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Microencapsulation Based Colon Drug Delivery Systems-An Over View

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ABSTRACT

Targeted drug delivery systems deliver the drug to the site of action. Colon Targeted drug delivery is considered as one of the most convenient pathway for the delivery of the drugs or therapeutic agents and used in the treatment of the local diseases. Microencapsulation is widely used in the pharmaceutical and other sciences to mask taste/odors, prolong release, impart stability to drug molecules, improve bioavailability, and as multiparticulate dosage forms to produce controlled or targeted drug delivery. Microencapsulation is the process in which small droplets or particles of liquid or solid material are surrounded or coated by a continuous film of polymeric materials. Microencapsulation system offers potential advantages over the conventional drug delivery systems. In this present article various technologies for the preparation of microcapsules for the purpose of colon targeted drug delivery systems are reviewed.

Keywords: Colon Targeted Drug Delivery, Approaches, Microcapsules, Technologies, Evaluation.

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INTRODUCTION

During the past decades research is going on in developing the methods to target the drug to the specific region. The goal of targeted drug delivery is to deliver the drug to the specific organ. Colon targeted drug delivery is used to deliver the substances that are degraded by the digestive enzymes in the stomach such as proteins and peptides. It is also used for the treatment of various diseases like ulcerative colitis, crohn's disease, intestinal cancer, diarrhea, for the treatment of diseases sensitive to circadian rhythms like Asthma, Angina, for the delivery of steroids, etc. colon targeted drug delivery of drugs reduces the systemic side effects. Colon targeted drug delivery system increases the absorption of poorly absorbable drugs due to the high retention time of the colon.

Advantages

1. Used for the effective treatment of inflammatory bowel diseases like ulcerative colitis, crohn's disease, etc.
2. Decreases the side effects in the treatment of colon diseases.
3. Prevents gastric irritation resulting due to the administration of NSAIDs.
4. Minimizes first pass metabolism.
5. Provides suitable environment for proteins and peptides that are sensitive to gastric fluid and digestive enzymes.
6. Increased patient compliance.
7. Decreased frequency of administration. Hence decreased cost of drugs.
8. High retention time thus increasing the bioavailability of poorly absorbable drugs[1].

Need For Colon Targeted Drug Delivery

To ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon-specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved. Topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease is usually treated with glucocorticoids and Sulphasalazine[22]. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon. Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides[2].

Criteria for selection of drug for colon drug delivery system (CDDS)

Drug Candidate

Drugs which show poor absorption from the stomach or intestine including peptide are most suitable for CDDS. The drugs used in the treatment of inflammatory bowel disease (IBD), ulcerative colitis, diarrhea and colon cancer is ideal candidates for local colon delivery. Criteria for selection drugs for CDDS are summarized in Table 1.

Table 1: Criteria for selection of drugs for CDDS

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolol, Metoprolol, Nifedipine	Antisense oligonucleotide
Drugs poorly absorbed from upper GIT	Antihypertensive and Antianginal drugs	Ibuprofen, Isosorbides, Theophylline,	Cyclosporine, Desmopressin
Drugs for colon cancer	Antineoplastic drugs	Pseudoephedrine	Epoetin, Glucagon
Drugs that degrade in stomach and small intestine	Peptides and Proteins	Bromophenaramine, 5 Flourouracil, Doxrubicin,	Gonadoreline, Insulin, Interferons
Drugs that undergo extensive first pass metabolism	Nitroglycerin and Corticosteroids	Bleomycin, Nicotine	Protirelin, Sermorelin, Saloatonin
Drugs for targeting	Antiarthritic and Antiasthamatic drugs	Prednisolone, Hydrocortisone, 5-Amino-salicylic acid Amylin,	Somatropin, Urotoilitin

Drug Carrier

The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of the drug and the type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule.

The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems[3].

Anatomy and Physiology of Colon

The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts. These are the colon, the rectum and anal canal. The entire colon is about 5 feet (150 cm) long, and is divided in

to five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon. The left colon contain the left half of the transverse colon, descendincolon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus. The human colon were shown in Figure1.The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed (Figure1)[4].

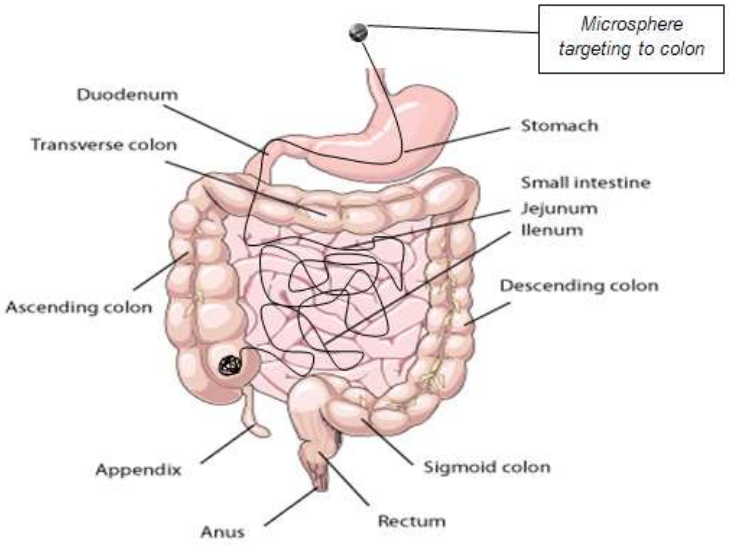

Figure 1: Anatomy of colon

Approaches Used For Site Specific Drug Delivery to Colon

Several approaches are used for site-specific drug delivery. Among the primary approaches for CDDS, These include:

Primary Approaches of Colon Specific Drug Delivery System

PH- dependent delivery

In the stomach, pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. From the ileum to the colon, pH declines significantly. Most commonly used pH dependent coating polymers are methacrylic acid copolymers, commonly known as Eudragit S, more specifically Eudragit L and S. Colon targeted drug delivery systems based on methacrylic resins has described for insulin, prednisolone, quinolones, salsalazine, cyclosporine, beclomethasone dipropionate and naproxen.

Dissolution studies performed on the mesalazine tablets further confirmed that the release profiles of the drug could be manipulated by changing the Eudragit L100-55 and Eudragit S100 ratios within the pH range of 5.5 to 7.0 in which the individual polymers are soluble respectively, and a coating formulation consisting of a combination of the two copolymers can overcome the issue of high GI pH variability among individuals[5-6].

Delayed (Time controlled release system) release drug delivery to colon

Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising. However due to potentially large variation of gastric emptying time of dosage forms in humans, in this approach colon arrival time of dosage forms can not accurately predicted, resulting in poor colonical availability. The dosage forms may also applicable as colon targeting dosage forms by prolonging the lag time of about 5.5 hours (range 5 to 6 hours).

Disadvantages of this system are-

1. Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
2. Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.
3. Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea and the ulcerative colitis.

Microbially triggered system

These systems are based on the exploitation of the specific enzymatic activity of the microflora (enterobacteria) present in the colon. The colonic bacteria are predominately anaerobic in nature and secrete enzymes that are capable of metabolizing substrates such as carbohydrates and proteins that escape the digestion in the upper GI tract6-8. Bacterial count in colon is much higher around 1011-1012 CFU/ml with some 400 different species which are:

Fundamentally aerobic, predominant species such as Bacteroides, Bifid bacterium and Eubacterum etc., whose major metabolic process occurring in colon are hydrolysis and reduction. The enzymes present in the colon are:

1. Reducing enzymes: Nitroreductase, Azoreductase, N-oxide reductase, sulfoxide reductase, Hydrogenase etc.
2. Hydrolytic enzymes: Esterases, Amidases, Glycosidases, Glucuronidase, sulfatase etc.

Prodrug approach for drug delivery to colon

Prodrug is the main approach of microbial triggered drug delivery system in which the drug release from the formulation is triggered by the microflora present in the gut. Prodrug is the inactive form

of an active parent drug that undergoes enzymatic transformation to release the active drug (Figure 2). The prodrugs are prepared by linking the active drug with hydrophobic moieties like amino acids, glucoronic acids, glucose, galactose, cellulose, etc.

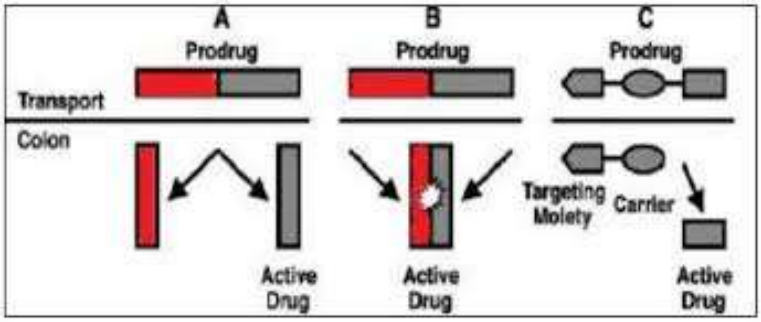

Figure 2: Prodrug approach for CDDS

Polysaccharide based delivery systems

Polysaccharide based delivery system is the other form of microbial triggered drug delivery system. Naturally occurring polysaccharides like guar gum, xanthan gum, chitosan, alginates, etc. are used in targeting the drug delivery. These are broken down by the colonic micro flora to simple saccharides.

NEWLY DEVELOPED APPROACHES FOR CDDS

Pressure-controlled drug-delivery systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine, have developed pressure controlled colon-delivery capsules prepared using ethyl cellulose, which is insoluble in water. In such systems drug release occurs following disintegration of a water-insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure-controlled ethyl cellulose single-unit capsules the drug is in a liquid[7,10].

Pulsatile colon targeted drug delivery

Pulsincap system

In this system (Figure 3) the formulation is developed in a capsule form. The plug placed in the capsule controls the release of the drug. Swellable hydrogels are used to seal the drug contents. The capsule gets swelled when it comes in contact with the dissolution fluid and after a lag time the plug gets pushed off from the capsule and the drug will be released. Polymers such as different

grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs.

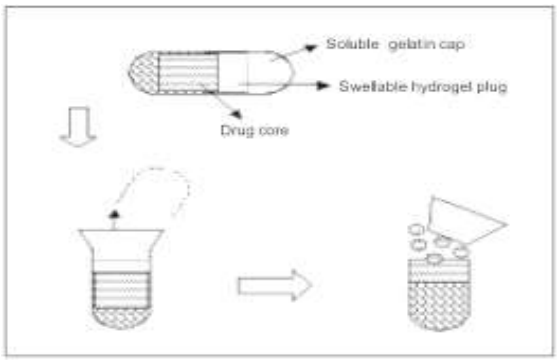

Figure 3: Drug release mechanism of Pulsincap system

Port system

In this system (Figure 4) the capsule body is enclosed in a semi permeable membrane. The capsule body consists of an insoluble plug consisting of osmotically active agent and drug formulation.

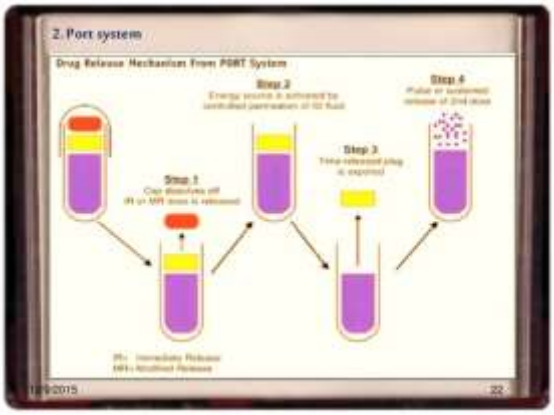

Figure 4: Drug release mechanism of port system

When the capsule comes in contact with the dissolution fluid the semi permeable membrane permits the fluid flow into the capsule resulting in the development of pressure in the capsule body which leads to release of drug due to expelling of the plug. The drug is released at regular intervals with time gap between the successive intervals[8].

OSMOTICALLY CONTROLLED SYSTEM (ORDS- CT)

The OROS-CT (Alza Corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule, Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi permeable membrane. An

orifice is drilled through the membrane next to the drug layer (Figure 5). Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units' dissolves[14].

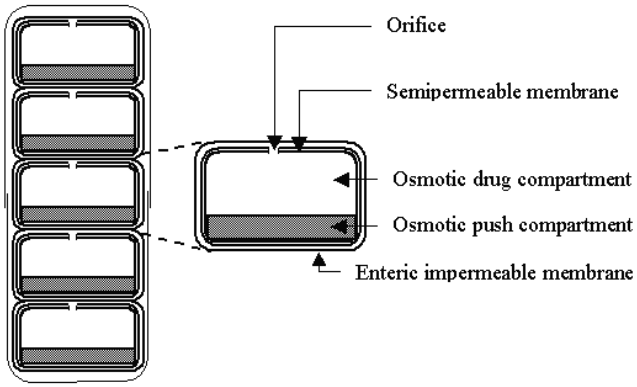

Figure 5:Osmotically controlled CDDS

CODES TECHNOLOGY (COMBINATION OF PH DEPENDENT AND MICROBIALLY TRIGGERED CDDS)

This method is developed to minimize the problems associated with the pH and time dependent drug delivery systems. In this system the pH sensitive polymers are used along with the

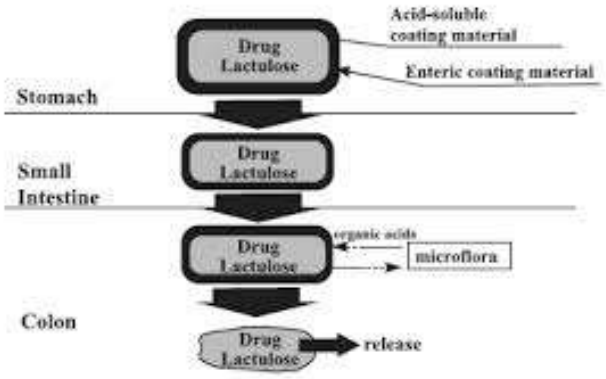

Figure 6: CODES system

Polysaccharides that are degraded only by specific bacteria present in the intestine. This system consists of a core tablet coated with three layers of polymer coatings. The outer coating is composed of the polymer Eudragit L. This coating gets dissolved once the tablet passes though the pyloric and duodenum and exposes the next coating. This released lactulose gets metabolized into short chain fatty acids that lower the surrounding pH where the Eudragit E layer dissolves. (Figure 6)[7-8].

MICROENCAPSULATION

Microencapsulation is the process in which small droplets or particles of liquid or solid material are surrounded or coated by a continuous film of polymeric materials. Microencapsulation is widely used in the pharmaceutical and other sciences to mask taste/ odors, prolong release, impart

stability to drug molecules, improve bioavailability, and as multi-particulate dosage forms to produce controlled or colon targeted drug delivery[26].

One such approach is using microspheres as carriers for drugs. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having particle size less than 200 μm[27].

THE REASONS FOR MICROENCAPSULATION

The reasons for microencapsulation are countless. In some cases, the core must be isolated from its surroundings, as in isolating vitamins from the deteriorating effects of oxygen, retarding evaporation of a volatile core, improving the handling properties of a sticky material, or isolating a reactive core from chemical attack. In other cases, the objective is not to isolate the core completely but to control the rate at which it leaves the microcapsule, as in the controlled release of drugs or pesticides. The problem may be as simple as masking the taste or odor of the core, or as complex as increasing the selectivity of an adsorption or extraction process[17].

APPLICATIONS OF MICROENCAPSULATION

Some of the applications of microencapsulation can be described in detail as given below:

1. Prolonged release dosage forms. The microencapsulated drug can be administered, as microencapsulation is perhaps most useful for the preparation of tablets, capsules or parenteral dosage forms.
2. Microencapsulation can be used to prepare enteric coated dosage forms, so that the medicament will be selectively absorbed in the intestine rather than the stomach.
3. It can be used to mask the taste of bitter drugs.
4. The hygroscopic properties of many core materials may be reduced by microencapsulation.
5. Many drugs have been microencapsulated to reduce gastric irritation.
6. Microencapsulation method has also been proposed to prepare intrauterine contraceptive device.
7. In the fabrication of multilayered tablet formulations for controlled release of medicament contained in medial layers of tableted particles[23].
8. To mask the bitter taste of drugs like Paracetamol, Nitrofurantoin etc.
9. A liquid can be converted to a pseudo-solid for easy handling and storage. Eg. Eprazinone.
10. Hygroscopic properties of core materials may be reduced by microencapsulation eg. Sodium chloride[15-17].

MAJOR COMPONENTS OF MICROCAPSULES

Core material

The core material is defined as the material to be coated (liquid or solid). It consists of active constituents, diuents, stabelizers or release rate inhibitors.

Coating material

The coating material used in microencapsulation should be capable to form a film on core material and should be compatible with drug and other ingredients.

Examples

Water soluble resins: Gelatin, Starch, Methylcellulose, Polyvinyl alcohol, etc.

Water insoluble resins: Ethylcellulose, Polyamide, Polyethylene, Silicones, etc.

Enteric resins: Zein, Shellac, Cellulose acetate phthalate, etc.

Waxes and lipids: Paraffin, Stearyl alcohol, Beeswax, etc[21].

MICROENCAPSULATION METHODS

There are a number of techniques that can be used to fabricate microcapsules, depending on the desired characteristics and applications of the final microcapsule formulation. These techniques can be broadly categorized into chemical, physical and physicochemical methods.

PHYSICAL METHODS:

Pan coating:

The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly.

Air-suspension coating:

Micro-encapsulation by air suspension is a technique that gives improved control and flexibility compared to pan coating. Solid, particulate core material is supported in a rising air stream and spray coating applied to the air suspended particles. The design of the coating chamber is arranged so that the solid particles pass up through the coating zone, then disperse into slower moving air and sink back to the base of the coating chamber, making repeated passes through the coating zone until the desired thickness of coating is achieved. Drying of the coated particles takes place simultaneously by the passage of hot air for suspending the particles.

Spray–drying:

Spray drying serves as a microencapsulation technique when an active material is dissolved or suspended in a melt or polymer solution and becomes trapped in the dried particle. The main advantages are the ability to handle thermo labile materials because of the short contact time in the dryer; in addition, the operation is economical[27].

PHYSICO-CHEMICAL METHODS

Coacervation:

Currently, two methods for coacervation are available, namely simple and complex processes. The mechanism of microcapsule formation for both processes is identical, except for the way in which the phase separation is carried out. In simple coacervation a desolvation agent is added for phase separation, whereas complex coacervation involves complexation between two oppositely charged polymers.

The process consists of three steps:

- Formation of three immiscible phases: Solvent, Core material phase, Coating material phase.
- Deposition of the coating material on the core material.
- Stiffening the coating usually by thermal, cross linking or desolvation techniques to form a microcapsule[14].

CHEMICAL METHODS:

Interfacial polycondensation:

In Interfacial polycondensation, the two reactants in a polycondensation meet at an interface and react rapidly. The basis of this method is the classical Schotten-Baumann reaction between an acid chloride and a compound containing an active hydrogen atom, such as an amine or alcohol, polyesters, polyurea, polyurethane.

Interfacial cross-linking:

Interfacial cross-linking is derived from interfacial polycondensation, and was developed to avoid the use of toxic diamines, for pharmaceutical or cosmetic applications. In this method, the small bifunctional monomer containing active hydrogen atoms is replaced by a biosourced polymer, like a protein. When the reaction is performed at the interface of an emulsion, the acid chloride reacts with the various functional groups of the protein, leading to the formation of a membrane. The cross-linked protein microcapsules are biocompatible and biodegradable, and the presence of the protein backbone renders the membrane more resistant and elastic than those obtained by interfacial polycondensation. The method is very versatile, and the properties of the microcapsules (size, porosity, degradability, mechanical resistance) can be easily tuned by varying the preparation parameters. A carbohydrate can be added to the protein, for the modulation of particle biodegradability[18-27].

EVALUATION OF MICROCAPSULES

Encapsulation efficiency

Accurately weighed microcapsules were added, chloroform used as common solvent of drug and polymer. The drug was extracted three times from chloroform using phosphate buffer pH 7.4. Each time extraction was carried out using separating funnel with shaking time. After complete extraction of drug, the amount of drug was quantified spectrophotometrically by using UV-Visible double beam Spectro-photometer. The encapsulation efficiency of microcapsules was calculated by using the equation[20].

$$Encapsulation\ Efficiency\ = \frac{calculated\ drug\ content * 100}{Theoretical\ drug\ count}$$

Scanning electron microscopy (SEM)

Morphology and surface topography of the microcapsules were examined by scanning electron microscopy[19].

Infrared Spectroscopy (FTIR)

Drug-polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for empty and drug loaded microcapsules using FTIR. Samples were prepared in KBr discs. The scanning range was 400-4000 cm $^{-1}$ and the resolution was 2 cm $^{-1}$.

Differential Scanning Calorimetry (DSC)

The DSC analyses of empty and drug-loaded microcapsules were carried out using a DSC to evaluate any possible drug-polymer interaction. The analysis was performed at a rate 10.00^0 C min $^{-1}$ from 25^{0}C to 250^{0}C temperature range under nitrogen flow of 25 ml/min.

X-ray powder Diffractometry (X-RD)

X-ray powder diffractometry was carried out to investigate the effect of microencapsulation process on crystallinility of drug. Powder X-RD patterns were recorded on PW 3710 based diffractometer using a voltage of 40kV and a current of 30mA.The scanning rate employed was 50 min $^{-1}$, over the 50 to 400 diffraction angle (2θ) range. The X-RD patterns of empty and drug-loaded microcapsules were recorded.

In vitro drug release studies and release kinetic study

The in vitro release studies of drug-loaded microcapsules were carried out and 75 rpm using prepared HCL, Phosphate buffer, and phosphate buffer solutions in a USP dissolution apparatus type II (basket type) under sink conditions. Accurately weighed samples of microcapsules were placed in muslin cloth which was closely tied and kept in baskets. [25] At specific time intervals aliquots were withdrawn and replaced by an equal volume of fresh dissolution medium. After suitable dilution, the samples were analysed spectrophotometrically[11].

MECHANISM AND KINETICS OF DRUG RELEASE

Major mechanisms of drug release from microcapsules include diffusion, dissolution, osmosis and erosion:

Diffusion

The most common mechanism of drug release (core material) in which the dissolution fluid penetrates the shell then the core material comes into the contact with the dissolution fluid and leak out through the interstitial channels or pores. The drug release depends on the rate of drug dissolution in the dissolution fluid, rate of penetration of dissolution fluid to the microcapsules and rate at which the dissolved drug escapes from the microcapsule.

Dissolution

The release rate of the drug from the microcapsule depends on the dissolution rate of polymer coat, when the coat is soluble in the dissolution fluid. The solubility in the dissolution fluid and thickness of coat influence the release rate.

Osmosis

Another method of drug release is through osmosis. The essential requirement of osmosis is semi permeable membrane and in microcapsule polymer coat serve the purpose.

As the process progress an osmotic pressure is created between the outside and the inside membrane of microcapsule which result in release of drug through small pores.

Erosion

Erosion of coat generally occur due to pH or enzymatic hydrolysis and causes drug release with certain coat materials like bee's wax, stearyl alcohol and glyceryl monostearate. The drug release from microcapsules has become complex because of great diversity in physical forms of microcapsules with size, shape and arrangement of the core and coat materials. However, on the basis of various studies concerning with the release characteristics, the following considerations can be made:

Drug release rate from microcapsules follow the zero order kinetic.

- Total drug release and thereafter turn down exponentially.
- Microcapsules of monolithic type have the t1/2 dependant release rate for the first half of the Microcapsules of monolithic type containing excess of dissolved drug, the release rate are t1/2 dependent throughout almost the entire drug release.
- The path traveled by drug is not constant in monolithic capsules; as the drug at the center travels a large distance than the drug at the surface. Therefore, the release rate in monolithic capsules generally decreases with time[10].

Some new microencapsulated drugs which are available in market shown in Table 2.

Table 2: Microencapsulated Drugs available in market

Sl No.	Drug material	Purpose	Product
1.	Acetaminophen	Taste masking.	Tablet
2.	Aspirin	Taste masking, sustained release, reduce gastric irritation & incompatibilities.	Tablet or capsule
3.	Islet of Langerhans	Sustained normalization of diabetic condition.	Injectables
4.	Isosorbide dinitrate	Sustained release capsules.	Capsules
5.	Menthol	Reduction of volatility.	Lotion
6.	Progesterone	Sustained release.	Varied
7.	Potassium chloride	Reduced gastric irritation.	Capsules
8.	Urease	Perm selectivity of enzyme, substrate & and reaction product.	Dispersion

Data analysis

To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to Zero order, First order, Higuchi matrix, Krosmeyer`s Peppas model and Hixon Crowell model. In this by comparing the R-values obtained, the best-fit model was selected[12-13].

CONCLUSION

Targeted delivery system offers a site specific release of the drug. Microencapsulation can be considered a novel approach for the delivery of various drugs having problems in their bioavailability, bitter taste, reduced dissolution rate, facilitation of handling and also for the colon targeted drug delivery system. Microencapsulation system offers potential advantages over the conventional drug delivery systems. Therefore, this safe and efficient particular system should be developed in future.

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