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IMPORTANCE OF COLON TARGETED DRUG DELIVERY SYSTEMS IN HERBAL MEDICINES

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ABSTRACT: Now a day's world health organisation encourage, recommends and promotes traditional, herbal remedies in health care science, because these drugs are easily available at low cost and are safe but herbal medicines are not a simple task since many factor influence biological efficacy and reproducible therapeutic effect. These day's colonic diseases are commonly seen and needs lifelong medical attention. Because of safety, herbal medicines can play vital role in the treatment of colonic diseases. Various natural therapies, available for the treatment of colonic diseases like ulcerative colitis, Intestinal bowel syndrome, colon cancer, etc. It is possible to improve the effect of these herbal medicines by targeting to the colon. This article review a detailed study about various pharmaceutical approaches used for colon targeting such as tablet, capsules, micro-particles, micro-sponges, liposomes, etc. with herbal drugs and their effects. Effects of different process and formulation parameters on colon targeted drug delivery system are also discussed in following article.

INTRODUCTION: From time immemorial, plants have been source of medicines¹. Herbal drugs have fewer side effects, are widely available, inexpensive and therapeutically efficacious for lifestyle diseases compared to conventional medicines². There is growing evidence that many recent drug therapies overcome symptoms and neglect the underlying disease processes. In contrast, many herbal products target the cause of many diseases and yield better clinical results³. Colorectal disorders are common diseases that are often chronic in nature.

Phytoconstituents like curcumin, boswellic acid, etc. shows therapeutic effects on various colonic diseases. Herbal drugs delivery requires modification with the objective to achieve targeted delivery, to increase patient compliance, *etc.* The effectiveness of many herbal drugs is usually limited by their potential to reach the site of action. Most of the times only a limited amount of administered drug dose reaches the target site, whereas larger part of the drug get distributed throughout the body in correspondence to its physico-chemical and biochemical properties like low solubility, reduced absorption, rapid metabolism, instability in high acidic pH condition and excretion. Hence considerable attention has been given to development of colon targeted drug delivery system for herbal drugs⁴⁻⁵. Approximately 50% of the drug delivery systems present in the market are oral drug delivery systems and these

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systems better patient acceptance and ease of administration¹⁰. Oral colon-targeted drug delivery systems have currently attracted greater interest for their application in the local treatment of a variety of colonic diseases such as colorectal carcinoma, constipation, inflammatory bowel diseases (IBD's)^{11, 21}. The purpose of colon targeted drug delivery system is to improve patient compliance and treatment efficiency with reduction of drugs doses and systemic adverse effects¹³. The colon specific drug delivery systems need to protect the drugs that are incorporated in it from chemical and enzymatic degradation through the gastro intestinal track and should be released in colon. Thus designing oral colon targeted drug delivery system is complicated^{12, 14}.

TABLE 1: COLON TARGETING DISEASES AND HERBAL DRUGS USED^{2, 6, 8, 9}

Disease	Drug
Inflammatory Bowel Diseases, Irritable bowel disease and Crohn's disease.	Curcumin, Boswellic acid, Quercetin, <i>etc.</i>
Chronic pancreatitis	
Pancreatotomy and cystic fibrosis, Colorectal cancer	Berberine, Gallic acid, curcumin, <i>etc.</i>
Gastric irritation, Constipation	Rhubarb extract, Triphala, Calsiumsenoside, <i>etc.</i>

Anatomy and Physiology of Colon: The GI tract is divided into three parts as stomach, small intestine and large intestine. The large intestine is further divided in to three parts as colon, rectum and anal canal. Length of colon is about 5 feet (150 cm) long, and is sub divided in to five major sections as cecum, ascending colon, descending colon, hepatic flexure and right half of transverse colon. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid.

The last anatomic segment before the anus is the rectum. The human colon is shown in **Fig. 1**. Creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, and expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen are the major functions of the human colon. About 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed showing that the absorptive capacity of colon is very high¹⁵⁻¹⁷.

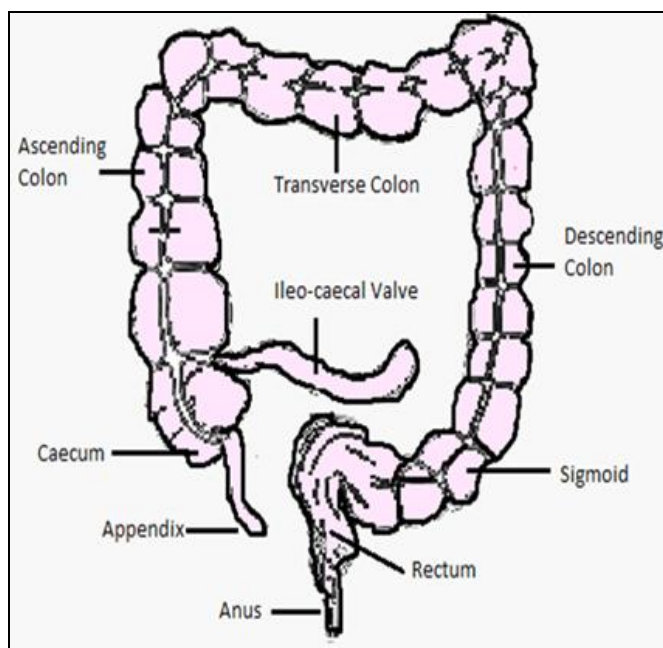


FIG 1: ANATOMY OF COLON

pH in the Colon: The gastrointestinal tract pH is sensitive to both inter and intra subject variations. The pH of the gastrointestinal fluid is influenced by diet, diseased state and food intake. The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery. The GI tract has a gradient pH ranging from 1.2 to 7.5. The difference between the pH of the stomach and small intestine has historically been used to deliver the drug to the small intestine by using pH sensitive enteric coatings. Due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides there is a fall in pH on the entry into the colon¹⁸.

Need of Colon Targeted Drug Delivery: Targeted drug delivery system provides direct treatment at the disease site, thus lowering dose and exhibiting fewer systemic side effects. Colon specific drug delivery system can give local, systemic and prolonged effect. Formulations targeting colon are useful for delivery of drugs that are polar and/or chemically or enzymatically degradable in upper GI tract and are highly affected by hepatic metabolism. Treatment of inflammatory bowel diseases, *e.g.* ulcerative colitis and Crohn's Disease are generally treated with glucocorticoids and Sulphasalazine. Other various diseases of the colon, such as colorectal cancer, might also be capable of being treated more successfully if drugs were targeted to the colon^{15, 16}.

Advantages of Colon Targeting Drug Delivery System:^{15, 16, 17}

- Colon is an excellent site for the delivery of drugs for treatment of local diseases of the colon *e.g.* Ulcerative colitis.
- Smaller drug quantities are required.
- Reduced frequency of dosing hence lowers cost of expensive drugs.
- Lower side effects and drug interaction.
- Poorly absorbed drugs can have an improved bioavailability.
- Lower GI irritation.
- First pass metabolism can be bypassed.
- Extended activity is seen. (Day time or night-time).
- Improved patient compliances.

Limitations of Colon Targeting Drug Delivery System:^{18, 19}

- Several manufacturing steps are required.
- The resident micro-flora in the colon could affect colonic performance due to metabolic degradation of the drug.
- Lower drug bioavailability observed because of insufficient release of drug due to nonspecific binding of drug to dietary residues, intestinal secretions, mucus or faecal matter.
- Prior to absorption, the drug need to be in solution form and thus not suitable for poorly soluble drugs.
- Uncertainty of the location and environment in which the pH sensitive coating ruptures
- Not suitable for pro-drug formulation since it depends on functional group present on active moiety for chemical linkage.

There are various approaches or methods by which colon targeting can be achieved, for example, coating with pH sensitive polymers and with biodegradable polymers, using polysaccharide formulation, timed dependant systems, pressure-controlled drug delivery systems, osmotic pressure controlled systems²⁰.

Colon Targeted Herbal Drug Delivery Systems: Conventional Drug Delivery Systems: The conventional drug delivery system such as tablets, capsules, pellets, can be coated with pH-sensitive polymer such as enteric coating to formulate a solid

dosage formulation. The polymers used in colon targeting, should be able to withstand the acidic pH of gastro intestinal tract and proximal part of the small bowel, it should also be able to disintegrate at the neutral or slightly high pH of the terminal ileum and preferably at the ileocecal junction²¹.

Colon Targeted Tablets: A work on development and optimisation of colon targeted drug delivery system using Eudragit L100 and ethyl Cellulose as coating material for tablet of Ayurvedic Churna showed colon targeting effect. In this study, the tablets were formulated using 1:1 ratio of dried drug extract and lactose using starch paste 5% w/v as granulating agent. The tablets were coated using Eudragit L100 and ethyl cellulose in equal ratio granulated using 1% w/v Acacia mucilage in water. Hardness, thickness, friability, % weight variation and % drug content were within the limit as per standard. *In-vitro* dissolution studies showed that % drug release was 98.97 % after the end of 17 hrs and showed first order kinetics of drug release. The *in-vitro* studies showed that the compressed coated tablets containing Eudragit L100 and ethyl cellulose as coating materials were found to be successful in delivering maximum amount of drug to the colon²².

Colon-specific delivery of sennosides was achieved using polysaccharide pectin as a compression-coating agent in the investigational study by M. Momin, *et al.*, In this investigation, pectin along with hydroxyl propyl methylcellulose (HPMC) was used for compression coating of the calcium sennoside core tablets. For colonic delivery, erosion of outer coat plays an important role in the release of the drug and coating material should have good swelling as well as stiff gel formation properties. After drug dissolution and erosion studies, it was found that pectin alone was not sufficient to protect the core tablets during entire gastrointestinal transit time because it forms a loose gel. Thus pectin was combined with hydroxyl-propyl methylcellulose. A 3² factorial design was prepared to study the effect of the amount of hydroxyl-propyl methylcellulose and coat weight of the tablets on the time taken for 50% erosion of tablet in presence of pectinase enzyme. It was observed that as the coat weight increases the time taken for the 80% drug release also increases and higher amount of HPMC lowers the drug release.

Thus it was concluded from the study that core tablets should be coated with a lower amount of hydroxyl-propyl methylcellulose and higher amount of coat weight and pectin-hydroxy-propyl methylcellulose coating as a favourable for colon delivery system for drugs like sennosides²³.

In the investigational study of development and evaluation of rhubarb matrix tablets, the effect of hydroxyl-propyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC) with pectin was studied for colon targeting. By wet granulation method, matrix tablets of rhubarb were prepared using pectin (10%) alone and in combination with hydrocolloids. Each formulation was evaluated in terms of hardness, friability, drug content, disintegration time and *in vitro* drug release study. After studying the release profile of all the formulations it showed that the drug release increases with the increase in amount of pectin and lower amount of HPMC and HEC. A formulation containing 10% pectin with 10% HEC was selected as an optimized formulation on basis of release profile conducted in presence of pectinase enzyme for 6 hr. But the optimized formulation was not able to retard the drug release in stomach and upper intestine completely. Thus it was further coated with a pH sensitive polymer as eudragit S-100 (ES 100). From the results obtained, pectin based matrix formulation containing 10% HEC with 6% coat weight of ES 100 shows good colon targeted effect²⁴.

An Andrographolide pH dependant tablets for colon-specific delivery was prepared and evaluated. The optimised coating solution was screened depending on the only single factor, and orthogonal design was used to optimize the coating solution. The release characteristic was checked *in vitro* using Eudragit S100 as the coating material and diethyl phthalate as the elasticizer. The *in vitro* tests revealed that drug release was not observed in gastric juice and artificial small intestinal juice even up to 4 hours. But 80% cumulative release was observed in 2 hours when further were placed in artificial colon juice. Andrographolide could not be identified when the tablets were placed into the gastric juice for 2 hours and the artificial small intestinal juice for 4 hours, but when it was placed into the artificial colon for 2 hours, 80% of the cumulative release rate were observed. From the

above *in vitro* study, it was concluded that the prepared formulation showed good colon targeted effect²⁵.

TABLE 2: VARIOUS POLYMERS AND THEIR RATIO USED IN COLON TARGETED TABLETS^{22, 23, 24, 25}

Drug Used	Polymers Used	Polymers Ratio
Ayurvedic Churna Sennosides	Eudragit L100 and Ethyl cellulose	1:1
Rhubarb	Pectin and hydroxypropyl methylcellulose	8:2
Andrographolide	Pectin and hydroxyethyl cellulose	1:1
	Eudragit S100 with diethyl phthalate as the elasticizer	3:1

Colon Targeted Pellets: Pellets are aggregates of fine powders or granules of bulk actives and excipients. They consist of tiny, free-flowing, spherical or semi-spherical solid particles and are designed for oral administration. Pellets are of great interest to the pharmaceutical industry for a variety of reasons. In dosage form design and development palletized products gives flexibility, improve safety and efficacy of bioactive agents. Pelletized products also are popular for controlled release of active agents to the site of action²⁶.

High molecular weight hydroxypropyl methylcellulose (HPMC) and biodegradable pectin was used for coating of pellets containing curcumin, to be released in the colon. The formulated pellets were free flowing and *in-vitro* study showed release of curcumin. The pellets remained intact up to pH 3.0 and disintegrated at pH 7.2, and released drug up to 12 hours. The ideal batch consisting of coating of Pectin: HPMC (1:3) showed minimum release at pH 1.2 and maximum release at pH 6.8. And increase in amount of curcumin in blood stream (1.287µg/ml) when compared to pure curcumin (0.5µg/ml). The drug release was showed to be retarded by the higher concentration and greater thickness of coating by HPMC on the pellets. Matrix erosion type of release kinetic was showed by the prepared formulation²⁷.

The present patent is related to the invention of andrographolide enteric targeting micro pellet and its method for preparation; for the treatment of inflammatory bowel disease. The prepared

formulation consists of three layers; micropellet is composed of blank pellet, drug layer which contains andrographolide as a drug and an enteric coating layer. Polymer A is the copolymer of methacrylic acid and methyl methacrylate and polymer B is the copolymer of methacrylic acid and ethyl acrylate whereas polymer A dissolved under condition of $\text{Ph} \geq 7.0$. The ratio of andrographolide and polymer A is said to be 1:2:1:0.2 by weight. Enteric coating layer contains the polymer B dissolved under condition of $\text{pH} \geq 5.5$ and the excipient such as plasticizer, anti-sticking agent, pigment, hydrophilic polymer and surfactant²⁸.

Novel Drug Delivery Systems: Drugs when formulated using novel drug delivery system addresses the drawbacks of the conventional drug delivery systems. Novel medicine treats a particular disease or disorder by targeting the affected area inside a patient's body and carrying the drug to that area. Drug delivery system is the approach by which a maximum amount of the concerned drug is given to the patient in such a way that it specifically reaches the site of action and starts releasing the drug. Novel drug delivery system tries to reduce all the disadvantages associated with traditional drug delivery systems. There are many approaches by which novel drug delivery can be achieved²⁹.

pH Sensitive Microparticles: Carrier technology offers a clever way for drug delivery by binding the drug to a carrier particle such as microparticles, nanoparticles etc, which modulates the release and absorption characteristics of the active moiety. Microspheres / microparticles found to be an important part of this particulate drug delivery system by virtue of their small size and good carrier characteristics. These drug delivery systems offer various advantages compared to traditional dosage forms, which include enhanced efficacy, reduced toxicity, improved patient compliance and convenience. Such systems usually use macromolecules as carriers for the drug moiety. Microparticles are a type of novel drug delivery system where the particle size varies from one micron to few mm. They are tiny particles of solids or small droplets of liquids surrounded by walls of natural and synthetic polymer films of ranging thickness and degree of permeability working as a

release rate controlling substance. This technology of microencapsulation allows protection of drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities, or masking of unpleasant taste^{30, 31}.

Release Mechanism of Microparticles: Microparticle drug delivery system of curcumin was constructed and studied by B. Xiao and his colleagues. In this study, an emulsion-solvent evaporation approach was used to prepare microparticles (MPs) using pH-sensitive Eudragit S100 (ERS100) and poly (lactide-co-glycolide) (PLGA). The MPs were loaded with an efficient anti-inflammatory agent curcumin. The prepared spherical MPs had a desirable particle size ranging from 1.52 to 1.91 μm . By changing the weight ratios of ERS100 and PLGA their loading efficiency could be regulated, with a few MPs exhibiting loading efficiencies over 80%. It was noticed that the rapid release of curcumin from MPs in buffers (pH 1.2 and 6.8) could be significantly decreased by increasing the PLGA concentration. ERS100 / PLGA MPs with a weight ratio of 1:2 (MPs-4) were capable of maintaining sustained release of curcumin, approximately 48% release of the initial drug load at pH 7.2-7.4 during 20hr incubation.

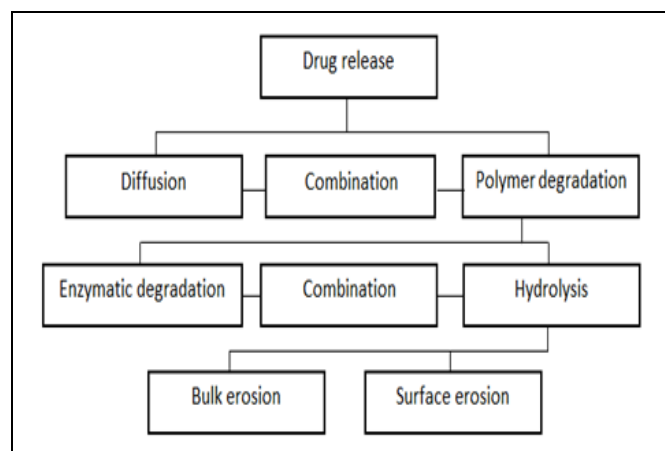


FIG. 2: RELEASE MECHANISM OF MICROPARTICLES

Most importantly, *in vivo* experiments showed that orally administered MPs had higher therapeutic efficiency in alleviating colitis in a ulcerative colitis mouse model, when compared to pure curcumin. The study exhibited that, the one-step-fabricated curcumin-loaded MPs have the characteristics of pH-sensitivity, controlled drug release, and colon targeting. Thus MPs may hold

promise as an easily scalable drug carrier for the efficient clinical treatment of ulcerative colitis.

pH Triggered Microspheres: An investigational study which deals with the development and evaluation (*in vitro* and *in vivo*) of pH sensitive/triggered chitosan microspheres of curcumin (CUR) coated with Eudragit for treating ulcerative colitis was carried out by R. Sareen and her co-workers. CUR-loaded chitosan microspheres were initially formulated by emulsion cross-linking method and then coated with Eudragit S-100. The pharmacodynamics of the prepared formulation was analysed in mice by acetic acid induced colitis model³². The prepared microspheres were of uniform spherical shape with good entrapment efficiency (73.88% to 82.50%). Uncoated CUR-chitosan microspheres exhibited rapid release within initial 4 hours whereas microspheres coated with Eudragit S-100 avoided premature release of CUR and showed controlled release up to 12 hours that followed Higuchi model. A negligible amount of CUR in the stomach and small intestine was shown in the *in-vivo* organ bio-distribution study confirming the integrity of microsphere in upper gastrointestinal tract. Significant reduction in severity and extent of colonic damage was observed in *in-vivo* study with the use of CUR-loaded microspheres in comparison to pure CUR. It was further provided by histopath study. Thus the *in vitro* and *in vivo* studies proved that developed microspheres is a promising system for pH-dependent delivery of active constituent to the colon³³.

In the study conducted by Madhavi M. and her colleagues, colon targeted curcumin microspheres were prepared using Eudragit S100. It was evaluated for *in vitro* / *in vivo* properties. "Oil in oil solvent evaporation" method was used in the fabrication of microspheres. The formulation was optimized by checking the influence of various process variables including stirring speed, drug polymer ratio and percentage of the emulsifying agent on the fabrication. *In vitro* parameters were such as surface morphology, particle size, percentage drug entrapment, percentage yield, drug polymer interaction, *in vitro* drug release in simulated gastrointestinal transit conditions and stability were studied.

Using an optimized formulation, the *in vivo* parameters such as drug release into the systemic circulation and organ distribution were investigated on male albino rats. The formulations of microspheres were optimised using 1:2 drug: polymer ratio, with stirring speed of 1000 rpm using 1.0% w/v concentration of emulsifier. The release studies of the optimized formulation showed that the aqueous solubility of curcumin was enhanced by 8 times in comparison to pure curcumin. The increase in solubility was attributed to the increase in the surface area of the drug substance. FTIR studies showed that there was no change in drug characteristics upon microsphere fabrication. Drug release of formulation was according to Korsmeyer and Peppas release model. Accelerated stability studies showed that the drug was stable in the prepared formulation for a period of at least 14 weeks at room temperature. *In vivo* studies demonstrated a sustained release of the drug into the systemic circulation after oral administration. Most of the drug load (79.0%) was delivered to the colon by eudragit microspheres, whereas only 28.0% of the total drug dose reached the target site using plain drug suspension. This study showed that the eudragit coated microspheres can act as a promising colon targeted drug delivery system³⁴.

Ginger extract (GE), a strong natural anticancer agent, exhibited low bioavailability and physicochemical properties. In a study conducted, pharmaceutical drug delivery design was used to improve the biopharmaceutical performance of GE for the treatment of colon cancer by prolonged and localized delivery of the drug in the distal parts of the gastrointestinal tract. Alginate beads entrapping 85.9 + or -1.78% of GE, were coated with Eudragit S100. It lead to 50% retardation in the release of GE and protected it from the stomach and upper part of the small intestinal. The formulation showed good solubility in pH > 7.0 which gave a colon targeted drug delivery system.

Preclinical evaluation conducted using 1,2-dimethylhydrazine - induced colon cancer model in male Wistar rats, in terms of histopathology, oxidative stress, mitochondrial complex activity, B-glucuronidase and ammonia concentration determinations showed GE loaded beads were significantly better than free GE for the treatment

of colon cancer. The study also exhibited recession of the cancer after 4 weeks of treatment with GE loaded coated alginate beads³⁵.

Yadav and his colleagues prepared solid lipid microparticles (SLMs) of curcumin for the treatment of inflammatory bowel disease. Curcumin loaded SLMs were formulated by using modified micro-emulsion technique. The oil phase, containing of 1-10% (w/w) lipid such as soya lecithin and 1% (w/w) curcumin and aqueous phase, consisting of 0.5% (w/w) poloxamer 188 and de-ionized water were used for formulation. It was observed that increase in the lipid content over 1-10% (w/w) resulted in larger mean particle sizes and broader size distributions of the micro-particles. Thus 1% (w/w) stearic acid concentration was found to be optimum concentration for the formulation of the SLMs. The study also showed that entrapment efficacy decreased as the amount of lipid increased since the curcumin was insoluble in lipid.

Thus surfactant was used to increase the entrapment efficiency. Entrapment efficacy was optimal at 1% lipid and 0.5% (w/w) poloxamer 188. At all the above optimal conditions, the mean particle size of developed SLMs and entrapment efficacy of curcumin was found to be 108 nm and 79.24% (w/w) respectively. Also the optimized formulation showed curcumin release of 79.24% within 12 hours with a 24.1% burst release within the first hour. The prepared colon specific delivery system of SLM formulations with curcumin was further studied for their anti-angiogenic and anti-inflammatory activity by using chick embryo and dextran sulfate (DSS)-induced experimental colitis model. Treated group with SLM curcumin showed a faster weight gain than the DSS control additionally it showed predominance of eosinophils in the chronic cell infiltrate. The above *in vivo* studies showed that degree of colitis caused by administration of DSS was significantly attenuated by colonic delivery of SLMs of curcumin³⁶.

Colon Targeted Microsponge: Microsponge is a recent novel technique offering controlled release and targeted specific drug delivery. The Microsponge delivery system is a patented polymeric system consisting of porous microspheres. They are small sponge-like non-

collapsible spherical particles that contain a myriad of interconnecting voids, with a large porous surface through which active constituents are released in under controlled manner. The size of the micro-sponges varies from 5-300 μ m in diameter and a regular 25 μ m sphere have up to 250000 number of pores and an internal pore structure equals to 10 feet in length, producing an average pore volume of around 1ml/g for large drug retention. The surface of micro-sponges ranges from 20 to 500 m²/g and pore volume varies from 0.1 to 0.3cm³/g. This result in a large reservoir within each micro-sponge that can have a loading capacity up to its own weight of active agent^{37, 38}.

A study was conducted by R. Sareen and her colleagues to develop and optimize the micro-sponges of curcumin for colon-specific drug delivery with a view to bypass the upper gastrointestinal tract (GIT) for enhanced therapeutic effect. Quasi-emulsion solvent diffusion method was used to develop micro-sponges by using 3² full factorial design. Prepared microsponges were optimized in order to check the effects of different independent variables (volume of ethanol and Eudragit L100) on the encapsulation efficiency, particle size, and release of the drug. After studying various parameters, it showed that increase in volume of ethanol resulted in smaller particle size along with increase in entrapment efficiency. The optimized batch was selected based on the particle size of 41.63 μ m, 78.13% of % entrapment efficiency, % cumulative drug release of 84.12%, and desirability factor of 0.83.

The optimized formulation was tested *in vivo* using acetic acid induced colitis model in rats. Release studies showed that the microsponges reduced the untimely release of curcumin in upper GIT and specifically released the active constituents at colonic pH. The drug release profile of optimized formulation was subjected to different kinetic models such as Higuchi model, which suggested diffusion as the main mechanism of drug release. Pharmacodynamic study revealed that curcumin loaded a microsponge causes a significant decrease in edema, necrosis, and haemorrhage of the colon as compared to pure curcumin solution. This investigational study proved that curcumin loaded microsponges could act as an encouraging drug delivery system for treatment of ulcerative colitis³⁹.

Colon Targeted Nanoparticles: Lately, particulate systems like nanoparticles have been used as a physical approach to change and improve the pharmacokinetic and pharmacodynamic characteristics of various types of drug molecules. They have been used *in vivo* to protect the drug entity in the upper GIT, restrict passage of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the specific site of action. Nanoparticles are defined as particulate dispersions or solid tiny particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of formulation, nanoparticles, nanospheres or nanocapsules can be prepared. In nanocapsules, drug is confined to a cavity encompassed with a unique polymer membrane. Whereas nanospheres are matrix systems in which the drug is physically and uniformly dispersed^{40, 41}.

The investigational study was conducted to design pH-sensitive, polymeric nanoparticles of curcumin, a naturally found anti-cancer agent, for the treatment of colon cancer. The objective of the study was to increase the bioavailability of curcumin, simultaneously decreasing the required dose by selectively targeting to the colon. Eudragit S100 was selected to aid targeting as the polymer dissolves at colonic pH to give selective colonic release of the entrapped active constituent. The solvent emulsion-evaporation technique was used to prepare the nanoparticles. The freeze dried formulation was checked for particle size, drug content, DSC studies, particle morphology.

The anti-cancer potential of formulation was demonstrated by using MTT assay in HT-29 cell line. Prepared nanoparticles were nanometric, homogeneous, spherical in shape with an encapsulation efficiency of 72%. Freeze-dried nanoparticles showed a negative surface charge, drug content of > 99% and the presence of a drug in amorphous form resulted in its increased absorption. MTT assay showed almost double inhibition of the cancerous cells by nanoparticles, in comparison to pure curcumin solution, tested at the same concentrations. Increased action was seen due to size influenced enhanced cellular uptake that resulted in a decreased overall dose requirement⁴².

The investigational study was done to prepare chitosan (CS) nanoparticles (NPs) and to study the targeting ability of chitosan nanoparticles (CS-NPs) coated with Eudragit S100 (ES-CS-NPs) in comparison with CS-NPs. pH sensitive ES was used to control the size of prepared formulation and was targeted to colon. The ionic gelation method was used to prepare the CU-loaded CS-NPs (CSNPs- CU). The coating of ES was performed by oil-in-oil solvent evaporation method using coat: core ratio (2:1). Both the formulations, CS-NPs-CU and ES-CS-NPs-CU were evaluated for particle size, size distribution, % drug entrapment, and *in vitro* drug release study. The average size of CS-NPs- CU was found to be 173 ± 4.5 nm and polydispersity index (PDI) of 0.16, whereas average size of ES-CS-NPs-CU was found to be 236 ± 3.2 nm and PDI of 0.22.

There was no significant difference between entrapment efficiency since ES-CS-NPs-CU and CS-NP-CU was found to be 42 ± 1.9 and 4.2 ± 1.5 , while in case of CS-NPs-CU were found to be 44 ± 1.3 and 3.9 ± 1.4 , respectively. *In vitro* release study indicated that higher amount of CU was released in colonic fluid from ES-CS-NPs-CU than CS-NPs-CU because of degradation of polymer by colonic pH. There was no major difference in cell viability between both the NPs when they were exposed to Caco-2 cells. The *in vivo* uptake studies showed the better uptake of ES-CS-NPs-CU in the colon, demonstrating that it was more bio-available than CS-NPs-CU. These results showed that ES-CS-NPs-CU formulation can be used as a potential delivery system for treatment of colon cancer⁴³.

Chuah L. and his colleagues studied the muco-adhesive properties and release of the curcumin incorporated in chitosan nanoparticles (CS-NPs). pH of 6.2 was registered by ionically gelling the CS-NPs with tripolyphosphate (TPP) as it was important to avoid agglomeration. Process parameters like Chitosan: TPP weight ratio and stirring time affects the average size of CS-NPs. There was no appreciable effect of CS: TPP weight ratio on the amount and percentage of curcumin encapsulated. The increase in stirring time from 30 min to 1 hr caused a slight reduction in of the size of CS-NPs. It was observed that higher the CS: TPP weight ratio, slower was the release from Curcumin CS-NPs.

The slowest release was observed at chitosan to TPP weight ratio of 3:1, with retention of 36% at the end of 6 hr. Freundlich and Langmuir models were fitted for adsorption isotherm of mucin on CS_NPs, which showed monolayer-limited adsorption on heterogeneous sites with varied affinities. Due to the H-bonding and π - π interactions between the phenolic moieties of curcumin and mucin, encapsulated curcumin exerted an effect on the adsorption of mucin. From the experimental study it was considered that formulation could be potentially used for muco-adhesion and delivery of curcumin at the colon⁴⁴.

In a study, Zhang M. and his colleagues demonstrated the efficient colon targeting of nanoparticles derived from edible ginger (GDNPs 2). The average size of GDNPs 2 was ~230 nm and showed a negative zeta potential. These nanoparticles contained high levels of lipids, ~125 micro RNAs (miRNAs), some amount of proteins and large amounts of ginger bioactive constituents (6-gingerol and 6-shogaol). They also showed that GDNPs 2 were nontoxic and primarily taken up by intestinal epithelial cells (IECs) and macrophages. Studies on various models of colitis showed that, they showed that GDNPs 2 reduced acute colitis and improved intestinal repair, and prevented chronic colitis and colitis-associated cancer.

Oral administration of GDNPs 2 increased the survival and proliferation of IECs, reduced the pro-inflammatory cytokines and increased the anti-inflammatory cytokines in colitis models, suggesting that GDNPs 2 has the potential to decrease the damaging factors and it promoted the healing effect. From the above study it was clear that nanoparticles derived from edible ginger, characterized a novel, natural delivery mechanism for improving the prevention and treatment of Irritable bowel disease with an increased benefit of overcoming the limitations such as potential toxicity and limited production scale that were commonly observed with synthetic nanoparticles⁴⁵.

Self-emulsifying Drug Delivery System: Self-emulsifying drug delivery systems (SEDDs) enhances solubility and bioavailability of poorly soluble drugs. SEDDS, are isotropic mixtures of oils, surfactants, solvents and co-solvents / surfactants, and can be used for the design of

formulations in order to increase the oral absorption of highly lipophilic drug compounds. The oral administration of SEEDs can be done by incorporating in soft or hard gelatin capsules^{46,47}.

A study was conducted by Sookkasem *et al.*, for developing calcium alginate beads containing self-emulsifying curcumin (SE-Cur) for colon targeting. All formulations were formulated by using ionotropic gelation method and coated with Eudragit® S-100. The beads were evaluated for particle size, % drug encapsulation and % drug release. Alginate and calcium chloride concentrations influenced the rate and amount of SE-Cur released from the beads. Greater degree of cross-linking and aggregation of alginate was achieved with higher levels of calcium chloride which increased gel strength and subsequently lowered the rate of drug release. Encapsulation efficiency was found to be in the range of 85-98% and emulsion droplet sizes were in the range of 120-202 nm in simulated colonic fluid.

The formulations having a combination of SE-Cur, 2-4% alginate and 0.1 or 0.3M calcium chloride could inhibit early curcumin release in simulated gastric fluid, simulated intestinal fluid and more than 60% of the drug was released in simulated colonic fluid within 12 hr, in comparison to 10-20% release from the beads containing curcumin powder. SE-Cur also exhibited IC₅₀ value of 10 μ g/mL against the human colon adenocarcinoma cell lines (HT-29) and higher antioxidant activity. Thus study demonstrated the possible use of SE-Cur loaded alginate beads for the delivery of poorly soluble drugs to the colon⁴⁸.

Pulsatile Drug Delivery System: In this drug delivery system, the formulation is developed in the form of a capsule. The drug release from the capsule is controlled by the plug placed in the capsule and the drug contents are sealed by using as well able hydrogels as the capsule comes in contact with the dissolution fluid it swells and the plug pushes off after a lag time and the drug is discharged. Different polymers such as various grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used hydrogel plugs. In the capsule body, the length and point of intersection of the plug controls the lag time⁴⁹.

Huang Y. and his colleagues developed and evaluated a colon-specific pulsatile capsule with tablet of curcumin loaded self micro-emulsifying drug delivery system (SMEDDS) filled in an impermeable capsule. A highly methoxylated pectin (Hpectin) / lactose tablet plug was used in the capsule mouth. The solubility of curcumin in water was enhanced by the SMEDDS tablet. An *in vitro* release study of the formulation showed a classic pulsatile release profile with a specific lag time. The lag time could be regulated by varying the H-pectin/lactose ratio. As the proportion of lactose increased in plug, the lag time decreased considerably. The erosion time of plug containing H-pectin was significantly shortened since it was resistant to enzyme degradation. These results showed that the pulsatile capsule formulation with SMEDDS tablet could act as a promising colon-specific drug delivery of water-insoluble drugs¹¹.

Liposome: Liposomes are simple microscopic vesicles of lipids in which lipid bilayer structure is present with an aqueous volume entirely enclosed by a membrane, composed of lipid molecules and they can be used to target the drug to particular site or tissue. Due to structure similarity between lipid bilayer and cell membrane, the liposome can penetrate and deliver the drug efficiently to the site of action^{50, 51}.

The preclinical antitumor activity of liposomal curcumin in colorectal cancer was evaluated by L. Li and his colleagues. In the study, comparison of efficacy of liposomal curcumin with a standard chemotherapy agent (Oxaliplatin) was done. For the formulation lipids like 1,2-dimyristoyl-sn-glycero-3-phosphocholine / 1, 2 - dimyristoyl-sn-glycero-3-[phospho-rac-(1-glycerol)] (sodium salt) or a pegylated version of 1,2-dimyristoyl-sn-glycero - 3 - phosphocholine / cholesterol / 1, 2 - dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy-(polyethylene glycol)-2000] were used. Different ratios of total lipid to curcumin (w/w) ranging from 10:1 to 4:1 were evaluated. The optimized ratio of 10:1 was selected based on tests to determine optimal encapsulation of curcumin by liposomes. *In vitro* study was done with curcumin liposome and a dose dependant growth inhibition and apoptosis in LoVO and Colo 2015 human colorectal cancer cell lines were observed. Synergism was also observed with 4:1 ratio of

liposome curcumin and oxaliplatin in LoVo cells *in vitro*. *In vivo* studies also showed significant tumour growth inhibition in Colo205 and LoVo cells, and the growth inhibition observed by liposomal curcumin was higher than that for oxaliplatin in Colo205 cells. An antiangiogenic effect was seen when tumours from animals were treated with liposome curcumin. An attenuation of CD31, vascular endothelial growth factor, and interleukin-8 expression was observed by conducting immuno-histochemistry. Thus curcumin liposome exhibited better *in vitro* and *in vivo* activity in colo rectal cancer⁵².

CONCLUSION: Plant based medicines have been widely used by physicians and patients all over the world for their better therapeutic value and fewer side effects in comparison to modern medicines. The therapeutic value of herbal drugs can be increased by use of different scientific approaches making it more targets specific that helps to reduce potential side effects. The therapeutic potential of herbal drugs used in colonic diseases depends on its ability to reach site of action. Therefore by using various colon targeting drug delivery systems, it is possible to use the herbal medicines in more effective manner for colonic diseases. Hence great potential lies in the development of colon targeted drug delivery system for formulations of herbal drugs.

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CONFLICTS OF INTEREST: No.

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