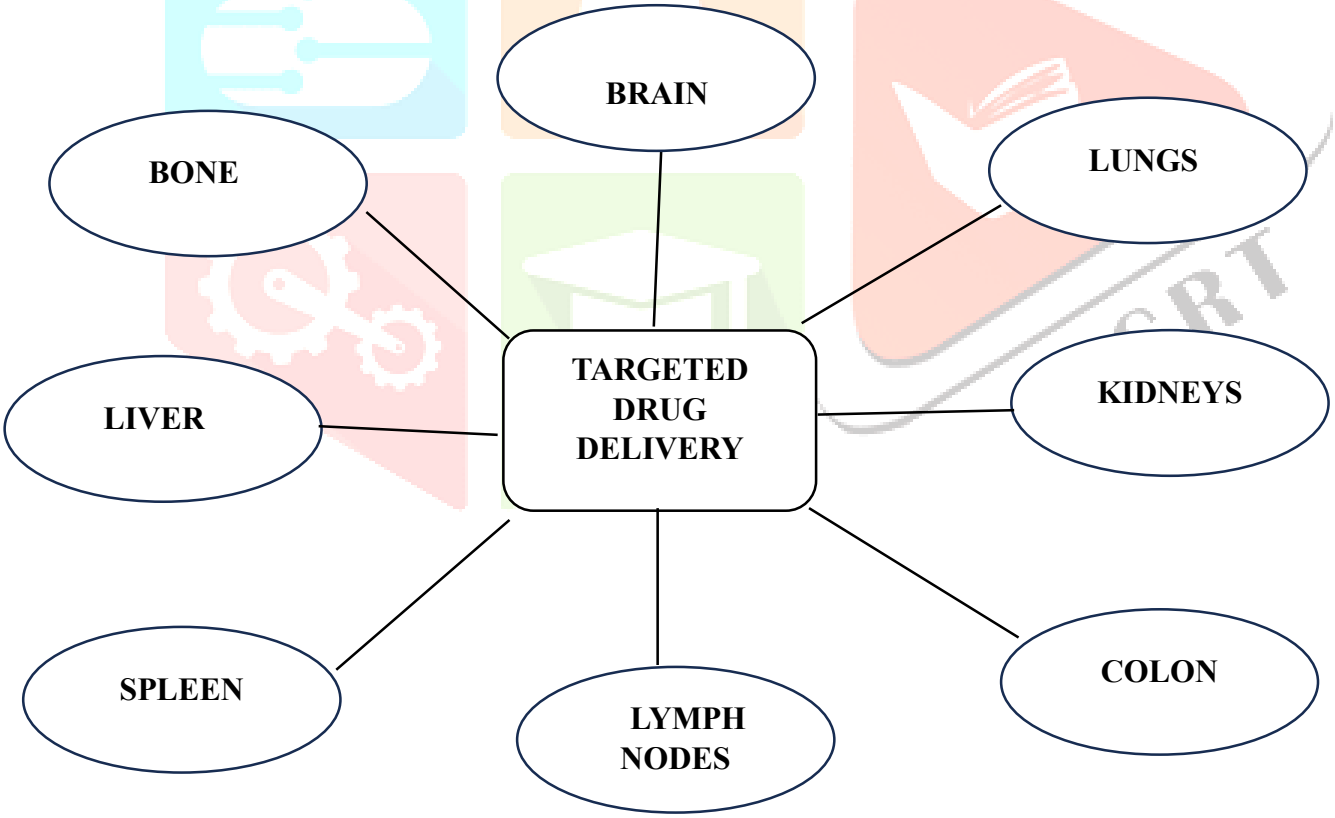
The 4 main key requirements of an effective drug delivery system are Retain evade, target and release. The main advantage of this system or technique has been the reduction in dose and side effect of the drug [10].

ADVANTAGES:

- ❖ The drug administration protocol is simplified.
- ❖ Avoid the first pass effect.
- ❖ The drug toxicity is reduced by targeting a specific enzyme or site.
- ❖ A small dose can achieved desired pharmacological effects.
- ❖ Drug absorption is improved on target site [11].

DISADVANTAGES:

- ❖ Hence dissolution is problem for water soluble drugs.
- ❖ Immune responses may be triggered by the carrier of the targeted drug mechanism.
- ❖ Drug deposition at the target location may cause toxicity.
- ❖ Some micro flora may degrade the drug.
- ❖ In-vitro In-vivo correlation is poor [12].



TYPES OF TARGETED DRUG DELIVERY SYSTEM:

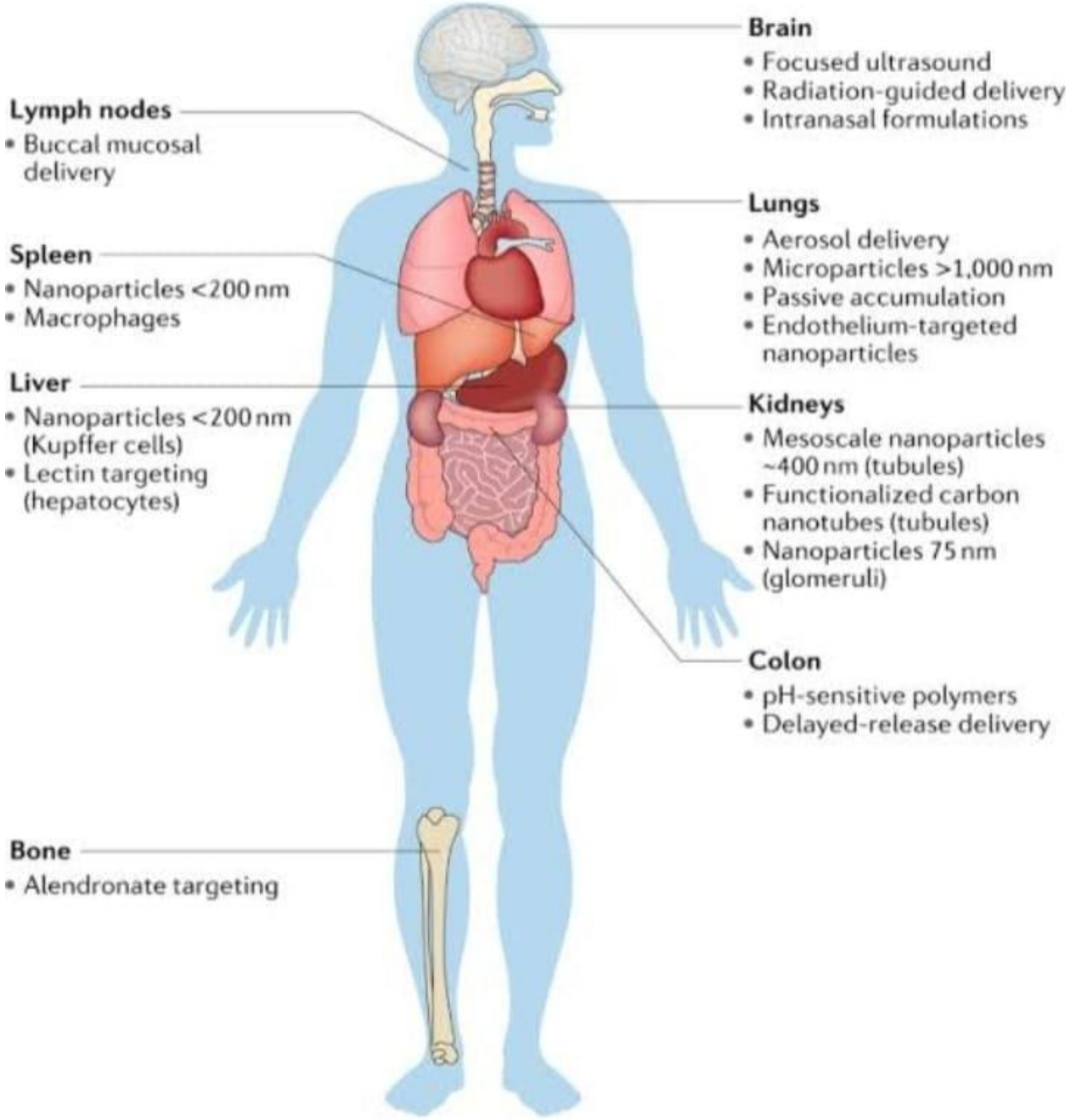


Fig: 6

DIFFERENT TYPES OF CARRIERS APPLIED FOR DRUG TARGETING:

There are plenty of carriers adapted in targeting drug delivery system as shown by

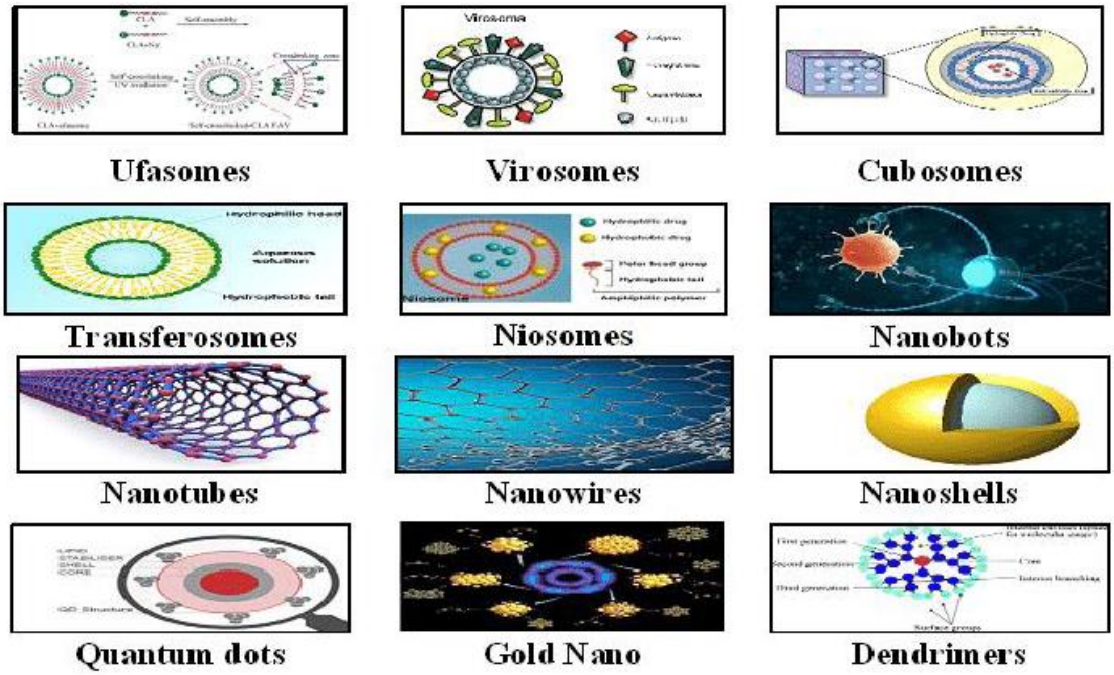


Fig: 7

TRANSFEROSOMES:

They are such extreme unique vesicular drug delivery system. Transferosomes are self- optimizing, self-regulating, ultra deformable, ultra flexible devices. It can penetrate into the skin efficiently by squeezing themselves through pores times less than their diameter [13].

- **VIROSOMES:**

Drug delivery system described as single lamellar vesicle prepared from phospholipids. The surface of virosomes contains sides to which virus delivered glycoprotein attached to facilitate the recognition and targeting of virosomes to the target site inside the body.

- **CUBOSOMES:**

They are nano structured drug delivery systems prepared from certain lipids. They are liquid crystalline with cubic structure that are appropriate for injection.

- **NANOBOTS:**

It is a novel technology of drug delivery system. They are in 10^-9 M in diameter nanoscale machine.

- **DENDRIMERS:**

They are nanoparticles that have a particular diameter. They are assembled of a control core enclosing by a polymer layer [14].

- **NANOWIRES:**

It is a wire having very fine diameter made of metal and other organic compounds. It owns a broad surface area this system can treat Parkinsonism and other diseases.

- **GOLD NANOPARTICLES:**

Gold nanoparticles are used by the scientists to establish drastic- sensitive detection systems for DNA and the hydrophilic and lipophilic characters.

- **NANO TUBES:**

Nanotubes are a type of drug delivery system. It is a halo cylindrical tube made of carbon they are usually used for the delivery of drug to cancer cells [15].

- **QUANTUM DOTS:**

They are nanocrystalline semi – conductor particles that allow them to be employed tumor imaging. This carrier is efficient for delivering cancer medicines.

- **NIOSOMES:**

They are nano- ionic surfactant vesicles have ability of encapsulating both hydrophilic and lipophilic drugs because of the natural criteria of phospholipids niosomes or extra stable then liposomes. They are effective in targeting anticancer, anti-inflammatory, anti-bacterial and antifungal [16].

COLON TARGETING DRUG DELIVERY SYSTEM:

Drug delivery to the colon is a medically desirable and helpful method in a range of illness colon is a favorable site for both local and systemic administration. Colon targeting has good healing power (therapeutic potential) for local action in number of diseases including irritable bowel syndrome, and colon cancer.

Amino salicylate corticosteroids, immune suppressive agents, cationized antioxidant enzymes, genetically engineered bacteria, cytokines, probiotics, nicotine and other drugs have been successfully tested and improved efficacy when delivered to the colon in splendid isolation [17].

Colon specific drug delivery system (CDDS) should be capable of protecting the drug enroute of the colon, Which means drug released and absorption should not occur in the stomach or small intestine and bioactive agent should not be degraded in either dissolution site, but only released and absorbed once the system reaches to the colon [18]. Although the oral route is the most convenient and preferable additional CDDS methods can be employed the quickest way to deliver medications to the colon is rectal administration however rectal administration makes it complicating to reach the proximal section of the colon. This type of administration can also be painful for patients and compliance may be low [19].

Drug reparation for intrarectal administration is available in the form of liquid form and suppositories. Intra rectal is utilized for systemic dosage as well as the delivery of topically active drugs to large intestine [20]. Human colon contains about (400 unit) types of bacteria as resident flora, density up to 1010 bacteria per gram of colonic gut gram of colonic contents through gut bacteria azoreduction and enzymatic cleavage i.e., glycosides [21].

NEED FOR COLON TARGETING DRUG DELIVERY:

- Drug distribution to the colon is targeted to provide direct treatment at the illness site (local delivery), reduced dose, and fewer systemic side effects.
- A site – specific or targeted drug delivery system would be beneficial.
  Allow peptide and protein medications to be administered only.
  A product tailored to the colon could also be employed.
- A targeted drug delivery system for the colon is seen as advantageous in treating colon ailments.
- The colon presents an opportunity for achieving either local or systemic drug delivery particularly for treating inflammatory bowel diseases topically. E.g. Ulcerative colitis or crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulfasalazine.
- A number of others serious diseases of colon. E.g.Colorectal cancer could potentially be treated more effectively as well [22].

ADVANTAGES:

- Reduces the frequency of dosing, resulting in decreased drug cost.
- The colon is an attractive site poorly absorbed drug molecule.
- Reduce the gastric irritation generated or promoted by several medications.
- Targeted drug delivery system.
- Better patient compliance.
- By pass initial first pass metabolism
- Activity extending into both daytime and nighttime [23].

DISADVANTAGES:

- Low dose frequency.
- Higher need of excipients.
- Absence of manufacturing reproducibility and efficacy.
- Several formulation steps are needed.
- Advanced technology should need.
- Variability in transit time.
- Patient compliance [24].

LIMITATIONS OF COLON TARGATED DRUG DELIVERY SYSTEM:

The improvement of colon specific drug delivery system is connected with specific limitations:

- Multiple manufacturing steps.
- Drug release is incomplete.
- Drug bioavailability may be low due to potentially binding of drug in a nano specific way.
- More prodrugs are new chemical entities and need a large amount of evaluation before being used as a carrier.
- To reach the targeted site an orally administered dosage form must travel the length of alimentary canal [25].
- Colon is located in the distal region of the gastro intestinal tract which presents a significant and a visible barrier.
- These barriers can block the ability and efficient transport of medicine to the colon.
- Low volume of colonic luminal fluid having higher viscosity and neutral PH.
- Extensive interactions of the drug with colonic content.
- Bioavailability of the drug may be low [26].

DIFFERENT APPROACHES USED FOR COLON TARGETING:

1. Primary techniques of colon specific drug delivery:

a. PH sensitive polymer layered drug delivery system.

b. Delayed (Time controlled release system) release drug delivery system.

c. Microbial triggered system.

d. Pro- drug strategy for drug delivery to colon.

e. Polysaccharide based delivery system.

2. Newly developed approaches for CDDS.

a. Pressure controlled drug – delivery system.
b. Pulsatile colon targeted drug delivery.
    1. Pulsin Cap system.
    2. Port system.
c. CODES technology.

d. Osmotic controlled drug delivery (ORSO- CT).
e. Multi particulate system based drug delivery.
f. AZO hydrogel.
g. Probiotic approach.

1. PRIMARY TECHNIQUES OF COLON SPECIFIC DRUG DELIVERY:

a. PH sensitive polymer layered drug delivery system: Many different methods of invention have been found to create PH differences in the colon. The GI tract is one of the main approach to achieve colon targeting numerous strategies have been discovered to achieve colon medication targeting the most common procedures involve while coating the formulation with a natural or artificial polymer. The API and excipients make up the basic formulation derivatives of cellulose and acrylic acid are the most widely used PH dependent polymers.

b. Delayed release drug delivery system (Time controlled release system): A very promising drug release technique is the controlled release system. This includes dose forms with sustained or delayed release. The goal of time release system design is to withstand the PHs acidic environment of the stomach usually a lag time of 5 hours is sufficient for the time needed for the colon to transit from the mouth since small intestine is about 3-4 hours which is relatively constant.

c. Microbial triggered system: Various targeting of drugs of various colonic disease microbial triggered delivery systems is most convenient and highly site approach for targeting drug to the colon than all targeting system. The upper part of GIT i.e. the stomach and duodenum has a micro flora of colon on the other side 10^3-10^4 CFU/ml. The micro flora of colon on the other side is in range of 10^11- 10^12 CFU/ml consisting mainly of anaerobic bacteria. EX: Bactericides, Bifid bacteria, Eubacteria.

d. Pro drug strategy for drug delivery to colon: These are chemical derivatives lacking pharmacological activity, which can temporarily modify the physicochemical properties of a drug. Pro drug is the main approach of microbial triggered drug delivery system. Bio transformation is carried out by a variety of enzymes are azoreductase galactosidase, nitroreductase generally; a pro drug is successful as a colon carrier of its hydrophilic and bulky to minimize absorption from the upper GI tract.

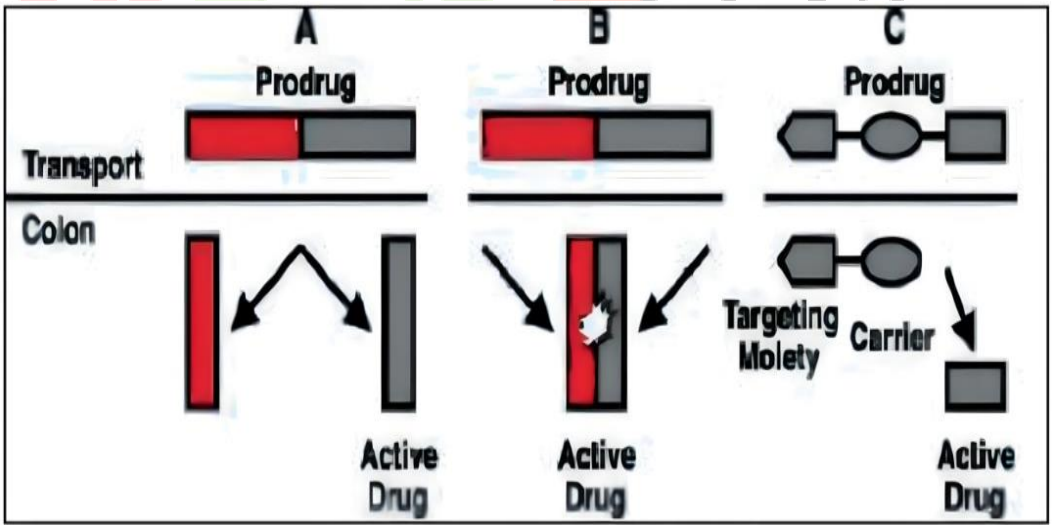


Fig: 8

e**. Polysaccharide based delivery system:** The other type of microbial induced drug delivery system is based on polysaccharide. Certain GIT enzymes have inability to digest certain polysaccharide as it is taken as an advantage to develop colon specific drug delivery system the substance is integrated into the matrix core by squeezing the biodegradable polymer. These are many naturally occurring polysaccharides like guar gum, pectin, dextran and chondroitin sulphate have their roots in basis of investigation for their potential in innovating colon specific drug delivery they can be easily modified chemically and biochemically. These

polysaccharides are highly stable safe, non-toxic and hydrophilic. In order to develop drugs that target the colon, the use if naturally, occurring polysaccharides is receiving a lot of interest. Since these polymers are found in abundance, have wide availability and inexpensive [27].

2. NEWELY DEVELOPED APPROACHES FOR CDDS:

a. Pressure controlled drug – delivery system: The pressure controlled drug delivery system has been developed to address the challenges of peristalsis in the colon, which results in higher pressures. The system consists of a capsule with a drug inside, coated with a water-insoluble polymer like ethyl cellulose. The drug is introduced into the capsule and the suppository base dissolves the water from the intestine, increasing the viscosity and pressure. The capsule is then expelled into the colon, avoiding second-time dosing. The lag time is controlled by coating thickness, and the drug is released at the desired location. Swellable hydrogels have shown good correction in lag time in-vitro experiments. CODES technology, a combination of PH-dependent released polymers, has been designed to overcome problems with HPMC, poly methacrylate, and polyvinyl-associated system. The drug release is controlled by the length and point of intersection of the capsule.

b. PULSATILE COLON TARGETED DRUG DELIVERY:

1. Pulsin cap system: Pulsin cap system is one of the fine methods acquiring through colon targeted drug delivery systems. The system consists of a water insoluble capsule body containing the drug a hydrogel plug which seals the opened end of this capsule body and a water soluble cap which covers hydrogel plug. In addition with the capsule is coated with an acid insoluble film coating which prevents the drug from being released in stomach. The hydrogel seal begins and enlarge when this enteric coating dissolves in the small intestine. A study found that no significant drug release occurred within 5 hours from the start of experiment and it was concluded that this modified pulsing cap system can successfully target metronidazole in to the colon [28].

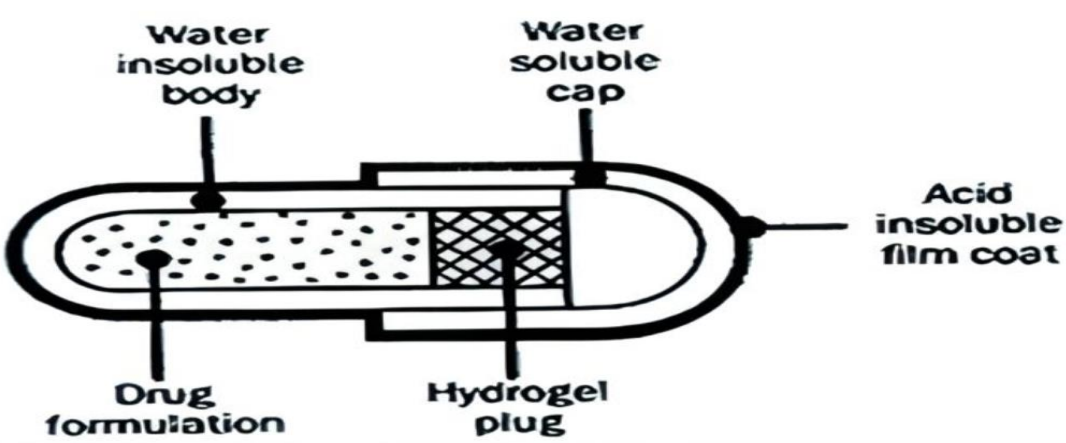


Fig: 9

2. Port system: The port system is a therapeutic system is a therapeutic system that expels the drug into the colon through a capsule coated with a semi- permeable membrane. Inside the capsule is an insoluble plug, which is expelled after a lag time. This system is developed for school children during daytime and avoids second- time dosing.

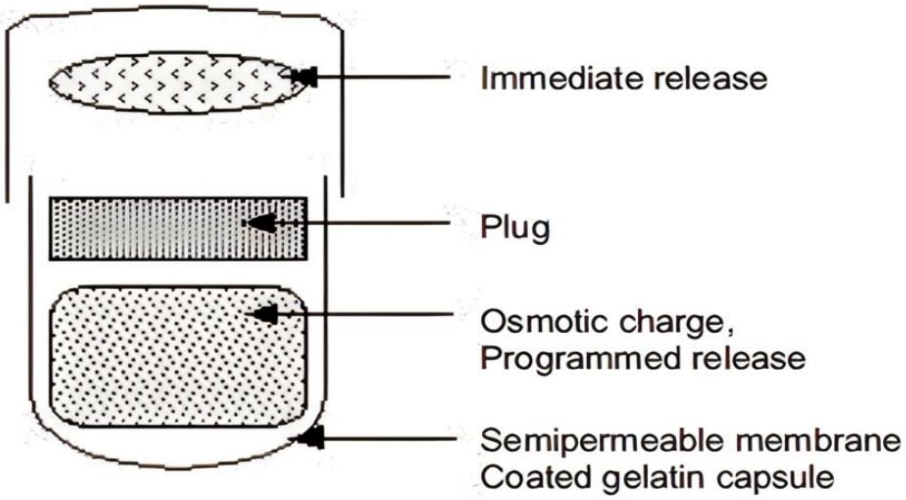


Fig: 10

c. CODES technology:

Swellable hydrogels have shown good correction in lag time in in-vitro experiments and have been used in in-vivo experiments in humans. CODES technology, a combination of PH-dependent released polymers, was designed to overcome problems with HPMC, polymethyl methacrylate, and polyvinyl- associated systems. The log time is microbial triggered, controlled by the length and point of intersection of controls the drug release at the desired location.

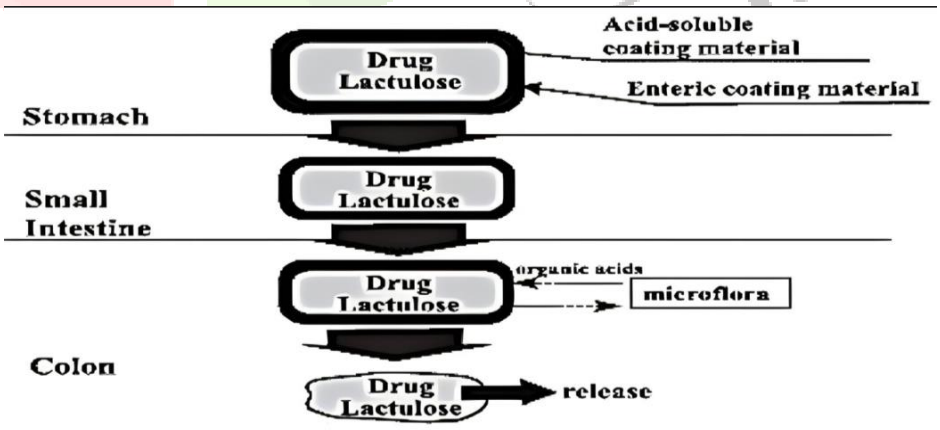


Fig: 11

d**. Osmotic controlled drug delivery (OROS-CT):** Osmotic controlled delivery system although the concept of osmotic controlled drug delivery has been around for several years.

In the past 10 to 15 years, the utilization of this technology in crafting oral dosage forms specific to the colon has become increasingly popular. The OROS – CT is an example of a system controlled by osmotic pressure.

It consists of a hard gelatin capsule which dissolves in PH of small intestine and allows water to enter the unit. This then causes it to swell and drug is forced out these are about 5 – 6 units in each capsule and each unit is surrounding by a drug impermeable enteric coating which prevents water from entering in acidic environment of stomach. There is a semipermeable membrane which encompasses an osmotic push compartment as well as drug compartment the water causes the compartment to swell and forms get in drug compartment. The drug's outflow rate is controlled on the rate of water influx.

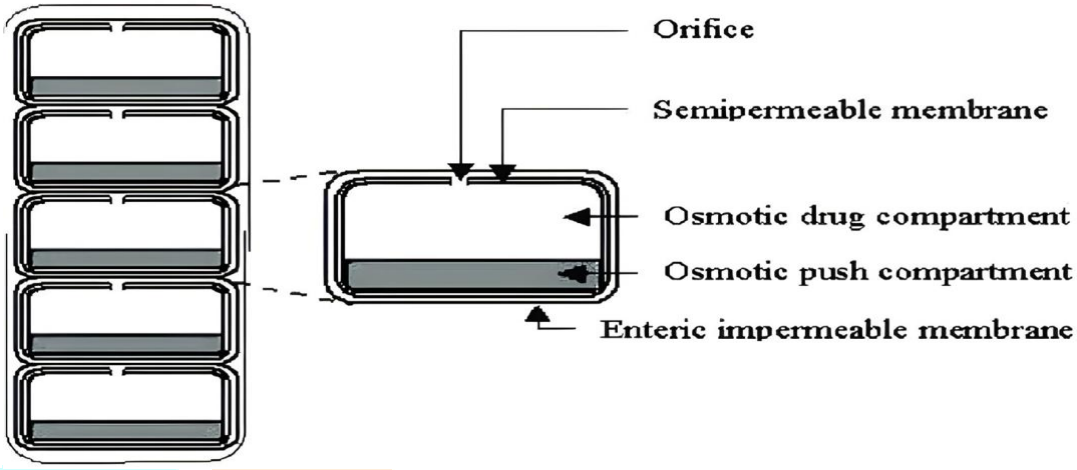


Fig: 12

e. Multi particulate system based drug delivery: Multi particulate systems have a smaller particle size compared to single unit systems, and studies have shown that they can studies have shown that they can reach colon more quickly since they pass through GI tract more easily microspheres are one of the examples of multi particulate system that can be coated with a drug far colonic delivery, microsphere that are prepared using biodegradable components can be taken up by macrophages Vaidya all developed a multi particulate system in which microsphere of polysaccharide pectin were coated with a PH sensitive polymer, eudragit. The in – vitro drug release studies showed that no metronidazole was released at acidic PH of the stomach. Metronidazole release was notably enhanced in the presence of rat caecal contents, suggesting that this system is not only pH-sensitive but also biodegradable. The in-vivo evaluation of colon targeting and prepared budesonide microspheres effectively delivered budesonide to colon in high concentrations.

f. AZO hydrogen's: The colon specificity is produced by the hydrogels PH sensitive monomers and azo cross linking agents. These hydrogels inflate as the PH rises in their journey through GIT. This swelling of hydrogels cleaves the cross connections in the hydrogel network, allowing drug contained in the hydrogel to be released. These hydrogels are created by cross- linking N-substituted (Meth) acrylamides, N-tert-butyl acrylamide, and acrylic acid with 4, 4-di (methacryloylamino) azobenzene".

g. Probiotic approach: The colon contains many species of anaerobic bacteria which obtain their energy by fermenting substrates such as polymers which have not yet been digested bacteriods, eubacteria, enterococci and enterobacteria are some examples for colon specific species and they produce numerous enzymes such as glucuronidase , xylosidase , nitro reductase and azoreductase to ferment these polymers. Polymeric used in development of CDDS can be chemically modified and this modification can influence the eluent of enzymatic degradation [29].

EVALUATION:

❖ **In – vitro evaluation:**

There is no standardized evaluation technique for CDDS because an appropriate in vitro model should include GIT conditions such as PH, volume, stirring, bacteria enzymes, enzyme activity, and other dietary components. In general, these parameters are impacted by nutrition and physical stress, making it challenging to develop a conventional in vitro model. The in vitro evaluation of colon focused drug delivery systems involves a dissolution study and an enzymatic test.

1. **Test for In-Vitro Dissolution:** The traditional basket method is used for dissolving testing. Dissolution testing is performed in several buffers to evaluate the behavior of the formulation at various PH levels. The diverse media employed for colon targeted drug delivery dissolution testing are PH 1.2 to stimulate stomach fluid, PH 6.8 to replicate small intestine, and PH 7.4 to model large intestine. The colon focused drug delivery is assessed for two hours in 0.1N HCl, three hours in PH 6.8 phosphate buffer, and finally for two hours in PH 7.4 phosphate buffer. Buffers of the aforementioned PH are being created in order to analyze the colon focused medication delivery system.

S.NO	MAIN PART	SUB PART	PH(18-20)
1	Stomach		1to2
2.1	Small intestine	Proximal small intestine	6.5
2.2		Distal small intestine	7.5
3	Large intestine		
3.1		Ascending colon	5.7
3.2		Transverse colon	6.6
3.3		Descending colon	7.0

2. In-vitro enzymatic test:

The in vitro enzymatic test consists of two tests. The carrier drug system is cultured in a fermenter containing bacteria- friendly media. The amount of medicine released at various time periods is calculated. The drug release investigation is carried out in a buffer medium containing pectinase, dextranase, or rat, guinea pig, or rabbit cecal contents. The amount of medicine released in a given time is directly related to the rate of breakdown of the polymer carrier.

❖ **In-vivo evaluation test:**

The CDDS is evaluated in vivo in dogs, guinea pig, and pigs since their anatomic and physiological conditions are similar. The distribution of different enzymes in the GIT of rats and rabbits is comparable to that oh humans [30].

COLON DISEASE / DISORDER	DRUGS	DELIVERY SYSTEM
Inflammatory bowl disease	Mesalazine	
Ulcerative colitis	Asacol®	DR tablets
Chron's Disease	-Pentasa®	TR capsules
	Sulfasalazine	
	-Azulfidine EN-tabs®	DRtablets
	Prednisone	
	-Rayos®	DR tablets
	Budesonide	
	-MMX	Multi-matrix tablets
	-Uceris ®	ER tablets
	-Clipper®	Gastro- resistant prolonged -release tablets
	Prednisolone[colal-pred®]	Oral colon -targeted pellets
	Metronidazole [Flagyl® ER]	ER tablets
	Azathioprine [azasan®]	IR tablets
	Mercaptopurine [purinethol®]	IR tablets
	Cyclosporine [gengraf®]	IR capsules, Oral solutions
Diverticulosis And Diverticulitis	Methylcellulose [Citrucel®]	Oral powders, IR tablets
	Psyllium [Metamucil®]	Oral powders, IR capsules
	Mesalazine [asacol®]	DR tablets
	Rifaximin [xifaxan®]	IR tablets
Colonic amoebiasis	Doxycycline [doryx®]	DR tablets
	Metronidazole [flagy ER®]	ER tablets
Irritable bowl syndrome	Methylcellulose [Citrucel®]	Oral powders, IR tablets
	Psyllium [Metamucil®]	Oral powders, IR capsules
	Loperamide [Imodium®]	IR capsules
	Dicyclomine [bentyl®]	IR tablets IR capsules
	Hyoscyamine [levbid®]	ER tablets
	Lubiprostone [Amitiza®]	Soft gelatin IRcapsules
	Linaclotide [linzzess®]	IR capsules
	Rifaximin [xifaxan®]	IR tablets
	Amitriptyline [Elavil®]	IR tablets

CONCLUSION:

Colon- targeted drug delivery systems represents a promising approach in pharmaceutical research and development .These systems (offers) provides a targeted and controlled release of drug with in the colon reduce systemic side effects and improves therapeutic outcomes colon specificity is more likely to be achieved with the system that utilize natural materials that are degraded by colonic bacterial enzymes .These are various approaches like pressure controlled to primary approaches both natural and biodegradable polymers are used for the colon specific delivery of the drug. Evaluation tests are done to co-relate the invitro – in vivo dissolution studies results in the delivery of drugs in safe, effective and less expensive manner. This colon – targeted drug delivery system ultimately benefiting the patients and health care centers (or) donars.

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