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COLON SPECIFIC TARGETED DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

In the recent years there's new development in field of colon specific drug delivery system. Colon targeted drug delivery system delivered as both local and systemic delivery of drugs. Local delivery might, for example, allow topical treatment of inflammatory bowel disease (IBD). Treatment might be increased once drug delivered to the target web site on the colon. Systemic side effects could also be reduced. Colon specific systems is most significant delivery of these drug that square measure unremarkably inactivated within the higher elements of the canal (GIT). Colonic drug delivery has gained augmented importance not only for the delivery of the medicine for the treatment of native illness related to the colon like Crohn's disease, colitis, etc. but conjointly for the general delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. New systems and technologies are developed for colon targeting and to beat permeable method's limitations. Colon targeting holds an excellent potential and still want a lot of innovative work. This review article discusses introduction of colon, need and approaches of colonic drug delivery, factor effecting colonic transition, colonic diseases and the novel and emerging technologies for colon targeting.

KEYWORDS

Colon targeted drug delivery, Delivery of proteins First –pass metabolism and Emerging technologies.

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INTRODUCTION

Significant advances are created in drug delivery technologies throughout the past three decades, and drug delivery at a desired unharness rate is currently attainable. Even highly sophisticated drug delivery technologies, however, often fail to produce marketable oral modified-release dosage forms, as a result of the physiological limitations of the gastrointestinal tract and/or the utilization of non-feasible pharmaceutical components. In oral drug delivery, there are several scientific challenges that

might be studied for years to return, and breakthrough technologies are needed to come up with novel dose forms raising drug delivery to higher level.

Modified release delivery systems may be divided conveniently in to four categories.

A. Delayed release
B. Sustained release
1. Controlled release
2. Extended release LIV
C. Site specific targeting
D. Receptor targeting

Delayed Release

These systems area unit people who use repetitive, intermittent dosing of a drug from one or additional immediate unharness units incorporated into one dose kind. Samples of delayed unharness systems embody repeat action tablets and capsules and enteric-coated tablets wherever regular unharness is achieved by a barrier coating.

Sustained Release

These systems embody any drug delivery system that achieves slow unharness of drug over an extended amount of your time.

Controlled Release

These systems additionally offer a slow unharness of drug over AN extended amount of your time and can also offer some management, whether or not this be of a temporal or special nature, or both, of drug unharness within the body, or in alternative words, the system is eminent at maintaining constant drug levels within the target tissue or cells.

Extended Release

Pharmaceutical dose forms that releases the drug slower than traditional manner at preset rate cut back the dose frequency by 2 folds.

Website specific targeting

These systems seek advice from targeting of a drug on to a definite biological location. During this case the target is adjacent to or within the unhealthy organ or tissue.

Receptor targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems[1-9].

COLONIC DRUG DELIVERY

Delivery of orally administered drugs especially to the colon has a number of important implications in the field of pharmacotherapy. Diseases of the colon such as irritable bowel syndrome, Crohn's disease and ulcerative colitis are effectively treated when the anti-inflammatory agents are applied directly to the affected area. The most important role of a drug delivery system is to get the drug "delivered to the site of action in sufficient amount and at the appropriate rate" however, it must also meet a number of other essential criteria. These include physical and chemical stability, ability to be economically mass-produced in a manner that assures the proper amount of drug in each and every dosage unit and in each batch produced and as far as possible, patient acceptability[10].

Until recently, colon was considered as a site for water reabsorption and residual carbohydrate fermentation. This part of GIT is also being considered as a site for administration of protein and peptide drugs. This is because colon provides a less hostile environment for drugs due to low diversity and intensity of digestive enzymatic activities, and a near neutral pH. Moreover, colon transit time may last for upto 78 h, which is likely to increase the time available for drug absorption[11]. Further, considering that this site is more responsive to absorption enhancers, its suitability as a site for drug administration appears promising. Additionally, colonic delivery of drugs may be extremely useful when a delay in drug absorption is required from a therapeutic point of view e.g. in case of diurnal asthma, angina, arthritis, etc.

INFLAMMATORY BOWEL SYNDROME

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn's disease and ulcerative colitis. The main difference

between Crohn's disease and Ulcerative Colitis is the location and nature of the inflammatory changes. Crohn's can affect any part of the gastrointestinal tract, from mouth to anus, although a majority of the cases start in the terminal ileum. Ulcerative colitis, in contrast, is restricted to the colon and the rectum. Microscopically, ulcerative colitis is restricted to the mucosa (epithelial lining of the gut), while Crohn's disease affects the whole bowel wall[12].

Site of disease

- In Ulcerative Colitis, sites of inflammation extend to the more proximal regions of the colon over time.
- In Crohn's Disease, the predominate site of inflammation is the distal ileum, between 30% and 40% of patients also have significant colonic involvement.

Thus, a delivery system for patients with Ulcerative Colitis will probably differ from one used to treat Crohn's Disease.

Luminal pH

Local pH within the lumen of the GIT can directly affect delivery systems, such as those relying on enteric coatings, and indirectly by altering local enzymatic activity. Since the pH gradient along the GIT forms the basis of several targeted lower intestinal delivery systems, understanding how this gradient varies in health and disease is important. The pH along the GIT of healthy subjects is reasonably well characterized. The luminal pH of the distal intestine in patients with IBD can be lower than that seen in healthy volunteers. In one study involving six UC patients, luminal pH was highly variable. Several patients had colonic pH ranging from 5.0 to 7.0, in three subjects however, lower pH were measured (2.3, 2.9 and 3.4)[13]. In patients with Crohn's Disease, relatively low intraluminal pH were also measured (pH 5.3±0.3) in the right colon and more acidic conditions were measured in the distal colon[14].

Location of inflammation at diagnosis in 783 patients with Ulcerative Colitis (A) and in 195 patients with Crohn's Disease (B). The data indicate the percentage of patients with involvement in intestinal segment[15].

Intestinal transit

Intestinal transit time is important for nearly all orally targeting delivery systems. Transit of a wide range of materials (meals, tablets, particulates, liquids) has been studied in both health and diseased state. This difference is due largely to mucosal inflammation and the disturbances it produces[16]. Commonly, Ulcerative Colitis patients exhibit diarrhea (accelerated transit, at least through the distal large intestine). Whole gut transit times were relatively long, ranging from 56 to 78 h. Stool weights increased significantly with active disease presumably due to exudates from inflamed epithelium, increased mucus secretion, and reduction in reabsorption of fluid and electrolytes[17].

Gut micro flora and their enzymes

Intestinal enzymes are used to trigger drug release in various parts of the GIT. Usually, these enzymes are derived from gut microflora residing in high numbers in the colon. As explained below, these enzymes are used to degrade coatings/matrices as well as to break bonds between an inert carrier and an active agent (i.e., release of a drug from a prodrug). A number of delivery systems rely on hydrolysis of glycosides or polysaccharides to control drug release in various segments of the GIT. In general, the types and activities of bacterial glycosidase are unchanged in Ulcerative Colitis relative to those in healthy volunteers[18]. However, in Corhn's Disease patients, differences have been noted both in terms of concentration of microbes and their enzyme activity. In general, glycosidase activity in Crohn's Disease patients is reduced relative to healthy subjects[19].

Drug dissolution in the colon

A drug must be in solution before it can be absorbed from the lumen of the GIT. In the more distal portions of the GIT, conditions are heterogeneous and drug dissolution is subject to the high viscosity of colonic contents. While not significantly affecting the dissolution of water soluble drugs, viscous luminal contents in the colon can impede dissolution of drugs that are less water soluble[20].

DELIVERY SYSTEMS FOR TARGETED DELIVERY IN THE GIT

Different systems are being developed for the purpose of site-specific drug delivery to the colon. These include

1. The passage of time (temporal control of delivery)
2. pH-based (triggered by a change in local pH as the formulation passes down the GIT).
3. Enzyme-based / Pro-drug (the enzymes found locally in a region of the gut breakdown a prodrug or a formulation to release drug).
4. Pressure-based systems (variations in pressure along the lumen of the GIT is used to trigger drug release).

Time-based delivery systems

Time-controlled release system may be, swellable, soluble coating, or a matrix type, which can resist the release of majority of drug from the formulation for an additional 3 h (i.e. the usual small intestinal transit time) and can deliver drug primarily to the colon. Sustained release dosage forms are designed to prolong drug dissolution and hence absorption. These formulations move down the GIT at rates dependent on their location. As drug is released from the formulation as it passes down the gut, it is absorbed at a rate depending on the drug's permeability properties and other factors. Unabsorbed drug or drug not released from the formulation is excreted in the feces. Simple sustained release systems are used to deliver drugs to various sites. Sustained release is the basis of Pentasa (mesalamine), which relies on ethyl cellulose coated beads to slowly release mesalamine, as they pass down the GIT. It is indicated for treatment of UC, despite the fact inflammation is located in the distal intestine. The relative bioavailability of mesalamine from this formulation is low. If mesalamine is released from the formulation but unabsorbed, it can still reach the inflamed mucosa and possibly exert a local anti-inflammatory effect[21].

Conventionally, various polysaccharides/polymers are used in the tablet formulations to retard drug release. These have been used either as matrices or as a coating material. For matrices generally, a high concentration of polymer is required. Alternatively, these can be used as binders in tablets. A solution of these polysaccharides/polymers as binders probably on drying enables the granules to be coated by them. Thus, varying the polysaccharide/polymer and their concentration affects drug release from the prepared tablet[22].

pH-based systems[23]

Enteric coatings are well-known and several marketed IBD products rely on them to delay release in an attempt to increase local drug delivery. Enteric polymers are insoluble in the contents of the stomach and they prevent drug dissolution until the formulation passes into the small intestine. The polymers, depending on their chemical composition, dissolve as the pH rises from 5 to 7 following gastric emptying.

Enzyme-based systems – Prodrugs

Delivery of a drug in IBD patients can also be accomplished by using enzymes located near the target site. There is a steep gradient of enzyme activity along the GIT. These enzymes are derived from gut microflora. In humans, the stomach and small intestine contain roughly 10^3–10^4 colony forming units (CFU)/ml[21]. However, the concentration of microflora rises dramatically passing from the terminal ileum to the ascending colon. Here, the numbers reach 10^{11}–10^{12} CFU/ml. These bacteria survive by fermenting a wide range of substrates (e.g., oligosaccharides, polysaccharides, mucopolysaccharides, etc) left undigested in the small intestine. Enzymes that ferment these substrates include azoreductases, β-glucuronidase, β-xylosidase, dextranases, esterases, nitroreductase, etc.[22]. These enzymes are exploited in colonic drug delivery by using them to degrade polymeric matrices and coatings and also to trigger release of a drug from pharmacologically inactive drug derivatives (prodrugs).

A successful prodrug-based delivery system is one in which the promoiety (i.e, inactive portion of the pro-drug) minimizes absorption until the active is released (usually by enzymatic action) near the

target site. Thus, the promoiety is used to increase the hydrophilicity of the parent drug, increase molecular size, or both, thus minimizing absorption of the drug prior to reaching the target site[23].

Azoreduction[48,49]

The classic example of a targeted prodrug composition is sulphasalazine, olsalazine (This compound, upon activation by reduction of an azo-bond, generates two molecules of mesalamine).There are a number of variations on this theme (mesalamine linked to another molecule via an azo-bond). These variations include polymeric prodrugs of varying complexity.

A targeted polymer-drug conjugate

The prodrug (polymer-drug conjugate) structure normally confers increased water solubility on the drug and, due to its large size and biospecific targeting moiety, it alters the drug's pharmacokinetics compared with those of the unconjugated drug[24]. The biodegradable spacer between the polymer carrier and the drug can be used to control the site and rate of release of the active agent.

Eg: Colon-specific dendrimers like

HPMA: N-(2-hydroxypropyl) methacrylamide copolymer-drug conjugate.

PAMAM: Polyamidoamine dendrimer.

**Coupling this drug to a polymer substantially increases the mass required, thus polymeric approach will have greater utility with potent drugs rather than 5-ASA.

Hydrolysis

Cyclodextrins (CD)

An inert carriers for targeting in the GIT. CDs are cyclic oligosaccharides consisting of 6–8 glucose units. They are fermented into small saccharides by colonic microflora[25-27]. Since CDs are poorly absorbed from the GIT due to their size and hydrophilicity and degraded in the large intestine, it is possible to use them as carriers for delivery of drugs in the lower intestine.

Dextrans

Dextrans contain a relatively large number of hydroxyl groups. These groups are used to link drugs to the polymer. A simple approach to linking a drug to dextran involves attaching carboxyl acid groups on the drug to hydroxyl groups on the polymer. In the absence of a carboxylic acid group on the drug, a spacer molecule such as succinic or glutaric acid can be used[26]. This prodrug approach shows effective deliver of anti-inflammatory drugs to the lower intestine of rats based on pharmacokinetic data[27].

Enzyme-based systems-coatings and matrices

A number of naturally occurring polysaccharides are stable in the upper intestine yet susceptible to hydrolytic degradation in the lower intestine[28,29]. Most polysaccharides can be chemically modified to optimize specific properties, such as the ability to form impermeable films[30].

Pectin is a non-starch linear polysaccharide composed mainly of a-(1→4)-linked d-galacturonic acid groups with some 1→2 linked l-rhamnose groups. Pectin, like many other polysaccharides, is stable in the stomach and small intestine but susceptible to enzymatic degradation in the large intestine[31,32]. Calcium[33] and zinc salts[34] of pectin are preferred for lower intestinal delivery since they have lower water solubility and hence better dissolution delaying properties than sodium pectinate or pectic acid. Guar gum[35,36], Chitosan[37], Chondroitin sulfate[38], Amylose[39,40], Alginates[41], Inulin[42].

Pressure-based systems

Another approach to controlling the site (and potentially the rate) of drug release in the GIT is using the pressure. Due to the reabsorption of water from the large intestine, the viscosity of the luminal contents increases[43,44]. As a result, intestinal pressures increase due to peristalsis in the distal intestine providing a potential means to trigger release of a drug from a formulation susceptible to pressure changes. Such a formulation approach, called pressure-controlled colon delivery capsule (PCDC) system.

Formulations susceptible to changes in pressure are prepared from capsule-shaped suppositories coated with ethyl cellulose. The materials polyethylene glycols (PEG) are used, they are selected so that they melt at body temperature. The system behaves

as a balloon once the PEG liquefies. In the upper intestine, there is sufficient fluidity to maintain the integrity of balloon and no drug release occurs. In the large intestine however, pressures induced by peristalsis directly affect the ethyl cellulose balloon leading to rupture and subsequent drug release.

COMPLEXATION

Cyclodextrin inclusion complexation[9,45] has been mainly used in the pharmaceutical field to increase the solubility, stability and bioavailability[46-48] of drugs, but also to reduce their irritancy and toxicity, convert liquid drugs into microcrystalline powders, prevent drug–drug or drug-additive interactions, and suppress unpleasant taste and smell.

THERMODYNAMICS OF COMPLEX FORMATION[59]

Formation of CD inclusion complexes is generally owing to a negative standard enthalpy change (Δ H) accompanying the inclusion process. The standard entropy change (ΔS) can be either positive or negative, although the majority of guest molecules appear to have negative (ΔS) values. Several intermolecular interactions have been proposed as being responsible for the formation of CD inclusion complexes in an aqueous solution. They are

- Hydrophobic interaction
- Vander Waals interaction mainly induction and dispersion forces.
- Hydrogen-bonding and dipole–dipole interactions
- The release of "high-energy water" from the CD cavity on substrate inclusion
- The release of conformational strain in a CD-water adduct, together with the Formation of a hydrogen-bonding network around the O (2), O(3) side of the CD macrocycle on substrate inclusion[48-54].

METHODS FOR STUDYING COMPLEXATION

To find out if a drug (substrate) can form a complex with any potential ligand molecule and the stability of the complex, one will need to measure the binding constants of complexes.

I. Solubility Measurement

The solubility of a substance will change on the formation of a complex with a second substance. The extent of solubility alteration directly relates to the binding affinity of the two compounds. Therefore, it is possible to evaluate equilibrium constants from solubility data[55-57].

Phase–solubility analysis

Phase–solubility analysis of the effect of complexing agents on the compound being solubilized is a traditional approach to determine not only the value of the stability constant but also to give insight into the stoichiometry of the equilibrium. Experimentally, an excess of a poorly water-soluble drug is introduced into several vials to which a constant volume of an aqueous vehicle containing successively larger concentrations of the CD are added. The need for excess drug is based on the desired to maintain as high a thermodynamic activity of the drug as possible. The vials are shaken or agitated at constant temperature until equilibrium is established. The suspensions are then filtered and the total concentration of the drug (Dt) determined based on appropriate analytical techniques (UV spectrophotometry, HPLC, etc). The phase–solubility profile is then constructed by assessing the effect of the CD on the apparent solubility of the drug (D)[58,59].

II. Ultraviolet-Visible Spectroscopic Analysis[60]

The spectral changes observed are similar to the effects caused by changes in solvent. These changes must be owing to a perturbation of the electronic energy levels of the guest, caused either by direct interaction with the CD, by the exclusion of solvating water molecules, or by a combination of these two effects.

Determining complexation constants

Spectrophotometric, spectroscopic or fluorescence methods are useful to determine the value of K if the complexation event induce changes in the compound spectra as a function of the guest-host interaction. These changes generally reflect an alteration in the microenvironment of the drug.

According to Benesi–Hildebrand[61]

$$\frac{L}{\Delta A} = \frac{1}{K[Dt]\Delta\varepsilon}\frac{1}{[CDt]} + \frac{1}{[Dt]\varepsilon}$$

According to **Scott**

$$\frac{[CDt][Dt]L}{\Delta A} = \frac{1}{\varepsilon}[CDt] + \frac{1}{K\Delta\varepsilon}$$

Where

ΔA is the difference in absorbance between the drug in the absence and presence of the CD at a particular wavelength, Δε is the difference in the molar absorptivity between the free and included drug, L is the path length.

Thus, for the Benesi–Hildebrand Eq. a plot of 1/ΔA versus 1/[CD]t should give a straight line (for a one-to-one complex) with the ratio of the intercept to slope generating the K value. In addition to changes in absorbance, changes in the molar ellipticity (i.e. associated with changes in the circular dichroism spectrum) may also be used as an additive properties to estimate the equilibrium constant.

Kinetic Method

The central CD cavity provides a lipophilic microenvironment into which suitably sized drug molecules may enter and include. No covalent bonds are formed or broken during the drug/CD complex formation and in aqueous solutions, the complexes are readily dissociated. The rates for formation and dissociation of drug/CD complexes are very close to the diffusion controlled limits and drug/CD complexes are continuously being formed and broken apart. The value of $K_{1:1}$ is most often between 50 and 2000M^{-1} with a mean value 490 for β-CD[62-64].

Mean K 1:1 [a] (M^{-1}) of β-Cyclodextrin: 490±8

a: Stability constants (binding constants) of 1:1 guest/CD

Complexes in aqueous solutions at 25±5 °C.

In all complexation processes including those associated with CDs, the measurement and knowledge of the stability or equilibrium constant (K_c) or its inverse, the dissociation constant (K_d) are crucial since these values provide an index of change of physicochemical properties that result upon host-guest binding including solubility.

For complexation, the equilibrium constant ($K_{n:m}$) can be written:

$$mCD + nD \overset{K_{m:n}}{\Longleftrightarrow} CDm \bullet Dn$$

$$[a - mx] \quad [b - nx] \quad [x]$$

$$K_{m:n} = \frac{[x]}{[a - mx]^m[b - nx]^n}$$

In addition, a dissociation constant can be defined as:

$$K_d = \frac{[a - mx]^m[b - nx]^n}{[x]} = \frac{1}{K_{m:n}}$$

Most methods for determining the K values for drug–CD interactions are based on titrating a certain chemical or physical property of the guest molecule with the CD and then analyzing the concentration dependencies. Additive properties of the drug or guest molecule that can be addressed in this way include aqueous solubility (phase–solubility relationships), chemical reactivity, molar absorptivity and other spectrophotometric properties, NMR chemical shifts and other spectroscopic properties, pKa values and HPLC retention times among others.

Titration Calorimetry

Titration calorimetry or thermometric titration calorimetry is a technique in which one reactant is titrated continuously into the other reactant, and either the temperature change or heat produced in the system is measured as a function of titrant added.

Titration calorimetry depends on calculation of the extent of reaction from the quantity of heat evolved. It depends on

- Equilibrium constant and the reaction conditions being such that the reaction occurs to a moderate extent (i.e., not to completion).
- Enthalpy of reaction being measurably different from zero.

Titration calorimetry provides information about the reaction enthalpy that is important in explaining the mechanism involved in the inclusion process.

Since the thermal events observed calorimetrically contain both chemical and nonchemical

components, all extraneous thermal effects must be subtracted from this composite of thermal events to obtain the relevant chemical reaction heat. Nonchemical thermal effects result from stirring, thermistor heating, heat transfer between the reaction vessel and the constant-temperature bath, and titrant/titrate temperature mismatch. Chemical thermal effects result from evaporation, dilution of the reactants, and chemical reaction heat.

MECHANICS OF DRUG RELEASE

THEORIES OF POLYMER EROSION

The calculation of percent polymer eroded for the HPMC matrices is calculated by using:

$$\%\ \text{Polymer Eroded} = \frac{\text{Weight initial} - \text{Weight remaining}}{\text{Weight initial}} * 100 \quad (\text{Eq: 1})$$

Where, Weight initial is the initial polymer weight, Weight remaining is the polymer remaining after each time point.

- The rate of polymer dissolution at the matrix surface and subsequent diffusion through the aqueous boundary layer increases with a decrease in polymer molecular weight.
- The erosion profiles of matrices comprised of different molecular weight, HPMC polymers are linear versus time, suggesting a rate-controlling mechanism.
- According to Reynolds[45], based on the linear erosion data, the rate-limiting step appears to be the diffusion of the polymer chains away from the matrix surface through the aqueous boundary layer.
- Weight average molecular weights of the polymer samples were calculated based on intrinsic viscosity measurements using the Mark-Houwink equation.[45,65].

$[\eta] = K (Mw)a$ (Eq: 2)

Where, K and a are constants specific for a given polymer solvent combination at a given temperature. The values of K and a used are 3.16E-3 and a = 0.55, respectively[46,66].

A summary of the intrinsic viscosities along with the respective molecular weights and erosion rates are displayed on Table No.4[6].

The power-law relationship which relates the polymer erosion rate and weight average molecular weight[7].

Polymer Erosion Rate $\propto (M_w)^a$ (Eq : 3)

Where, M_w is the weight average molecular weight, a is a factor related to the matrix composition.

Value of "a" is determined by using a log-log plot comparing the erosion rate ratios for each polymer to another polymer (ER_x/ER_y) versus the polymer weight average molecular weight ratios for each corresponding polymer relative to another polymer ($MW_{w,x}/MW_{w,y}$), the value of "a" was determined from the slope.

Polymer Erosion with Polymer Matrices[5,67]

The basic mass transfer relationship relates flux to concentration difference.

$J=K (C_s-C_b)$ (Eq :4)

Where, *J* is the flux of the transferring mass at the interface, C_s and C_b are the concentrations at the interface and in the bulk solution, respectively and *k* is a mass transfer coefficient.

Under sink condition during dissolution testing, the bulk solution concentration is considered negligible relative to the interface concentration. For dissolving polymeric matrix, it is considered to be equal to the disentanglement concentration, $C_{p,dis}$. Therefore, substituting $C_{p,dis}$ in Eq: 4 for Cs, Eq: 5 results which describes the erosion from a polymeric matrix.

$J_p=kC_{p.dis}$ (Eq: 5)

The functional form of the mass transfer coefficient, *k*, depends on whether the system is under free or forced convection conditions. The driving force for mass transfer is the value of the disentanglement concentration. In general, higher molecular weight polymers have lower disentanglement concentration values, while lower molecular weight polymer have higher disentanglement concentrations. In any reaction that involves consecutive stages, the overall rate of mass transport will be determined by the slowest step. In the case where polymer disentanglement occurs at a faster rate relative to transport of polymer chains away from the matrix surface, the rate-limiting step is the mass transfer process to the bulk solution. In unstirred conditions,

mass transfer can produce density gradients that result in fluid flow, often referred to as free convection. In stirred conditions, Eq:5 still applies, however, the functional form of the mass transfer coefficient will be different. Ju *et al*,[7] modeled HPMC release as a result of polymer release and its subsequent diffusion through the boundary layer to the bulk solution. Levich[8] expressed the mass transfer rate or flux as a function of the diffusion coefficient, the solution kinematic viscosity, the bulk solution velocity, and concentration difference. Accordingly, Ju *et al*,[7] arrived at an equation similar to that of Levich[8,68] by using an average diffusion coefficient and disentanglement concentration, $C_{p,\,dis}$ as shown in Eq 6.

$$J_p = (f_p D_p^{2/3} \nu^{-1/6} \omega^{1/2}) C_{p,dis} \quad \text{(Eq :6)}$$

Where, $(f_p D_p^{2/3} \nu^{-1/6} \omega^{1/2})$ represents the mass transfer coefficient under forced convection, f_p is a constant that varies with experimental settings, D_p is the average diffusion coefficient, ν is the solvent kinematic viscosity, ω is the rotational velocity replacing the bulk fluid velocity, u_b, when a rotating mechanism is used to create flow. It should be emphasized that the mass transfer coefficient is different under stirred and unstirred conditions.

In an attempt to relate polymer erosion to a polymer intrinsic property utilizing Eq: 6, the average diffusion coefficient and disentanglement concentration were the only variables that related to the matrix composition. They[69] developed a scaling law that related polymer erosion to molecular weight based on the depicted mass transfer equation for forced convection Eq: 6. The two intrinsic factors in this equation are D_p and $C_{p,\,dis}$. They further reported that the average diffusion coefficient and disentanglement concentration are both inversely proportional to HPMC molecular weight, and established a scaling law based on only these two variables. The power-law relationship was utilized in this study to relate polymer erosion rate, instead of flux, to number average molecular weight.

$$ER \propto M_n^{-a} \quad \text{(Eq: 7)}$$

Where, ER is the erosion rate. Using a log-log plot with the ratio of two polymers for polymer erosion rates versus the ratio of the corresponding polymer number average molecular weight, the value of *a* is determined from the slope.

The number-average molecular weight for a blend of polymers was calculated using the expression.

$$M_n \frac{1}{\sum W_i / M_i} \quad \text{(Eq: 8)}$$

Where, M_n is the number-average molecular weight, w_i is the weight fraction of the i^{th} monodisperse fraction, M_i is the homogeneous molecular weight.

This approach shows a limited demonstration of the versatility of the scaling law and suggests its potential usefulness in predicting polymer erosion from various mixtures of HPMC.

It is believed that polymer dissolution is mass transfer limited. The presence of agitation decreases the aqueous diffusion layer thickness and, thus, results in an increase in the mass transport from the matrix surface, which is consistent with the relationship between Jp and ω depicted in Eq: 6. Since polymer erosion is mass transfer limited in the presence of stirring, the same limiting condition will exist in the absence of stirring. In fact, polymer erosion remained linear over time under static condition, suggesting that polymer chain disentanglement does not play a limiting role in either free or forced convection polymer dissolution. However, chain disentanglement concentration is critical in establishing the driving force for mass transfer. It has been reported that the disentanglement concentration of a polymer follows a nonlinear, inverse relationship with molecular weight. Therefore, reducing the molecular weight of the polymer makes the matrix erode faster because this increases the disentanglement concentration.

Drug Release from HPMC Matrices in aqueous media

Drug release from HPMC matrices follows two mechanisms, diffusion through the swelling gel layer and release by matrix erosion of the swollen gel layer. HPMC matrices swell and eventually erode, providing an additional erosional component to the overall drug release. Initially drug release from HPMC matrices occur via a diffusion process until the outer gel layer reaches its critical

disentanglement concentration, and the additional release component due to erosion is manifested.

MODELS AND THEORIES FOR ORAL MODIFIED RELEASE SYSTEMS

There are several model and theories to explain the drug release form its formulations. Some of the best models, which best fits to my desired release formulation are.

Dissolution Controlled System

For water insoluble drugs, dissolution controlled systems are obvious choice for achieving sustained release because of their slow dissolution rate characteristic. Theoretically, the dissolution process at steady state can be described by Noyes – Whitney's equation. The rate of dissolution of a compound the function of surface area, saturation solubility and diffusion layer thickness. Therefore the rate of drug release can be manipulated by changing these parameter.

$$\frac{dC}{dt} = \frac{D * A\,(C_s - C_t)}{h * V} \qquad (Eq: 9)$$

Where, dc/dt is the dissolution rate, D is the diffusion coefficient, A is the surface area of the solid, C_s is the saturation solubility of the solid, C_t is the concentration at time, h is the diffusion layer thickness, V is the volume.

The above equation Eq: 9 predicts that the rate of release can be constant only if the following parameters are constant.

- Surface area
- Diffusion coefficient
- Diffusion layer thickness
- Concentration difference

But these parameters are not easy to maintain constant, especially surface area.

For spherical particles, the change in surface area can be related to the weight of the particle that is under assumption of sink conditions, above equation Eq: 9 can be rewritten as the cube root dissolution equation.

$$W_0^{1/3} - W^{1/3} = K_D t \qquad (Eq: 10)$$

Where, K_D is the Cube root dissolution rate constant, W_0 is the Initial weight, W is the Weight of the amount remaining at time t.

Diffusion and Erosion-Controlled Systems

A diffusion-controlled system is typically based on the drug diffusion through an inert membrane or a drug-carrying matrix. Sustained or controlled-release of water-insoluble drugs is achieved by a matrix diffusional system, in which the drug is homogeneously dissolved or dispersed throughout a matrix. The physical form of the drug-carrying matrix may be a liquid, semi-solid, or solid, and the finished dosage form may be a soft or hard gelatin capsule, or a tablet.

Matrix System

In this diffusion-controlled matrix system, drug in the outside layer of the matrix is exposed to the solution medium and dissolved first, it then diffuses out of the matrix as illustrated in figure below.

Diffusion-controlled matrix system for which the diffusion process is typically governed by Fick's Law (Eq: 12). The process continues at the interface between the bulk medium and solute and gradually moves toward the interior. In this approach, the dissolution rate of the drug within the matrix must be significantly faster than the diffusion rate of the dissolved drug. The release rate of a drug from a diffusion-controlled system can be mathematically described by a square-root-of-time relationship form the equation below.

$$M = kt^{1/2} \qquad (Eq: 11)$$

Where, M is the amount of drug released, k is the constant combining various contributing factors such as drug concentration in the matrix, porosity of the matrix and so forth.

Equation 11, is valid when the amount of drug release does not exceed 30-40% of the initial drug load of the matrix. On the other hand, case-II transport, which is completely governed by the rate of polymer relaxation, exhibits a linear-time dependence in both the amount diffused and the penetrating front position.

Note

A zero-order release cannot be achieved using a diffusion-controlled matrix system[70].

The process of diffusion is described by Fick's equation. This equation states that the amount of drug passing across a unit area is proportional to the concentration difference across that plane. The equation is given as

$$J = -D\frac{dC}{dx} \qquad \text{(Eq: 12)}$$

Where, J is the flux,(amount/ area-time), D is the diffusion coefficient of the drug ,(Area/time), d_C/d_X is the concentration gradient over the distance.

For the matrix system containing dissolved drug, the fractional released can be described by

$$\frac{M}{M_\infty} = \left(\frac{4}{l}\right)\left[\frac{Dt}{\pi}\right]^{\frac{1}{2}} \qquad \text{(Eq: 13)}$$

Where, M is the amount of drug released at time t, M_∞ is the total amount of drug released, l is the thickness of the matrix sheet, D is the drug diffusion coefficient in the matrix.

Bioerodible devices constitute a group of systems for which release characteristics are complex. The mechanism of release from simple erodible slabs, cylinders and spheres can be described by

$$\frac{M}{M_\infty} = 1 - \left(\frac{1 - K_o t}{A r}\right)^n \qquad \text{(Eq: 14)}$$

Where, r is the radius of a sphere or cylinder or the half height of a slab, *n* is 3 for a sphere, 2 for a cylinder and 1 for a slab.

For the system containing dispersed drug, where the drug loading per unit volume is greater than the drug solubility in the matrix, the drug release rate can be expressed by the Higuchi Equation[71].

$$M = [C_s(2A - C_s)Dt]^{1/2} \qquad \text{(Eq: 14)}$$

Where, Cs is the drug solubility in the matrix, A is the drug loading per unit volume.

Higuchi Equation (Eq: 14) was derived based on these assumptions:

1. A pseudo steady state exists.
2. The drug particles are small compared to the average distance of diffusion
3. The diffusion coefficient is constant.
4. Perfect sink conditions exist in the external media.
5. Drug release is exclusively through diffusion
6. The drug concentration in the matrix is greater than the drug solubility in the polymer
7. No interaction between drug and matrix takes place.

In the case where A >> C_s, then the above equation reduces to

$$M = [2DAC_s t]^{1/2} \qquad \text{(Eq: 15)}$$

Thus, the amount of drug released is proportional to the square root of A, time, D and Cs. In some cases, diffusion is not the only pathway by which a drug is released from the delivery system. The erosion of the delivery matrix following relaxation of the polymer and other functional excipients contributes to the overall drug release as well.

The drug release from a porous or granular matrix can be described by

$$M = \left\{D\, C_s \left(\frac{P}{T}\right)[2A - P\, C_s]t\right\}^{1/2} \qquad \text{(Eq: 16)}$$

Where, P is the Porosity of the matrix, T is the Tortuosity, C_s is the solubility of the drug in the release medium, D_s is the diffusion coefficient in the release medium.

This system is slightly different from the other matrix system in that, the drug is able to pass out of the matrix through fluid filled channels and does not pass through the polymer directly.

Membrane Reservoir Systems

Sustained or controlled-release of water-insoluble drugs can be achieved through another type of diffusion-controlled system i.e the reservoir. Such systems comprise a drug core and a surrounding polymeric membrane that controls or modifies the drug-release rate. Since drug-release kinetics can be controlled by changing the characteristics of the polymeric material(s) used for the rate-controlling membrane, a zero-order release profile could be attainable with the design. Drug release from such a delivery system is mathematically described for a simple slab-like system, and will vary depending on the geometry of the system[45,46,7] form the below equation.

$$\frac{dM_t}{dt} = \frac{ADK\Delta C}{d} \qquad (Eq: 17)$$

Where

dMt/dt is the steady state release rate at time t, A is the surface area of the reservoir system, D is the diffusion coefficient, K is the participant coefficient, C is the concentration difference across the membrane, d is the diffusion layer thickness.

The left side of equation Eq: 17 represents the release rate of the system. A true controlled release system with a zero- order release rate can be possible if all of the variables on the right side of equation remain constant. But it is very difficult to maintain all the parameters constant. Again depending on the device diffusion systems can provide constant release at steady state. For reservoir devices, a system that is used relatively soon after construction will demonstrate a large time in release, since it will take time for the drug to diffuse from the reservoir to the membrane surface. On the other hand, systems that are stored will demonstrate a burst effect, since, on standing the membrane becomes saturated with available drug. The magnitude of these effects is dependent on the diffusing distance. (i.e. the membrane thickness).

BIO-ADHESIVE

Bio adhesion could also be outlined because the state during which 2 materials, atleast one in all that is of biological nature, area unit control along for extended periods of your time by surface forces. For drug delivery functions, the term bioadhesion implies attachment of a drug carrier system to a selected biological location. The biological surface may be animal tissue, or the secretion coat on the surface of a tissue. If adhesive attachment is to mucous coat, the phenomenon is referred to as mucoadhesion.

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, joined by cross-linking agents. These compounds possess best polarity to create positive that they allow spare wetting by the secretion and best liquidity that allows the mutual surface assimilation and interpenetration of polymer and mucus to take place. Mucoadhesive polymers that adhere to the mucin–epithelial surface are divided into three classes.

- Polymers that become sticky once placed in water and owe their mucoadhesion to viscousness.
- Polymers that adhere through nonspecific, noncovalent interactions that area unit primarily static in nature (although chemical element and hydrophobic bonding could also be significant).
- Polymers that bind to specific receptor website on tile self-surface.

FACTORS AFFECTING MUCOADHESION

Polymer-Related Factors

Molecular Weight

The threshold needed for winning bioadhesion is a minimum of one hundred, 1000 molecular weight.

Concentration of Active Polymer

Optimum concentration of polymer produces maximum bioadhesion. In extremely targeted system, on the far side the optimum level, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chain available for interpenetration becomes limited.

Flexibility of Polymer Chains

As water soluble-polymers become cross-linked, mobility of an individual polymer chain decreases and the effective length of the chain that can penetrate into the mucus layer decreases, which reduces bio adhesive strength.

Swelling

Swelling depends on the compound concentration, the ionic strength, and the presence of water. During the dynamic method of bioadhesion, maximum bioadhesion in vitro occurs with optimum water content. Over hydration results in the formation of a wet slippery mucilage without adhesion.

Environment-Related Factors

pH of Polymer–Substrate Interface

pH can influence the formal charge on the surface of the mucus as well as certain ionizable

bioadhesive polymers. The pH of the medium is important for the degree of hydration of polymer.

Applied Strength

To place a solid bio adhesive system, it is necessary to apply a defined strength. The pressure ab initio applied to the mucoadhesive tissue contact website will have an effect on the depth of interpenetration. If high is applied for a sufficiently long amount of your time, polymers become mucoadhesive even though they do not have attractive interactions with mucin.

Initial Contact Time

Contact time between the bioadhesive and secretion layer determines the extent of swelling and interpenetration of the bioadhesive compound chains. Bioadhesive strength will increase because the initial contact time will increase.

Physiological Factors

Mucin Turnover

The mucin turnover is expected to limit the residence time of the mucoadhesives on the mucus layer. No matter how high the mucoadhesive strength, mucoadhesives are detached from the surface due to mucin turnover. Surface fouling is unfavorable for mucoadhesion to the tissue surface. Mucin turnover may also depend on the presence of food.

Disease State

The physiochemical properties of the mucus changes during disease conditions such as the common cold, gastric ulcers, ulcerative colitis[72-75].

EVALUATION METHODS TO STUDY MUCOADHESION

***In Vitro*/Ex Vivo Methods**

Methods Based on the Measurement of Tensile Strength

Measures the force required to break the adhesive bond between a model membrane and test polymers. The instruments usually employed are modified balances or tensile testers. Eg : Robinson's Method

Methods Based on the Measurement of Shear Strengths

Shear stress is a measure of force that causes the bioadhesive to slide with respect to the mucus layer in a direction parallel to the plane of contact.

Eg: Wilhelmy plate method

Fluorescent Probe Method[76]

Park and Robinson studied on conjunctival epithelial cell membrane to understand structural requirements for bioadhesion. The membrane lipid bilayer and membrane proteins were labeled with pyrene and fluorescein isothiocyanate, respectively. The cells were then mixed with candidate bioadhesive, and the changes in fluorescence spectra were monitored giving a direct indication of polymer binding and its influence on polymer adhesion.

Flow Channel Method[77]

Mikos and Peppas developed that utilized a thin channel made of glass and filled with 2% (wt/wt) aqueous solution of bovine submaxillary mucin, thermostated at 37°C. Humid air at 37°C was passed through the glass channel. A bioadhesive polymer was placed on the mucin gel. The static and dynamic behavior was monitored by using a camera.

Viscometeric Method[78]

Hassan and Gallo developed to quantify mucin–polymer bioadhesive bond strength. Viscosities of 15% (wt/vol) percine gastric mucin dispersion in 0.1 N HCl (pH 1) or 0.1 N acetate (pH 5.5) were measured with a Brookfield viscometer in the absence or presence of selected neutral, anionic, and cationic polymers. Viscosity components and the forces of bioadhesion were calculated.

***In Vivo* Methods**

Use of Gamma Scintigraphy[79]

It is a valuable noninvasively tool. This technique is useful for oral dosage forms across the different regions of GI tract, the time and site of disintegration of dosage forms, the site of drug absorption, and also the effect of food, disease, and size of the dosage form on the *in vivo* performance of the dosage forms.

Some of the radioisotopes used are Technetium (^{99m}Tc) and Indium (^{111}In).

X-ray Studies[80]

Chary *et al*. performed the in vivo adhesion testing of barium sulfate matrix tablet containing polymer and drug by X-ray study in rabbits

Use of Radioisotopes

It is an invasive method, hence not being deployed now a days. Cr-55 isotope used in order to investigate the GI transit of bioadhesive in rats.

Table No.1: Different Enteric Polymers

S.No	Enteric polymers	Optimum pH for Dissolution
1	Polyvinyl acetate phthalate (PVAP)	5.0
2	Cellulose acetate trimellitate (CAT)	5.5
3	Hydroxypropyl methylcellulose phthalate (HPMCP) HP-50 HP-55 and HP-55S	 ≥5.0 ≥5.5
4	Hydroxypropylmethylcellulose acetate succinate (HPMCAS) LF Grade MF Grade HF Grade	 ≥5.5 ≥6.0 ≥6.8
5	Methacrylic acid copolymer, Type C (Eudragit L100-55)	≥5.5
6	Methacrylic acid copolymer dispersion (Eudragit L30D-55)	≥5.5
7	Methacrylic acid copolymer, Type A (Eudragit □L-100 and Eudragit L12,5)	 ≥6.0
8	Cellulose acetate phthalate(CAP)	6.0
9	Methacrylic acid copolymer, Type B (Eudragit S-100 and Eudragit S12,5)	 ≥7.0
10	Eudragit □FS30D	≥7.0
11	Shellac	7.0

Table No.2: Mesalamine Marketed Formulation according to Polymer Coating

S.No	Drug	Trade Name	Formulation
1	Mesalamine	Asacol	Eudragit S Coated Tablets(Dissolves at pH 7)
		Salofac	Eudragit L Coated Tablets(Dissolves at pH 6)
		Claversal,Mesazal,Calitoflak	Eudragit L Coated Tablets(Dissolves at pH 6)

Available Marketed Formulations

Table No.3: Available Marketed Mesalamine Formulation acc. to delivery type

S.No	Delivery Type	Drug	Delivery Site	Brand Name
1	Azo bond / Pro-drug.	Sulfasalazine	Colon	Azulfidine, Azulfidine EN Tab.
		Olsalazine sodium	Colon	Dipentum
		Balsalazide disodium	Colon	Colazal
2	pH sensitive coating	Mesalamine	Distal ileum/Colon	Asacol.
3	Moisture sensitive coating (Ethycellulose coating)	Mesalamine	Stomach to colon	Pentasa
4	Suppositories	Mesalamine	Rectum	Canasa
5	Enema	Mesalamine	Rectum to splenic flexure	Rowasa

Table No.4: Erosion rates of different polymers

S.No	2% W/V Polymer Solution (mPa.s)	Intrinsic Viscosity (dL/g)	Molecular Weight	Erosion Rate (%Hr^{-1})
1	130	2.77	224,236	5.83
2	300	3.05	267,331	5.09
3	550	3.12	278,937	4.83
4	700	3.99	435,648	4.16
5	800	4.50	583,960	3.76
6	2700	6.15	954,655	2.37
7	4000	6.94	1,190,688	1.96
8	15000	8.69	1,791,493	1.28
9	75000	11.56	3,009,635	0.93

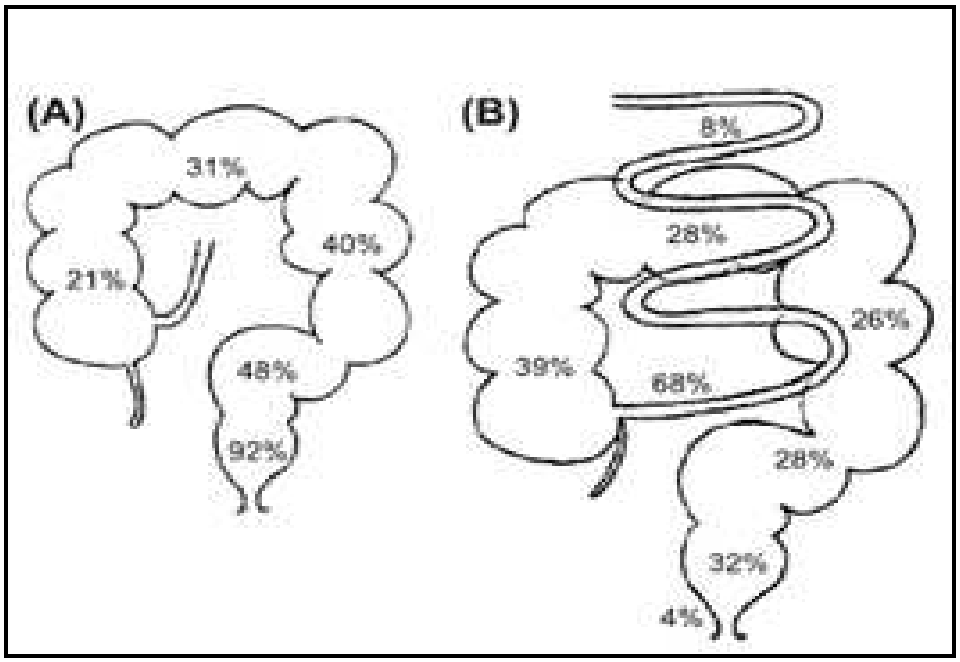

Figure No.1: Percentage of patients with suffering with IBS

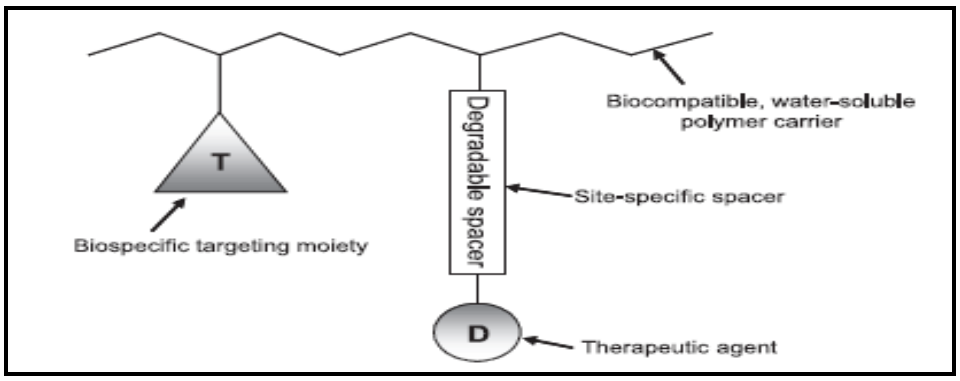

Figure No.2: Structure of targeted polymer-drug (prodrug) conjugates

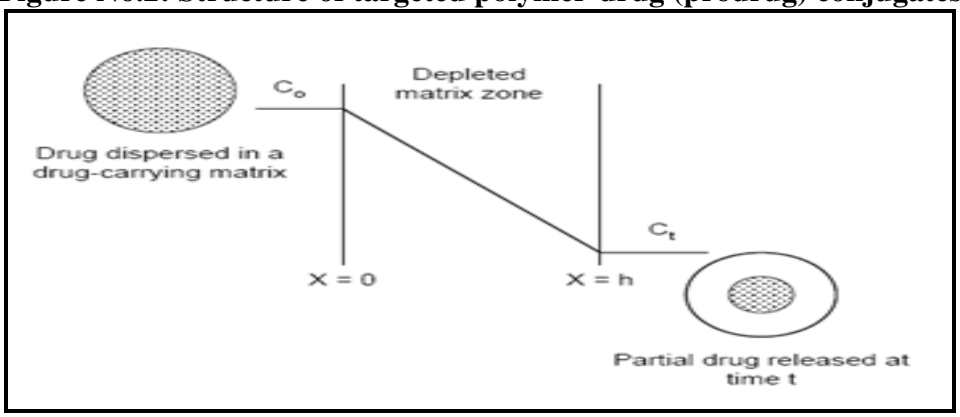

Figure No.3: Diffusion-controlled matrix system for diffusion process

CONCLUSION

Though there are different process of making Drug-Cyclodextrin Complexes, survey suggests, that kneading process exhibits good results, as concerned with amount of drug entrapment, % yield, preparation cost, time, scale up problems etc. In kneading process, Isopropyl alcohol was selected as a solvent for kneading of β-cyclodextrin and Mesalamine because of its low solubility. IPA has high vapour pressure making it easy to evaporate as compared with water. Hence making it an ideal solvent for production purpose. The produced M-CC was examined by FTIR, HSM, SEM. FTIR spectra reveals that there is a formation of non bonding (supra molecular association) association between mesalamine and β-Cyclodextrin. Suggesting the absence of only chemical bonding. HSM and SEM visuals showed good signs complexes. The Drug and β-Cyclodextrin ratio was finalized by the Solubility Studies with 1:1 ratio which shows effective solubility, complexation of drug with minimum β-Cyclodextrin. To develop an efficient colon specific acting drug is still a challenge because of its action mainly at colon only. Some of the works done in last two year were really good especially in overcoming the side effects. In future by combining various other strategies, colon targeted drug delivery will find the central place in novel drug delivery. The complex was prepared by dialdehyde konjac glucomannan and adipic dihydrazides to form steady Schiff base, and crosslinking with 5-aminosalicylic acid (5-ASA) through gularaldehyde as a cross-linking agent.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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