A REVIEW ON MICROCAPSULES BASED COLON TARGETED DRUG DELIVERY SYSTEM

Archana Chaudhary*, Ankaj Kaundal

1Assistant Professor in Pharmaceutics, Laureate Institute of Pharmacy, Kathog (H.P)
2Assistant Professor in Pharmaceutics, Laureate Institute of Pharmacy, Kathog (H.P)

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 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 multiparticulate dosage forms to produce controlled or targeted drug delivery. Various methods for the preparation of microcapsules are also reviewed. Microencapsulation system offers potential advantages over the conventional drug delivery systems.

KEY WORDS: Colon targeted, Microcapsules, Targeted Drug Delivery, Preparation of Microcapsules.

INTRODUCTION
Targeted drug delivery systems deliver the drug to the site of action or its target. 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 like: diarrhea Colon, constipation, ameobosis, inflammatory bowel disease, colonic cancer, (Crohn’s disease, ulceraer colitis). It is also used for the synthetic absorption of proteins, peptides.
and for those drugs where a delay in drug absorption is required for a therapeutic point of view e.g. cardiac arrhythmias, nocturnal asthma and arthritis, that are by circadian Biorythmias. Colon drug delivery system is useful in administering drugs that are irritant to the upper gastrointestinal tract such as non steroidal anti inflammatory agents or drugs such as peptides that are degraded by gastric juice or an enzyme present in the upper GI tract. Many of these drug products release drug for at a first-order rate. The successful targeted drug delivery of drugs to the colon by the GIT tract requires the protection of a drug from degradation and release in the stomach and small intestine and then ensures abrupt and controlled release in the proximal colon. Targeting relies on exploiting a unique feature of intended site and protecting the active agent until it reaches the site. The transit of orally administered formulation through the GI tract is highly variable and depends on various factors, e.g. disease state of the lumen (diarrhea, diabetes, peptic ulcer etc), concomitant administration of other drugs (cisapride, metoclopramide, domperidone etc), body posture (vertical or supine) and food type (fat and protein content) can influence the gastric emptying rate. Gastric transit time of non-disintegrating single-unit dosage forms has been reported to vary from 15 min to more than 3 h. At the same time, the small intestinal residence time is fairly constant and varies between 3-4 h. It is reported that the maximum mean colonic transit time in humans is to be as high as 33 h in men and 47 h in women. Due to the distal location of the colon several approaches have been developed for colonic drug delivery such as prodrug, pH dependent, pressure controlled, time dependent, bacterially triggered drug delivery system. Widely used colon targeted drug formulations are single unit dosage form and multiparticulate dosage forms. Single unit colon targeted drug delivery system may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or local therapeutic action in the colon. Recently much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single unit systems because of their potential benefits like increased bioavailability, less risk of systemic toxicity, less risk of local irritation. Multiparticulate approaches used for colonic delivery includes formulations like pellets, granules, microparticles and nanoparticles. 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 targeted drug delivery.\textsuperscript{6}

**Need For colon targeted drug delivery**\textsuperscript{4,7}

1. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dose and fewer systemic side effects.
2. The colon is a site where both local or systemic drug delivery could be achieved.
3. Targeted drug delivery would allow the oral administration of protein and peptides drugs.
4. Targeted drug formulations could also be used to prolong the drug delivery.
5. Formulations for colonic delivery are also suitable for the delivery of drug which are polar or susceptible to chemical and enzymatic degradation in the upper gastrointestinal tract, highly affected by hepatic metabolism.
6. Colon having the lower level of luminal and mucosal digestive enzyme as compared with the small intestine reduces the chance of drug degradation.

**Advantages**\textsuperscript{2, 3, 4, 5}

1. Various advantages of colon targeted drug delivery systems includes
2. Better bioavailability
3. Improve patient compliance
4. Requirement of lower dose of drug
5. Longer retention time
6. Mucosal protection from irritating drug
7. Enhanced absorption of poorly absorbed drug
8. Reduce incidence of side effects.

**Disadvantages**\textsuperscript{3, 8}

Along with above said advantages colon delivery systems have following drawbacks;
1. If coating is not proper than degradation of drug in the stomach due to the presence of HCl
2. Food effects drug absorption which is present in gastrointestinal tract
3. Release of drug at specific colon site is necessary
4. Qualified person is required for manufacturing of targeted drug delivery system
5. Toxicity due to dose dumping
6. Drug retrieval is difficult in case of toxicity, poisoning or hypersensitivity.
Major components of microcapsules\textsuperscript{9,10}

Core material
The core material is defined as the material to be coated (liquid or solid). It consist of active constituents, diluents, stabilizers 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.

Various technologies used for preparation of the microcapsule\textsuperscript{10,11,12}

1. Coacervation- Phase Separations
The two methods for coacervation are simple and complex process. 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 method a desolvation agent is added for phase separation where as complex coacervation involves complexation between two oppositely charged polymers. The three main steps in complex coacervation are i) Formation of three immiscible phases
ii) Deposition of coating
iii) Rigidization of the coating

2. Multi orifice Centrifugal Process
It is a process for producing microcapsules that utilize centrifugal forces to fling, a core material particle through an enveloping micro capsulation membrane. This method requires centrifugal force to throw a core material on the drug to be encapsulated. Slurry of encapsulated product can be prepared as a hardening media. Microcapsules of varying size can be prepared by this process.

3. Spray Drying and Spray Congealing
Both processes involve dispersing of the core material in a liquefied coating substance and
spraying or introducing the core coating mixture into some environmental condition that leads to rapid solidification of the coating material.

4. Pan Coating
In this process sugar beads are taken in the coating pan and on these sugar beads fine film of drug is applied and after that coating of polymer is done over the film of drug.

5. Solvent Evaporation
In this process the microcapsule coating is dispersed in a solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material to be encapsulated is dissolved or dispersed in the coating polymer solution. The core coating material is added to the liquid manufacturing vehicle phase with continuous agitation to obtain appropriate size microcapsule.

6. Interfacial Polymerization
In this method there is the reaction of monomer units located at the interface of a two phase system existing which cause condensation of polymers. Usually a liquid or gas is used as the continuous or core material supporting phase for the polymerization reaction, which occurs at a liquid-liquid, liquid-gas, or solid-gas interface. If the internal phase is a liquid, it is possible to disperse or solubilize the monomer in this phase and emulsify the mixture in the external phase until the desired particle size is reached. A cross-linking agent may be added to the external phase at this point. The microcapsules are prepared at suitable conditions using stabilizer.

Literature Review
Pandya, (2012)
Formulated Trihexyphenidyle microcapsules for parkinsonian’s disease by using biodegradable polymer Eudrajit L 100 and S 100. Trihexyphenidyle microcapsules were prepared by solvent evaporation method by using different drug-polymer ratio (1:2, 1:3, 1:4, 1:5). Prepared microcapsules were evaluated for the particle size, percentage yield, incorporation efficiency, flow property and \textit{in vitro} drug release at pH 6.8 for 12 hours. From the result it was concluded that as the concentration of polymer increases, it affects the particle size, percentage yield and drug release of micro capsules. The formulation containing drug polymer ratio 1:3 showed the excellent flow properties, particle size, percentage yield (91.24%), incorporation efficiency (94.59%) and percentage drug release (95.88%) for a period of 12 h.
Chawdhary and Dana, (2011)
Formulated and evaluated Diclofenac microcapsules by using ethylcellulose as a coating material. Microcapsules were prepared by an emulsion-solvent evaporation method and microcapsules were evaluated for size, drug content and microencapsulation efficiency, wall thickness, surface character by SEM and drug release kinetics. The ethylcellulose coated microcapsules prepared were found to be discrete, spherical, and free flowing. Drug content was found to be uniform in each batch of microcapsules and the microencapsulation efficiency was in the range 98.85-101.81%. Diclofenac release from the ethylcellulose coated microcapsules was slow and spread over a period of 12-16 h and depended on core: coat ratio, wall thickness and size of the microcapsules.¹⁴

Emami, et al. (2011)
Prepared microcapsules of theophylline with ethyl cellulose by emulsion-solvent evaporation method. Size, morphology, drug loading and release behavior of microcapsules were studied. Microcapsules were then formulated into suspensions to provide an oral liquid dosage form for drug and resulting suspensions were examined for stability and release characteristics at various storage times. The Result showed sustained release properties of microcapsules having drug to polymer ratio 1:1.4.¹⁵

Prabu, et al. (2009)
Aceclofenac was microcapsulated using rosin by o/w emulsion solvent evaporation method. It is accepted as a reliable one to deliver the drug to the target site with specificity to maintain desired concentration at the site of interest.¹⁶

Vashosaz, et al. (2011)
Prepared Budesonide microcapsules by using spray drying technique and evaluated for Differential scanning calorimetry, X-ray diffraction (XRD), drug release and loading efficiency. The results showed that microcapsules could target the drug to colon and its efficacy.¹⁷

Namujidin, et al. (2010)
Prepared Flurbiprofen microcapsules by solvent evaporation method using Eudragit L-100 and Eudragit S-100 mixture. The prepared microcapsules were evaluated for various physicochemical parameters such as percentage yield, particle size, drug polymer compatibility, incorporation efficiency, scanning electron microscopy and invitro drug
release of microcapsule (pH 6.8) for 12 hrs. Result shows that as the concentrate on of polymer increases it affects the particle size, percentage yield and drug release of microcapsules. The flow properties were found to be good and scanning electron microscopy confirmed their hollow structure with smooth surface. Formulations shows excellent particle size properties, percentage yield (90.24%), incorporation efficiency (95.59%) and percentage drug release (95.58%) for a period of 12 hrs.\textsuperscript{18}

**Venktesh, et al. (2011)**

Prepared Tegaserod maleate microcapsules by the emulsion-solvent evaporation method using drug and mixture of polymers. The prepared microcapsules were evaluated for physicochemical parameters such as particle size, surface characteristics, drug loading capacity, and \textit{in vitro} dissolution studies. The batch prepared using the 1:2 drug polymer ratio was selected as an ideal batch for compression to get the compressed tablet of the microcapsules. The compressed microcapsules were evaluated for physicochemical parameters such as average weight, friability, thickness, hardness and \textit{in vitro} dissolution studies. The modified tablets were also prepared employing the double compression technique and evaluated for hardness, friability, thickness, weight variation test, drug content, and \textit{in vitro} dissolution study. The comparative study showed that the drug release profiles from the microcapsules were found to be better than the compressed microcapsules and the modified tablets in the colonic environment.\textsuperscript{19}

**Nayak, et al. (2009)**

Formulated Famotidine microcapsules by using combination forms like (carbopol-934 and hydroxypropyl methyl cellulose, carbopol-934 and guar gum, carbopol- 934 and methyl cellulose carbopol-934 and sodium carboxy methyl cellulose) against carbopol-934. The microcapsules were formulated by orifice ionic gelation technique. Microcapsules were evaluated for percentage yield, particle size, drug entrapment efficiency, flow properties, surface morphology, sphericity measurement, percentage moisture loss, swelling property, \textit{in vitro} drug release study, drug release kinetic study and mucoadhesion study by \textit{in vitro} wash off test. Microcapsules exhibited slow release of famotidine over 9 hours with zero order release kinetic fashion.\textsuperscript{20}

**Yadav, et al. (2009)**

Formulated novel enteric Aceclofenac microcapsules for improved delivery to the intestine using the polymer ethyl cellulose as the retardant material. Microcapsules were prepared by
an emulsion solvent evaporation technique. The microcapsules were evaluated for size analysis, optical microscopy, encapsulation efficiency, wall thickness, drug content and drug release characteristics. All microcapsules obtained were uniform in size, free flowing and spherical in shape. The release of drug from microcapsules followed higuchi model and influenced by the size of the microcapsules. The release of drug from microcapsules over 12 hours was observed.21

Prakash, et al. (2007)
Prepared and evaluated lamivudine microcapsules by using various cellulose polymers. The microcapsules were prepared by the solvent evaporation technique. The prepared microcapsules were characterized for entrapment efficiency, scanning electron microscopy, FTIR, DSC, drug content and in vitro dissolution studies. The microcapsules were spherical and free flowing. The entrapment efficiency was 76-86%. The release of drug from the microcapsules was found up to 8 to 12 h. 22

Evaluation Parameters

Percentage yield

The total amount of microcapsules obtained was weighed and the percentage yield calculated taking into consideration the weight of the drug and polymer.20

Percentage Yeild = \[
\frac{\text{Practical Yeild}}{\text{Theoretical Yeild}} \times 100
\]

Particle size analysis

Size distribution determination can be carried out by using a set of standard sieves to separate different sizes in a batch. The amounts retained on different sieves were weighed.20

Scanning Electronic Microscopy (SEM)

The shape and surface morphology of the microcapsules can be studied by using scanning electron microscopy.13

Encapsulation efficiency

Encapsulation efficiency can be calculated by using the formula:20

\[
\text{Encapsulation Efficiency} = \frac{\text{Estimated % Drug Content}}{\text{Theoretical % Drug Content}} \times 100
\]
Flow properties

Flowability of microcapsules investigated by determining Angle of repose, bulk density, Carr’s index and Hausner ratio.

Loose bulk density

It is measured by putting the accurately weighed microcapsules into a graduated cylinder and the volume was calculated using following formulae: \(^{22}\)

\[
\text{Loose Bulk density} = \frac{\text{Weight of powder}}{\text{Volume occupied by powder}} \times 100
\]

Tapped density

The tapped density was determined by three tap method. Weighed quantity of Microcapsules is carefully introduced into a 10 mL graduated cylinder. The cylinder is dropped onto a hard wood surface three times from height of 2.5 cm. It can be calculated by using formula: \(^{23}\)

\[
\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Final volume after tapping}} \times 100
\]

Compressibility index

It is indirectly related to the flow rate, cohesiveness and particle size. It can be calculated by following formula: \(^{24}\)

\[
\text{Compressibility index} = \frac{\text{Tapped density} - \text{Loose bulk density}}{\text{Tapped density}} \times 100
\]

Hausner’s ratio

Hausner’s ratio is an index of ease of powder flow; it was determined by using the following formula: \(^{24}\)

\[
\text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Loose bulk density}}
\]

Angle of repose

Angle of repose of microcapsules can be determined by the fixed funnel method. A funnel with an open end fixed at a given height (h) above the graph paper placed on a flat horizontal surface. The microcapsules carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius (r) of the base of the pile determined and the tangent angle of repose (θ) can be calculated by following formulae: \(^{23}\)

\[
\tan \theta = \frac{h}{r}
\]
**Percentage moisture loss**

Microcapsules can be evaluated for percentage moisture loss which determines the hydrophilic nature. The microcapsules weighed \(W_1\) initially kept in desiccator containing calcium chloride at 37°C for 24 hours. The final weight \(W_2\) noted when constant weight of sample was obtained.\(^{19}\)

\[
\text{Percentage moisture Loss} = \frac{W_1 - W_2}{W_2} \times 100
\]

**Estimation of Drug Content**

Drug content in the microcapsules can be calculated by UV spectrophotometric method. The method validated for accuracy, linearity and precision. A sample equivalent to 100 mg dissolved in suitable solvent and the volume adjusted upto 100 ml using suitable phosphate buffer. The solution filtered through Whatman No. 1 filter paper. Then the filtrate assayed for drug content by measuring the absorbance at suitable wavelength of drug.\(^{25}\)

**Drug dissolution studies**

*In vitro* drug release study is carried out in USP type-II dissolution test apparatus. Microcapsules are placed in basket of dissolution vessel containing 900 ml of phosphate buffer. Aliquots of samples (5 ml) at an interval of 1 hour are withdrawn and filtered through a whatman filter paper. The samples are analyzed by UV-Visible spectrophotometer at suitable wavelength.\(^{13}\)

**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.

**REFERENCES**


