Gastric acid resistant capsules are enteric biology essay

Generally, the active pharmaceutical ingredients are delivered using two-piece capsules, which are filled with the drug, capsulated and taken orally. These capsules are made with materials like gelatin, hypromellose etc. The capsules release the encapsulated drug in the stomach by dissolving in gastronomical juices. However, some of the drugs affects the metabolism of gastric juices and are irritants. In these kinds of drugs, post gastric delivery is expected being intact in the stomach. In order to achieve these several investigation lead to development of acid resistant capsules called enteric capsules.

Enteric Capsules:

The capsules which are designed for intestinal delivery by being intact in the stomach are called as enteric capsules and this property is called enteric property. To achieve the intestinal delivery the capsule must be strong enough to resist the acidic environment in the stomach. Apart from the reason that the capsules may effect the gastronomical metabolism, some drugs require past gastronomical delivery to treat some local diseases like ulcerative collitas, irritable bowel syndrome (Crotty and Jewel, 1992) and to absorb polypeptides in the intestine (Davis, 1990). The endogenous enzymes are less in the colon and the transit time is long which will favor the absorption of polypeptides (Davis, 1992).

The capsule dissolution time cannot be determined exactly in the capsules which are released in the stomach as the residence time is highly irregular and depends on the several factors like the size of the fabricated capsule, fed or fasted state of the stomach etc (Wildey et al., 1992b). If the colon is

the desirable and perfect place for absorption of therapeutic polypeptides, which are orally consumed then there is a compulsory for enteric capsules which can target the colon release and can withstand the acidic gastronomical juices and state of gastronomical duct (Hardy et al., 1987, Van Den Mooter et al., 1992, Rubin stein et al., 1992, Lloyd et al., 1994).

For several decades these enteric properties are delivered to the capsules mainly by coating the hard gelatin capsules using acid resistant chemicals such as anionic polumethacryalates (copolymerasite of methacrylic acid and tither methul methacrylate or ethyly acrylate (Eudragit), cellulose based polymers such as cellulose acetate phthalate (Aquateric) or polyvinyl derivatives such as polyvinyl acetate phthalate (Coateric) (Ewart T. Cole et al., 2001), hydroxyl propyl methyl cellulose phthalate, sodium alginate stearic acid etc. These acidic polymers have very low permeability in their unionized state in low pH environments and when they reach high pH environments they ionize and resulting in increase of the permeability. As a result, the capsule erodes and releases the underlying drug. These kind pH variations can be seen in the stomach and intestine respectively. These enteric coatings showed a great advantage that it is independent of the encapsulated material. This advantage resulted in the decrease in the extent of research to develop a formulation, which is enteric by nature itself irrespective of any enteric coating applied.

Gelatin is the major polymer base for manufacturing capsules for many years. These enteric coatings are applied on the surface of these gelatin capsules. However, due to several considerations alternative materials like hypromellose are opted in some specific cases. Hypromellose has several

advantages when compared to gelatin capsules regarding their response towards organic coatings, aqueous coatings, storage, structure etc.

Hypromellose capsules over gelatin capsules:

Gelatin and Hypromellose are used to fabricate capsules, which can dissolve in the gastric juices of the stomach and release the encapsulated material. Inorder to incorporate the enteric properties to these gelatin and hypromellose capsules different coating technologies are invented and acid resistant polymers are coated. From several years enteric coated hypromellose capsules are of very high importance in dietary supplement industry. Hypromellose is a vegetarian supplement to the gelatin capsules (Ogura et al., 1998). Hypromellose proved their efficiency when compared to that gelatin capsules when regulatory, manufacturing, religious and dietary issues are considered. Previous studies proved that the hypromellose is more capable in case of polymer adhesion. Gelatin capsules when coated with organic polymers they are very sensitive and embrittlement of the shell material is resulted (Murthy et al., 1986). The gelatin surface is very soft and adhesion of the coating material require some friction on the surface of the of the capsule body which is which is less in case of soft gelatin capsules. So enteric properties of these gelatin capsules are not up to the mark (Thoma and Bechtold, 1992). Secondary techniques like application of pre coat are required to coat these soft gelatin capsules. The interactions between the organic polymer and gelatin surface are controlled by applying a pre coat on the surface of the capsule. However, application of precoat is highly time consuming and costly process. Considering the ecological impact of organic coatings, aqueous coatings are preferred (Cunningham and FEgely, 2001;

Wheatly et al., 1997).. These aqueous coatings make the gelatin capsules more sensitive because of aqueous solubility of gelatin. Hence the processing time is very long for aqueous coating of the gelatin capsules resulting in high fabrication costs. Hypromellose are advantageous in case of aqueous coatings when compared to gelatin capsules. For hypromellose capsule sealing of body and cap is required prior to coating to restrict the leakage of the encapsulated material through the merging part of the body and cap of the capsule. This sealing can be done manually using gelatin solution (Felton et al., 2002). Liquid encapsulation micro spraying technique can also be used for sealing the capsule.

Considering the advantages and disadvantages of gelatin and hypromellose capsules, hypromellose can be effective to deliver enteric properties to the capsules. Development of formulations using hypromellose as the base polymer and enhancing with other acid resistant materials can yield better results.

Enteric hypromellose capsules:

The technology of enteric coating has undergone through several fundamental improvement in recent years due to their potential advantages and ease. Several promising technologies like sugar coating technique, film coating process using organic and aqueous solvents are designed. The process of application of enteric coating has several steps which involve lot of labor and time ultimately effecting the economics of fabrication. Apart from the coating process proper attention should be taken such that the coating materials is capable enough to adhere and coalesce on the

substrate. The coating material must be able to loose moisture immediately so that the core penetration and dissolved coating material can be minimized (Els Mehuys et al., 2004). Aqueous coating cannot be applied to ingredients which are active towards moisture (Mehta, 1996).

The coating techniques are effected by several factors such as spraying rate, spraying temperature, pressure, volume and dimensions of the coating equipment (Els Mehuys et al., 2004). Lack of proper attention towards these control variables results in non-uniform coating layer and upscaling. Many other techniques are developed to overcome these disadvantages of the coating process and reduce the process time. Obara et al., 1999 developed a dry coating process. This process involves spraying of dry enteric powder on the capsule followed by curing and drying. Pearnchob and Bodmeir (2003) developed another dry coating process in which they used ethylcellulose as the enteric coating material. Holroyd (2004) developed another process called Phoqus Process in which an electric field is created to induce partial positive and negative charges to the capsule and enteric material, thus resulting in adhesion due to electrostatic attraction between the compounds. Though several innovations are made in the field of enteric coating all the process require supply of energy in the form heat or electricity is required. Even though several promising innovations are made to overcome the defects of the coating process, still these coating process proved to be disadvantageous in large scale production. The main impacts of coating process during large-scale production involve brittle capsules, environmental pollution, safety, cost of the process, process time etc. This will induce extra cost in fabrication of capsules when manufactured in a bulk scale.

A formulation designed which has enteric properties inherent can solve the extra cost and time due to enteric coating of the gelatin or hypromellose capsules. The previous studies showed that hypromellose shows some inherent enteric properties. Thus by enhancing these properties by using acid insoluble compounds like sodium alginate in the formulation itself can exhibit enteric properties. So additional coating can be prevented by optimsing these kind of formulations.

Enteric formulations using hypromellose as base polymer:

Certain formulations using hypromellose as base polymer are designed in which the HPMC acts as bulk film forming material. A gelling agent is added to the formulation like gellan gum such that it performs gelation action and help hypromellose to develop a solid structure and hold its structure firmly during moulding of the capsules. An acid insoluble tertiary polysaccharide (sodium alginate) is added to the formulation to induce and enhance the enteric characteristics to the formulation. Some pharmaceutical excipients such as lubricating agents (polyethylene glycol) , chelating agent (EDTA) and tonicity agent (Sodium Chloride) are added to the formulation.

By considering all the above stated materials following formulations are designed:

FORMULATION

HPMC % W/W

GELLAN GUM % W/W

SODIUM ALGINATE % W/W

NACL %

W/W

EDTA %

W/W

PEG %

W/W

1

19

0. 1

0

0. 1

0. 1

5

2

18

0. 2

1

0. 2

0. 1

5

3

17

0. 2

2

0. 2

0. 1

5

4

15

0. 2

5

0. 2

0. 1

5

5

15

0. 2

7. 5

0. 2

0. 1

5

Impact of formulation and process variables on the drug release:

Formulation variables:

Polymer Base:

Hypromellose is used as the polymer base material. There are several grades of HPMC that are commercially available. Generally different kinds of hypromellose is due to variation in the content of hydroxypropyl and methyl groups present in HPMC. In the present case rapidly hydrating grade hypromellose is used. The viscosity of the hypromellose depends upon the composition of hdroxypropyl group and methyl group. Improperly hydrated results in dose dumping as the gastric fluids can easily penetrate into the capsule (Dow pharmaceutical ecipients, 1986). The viscosity of the polymer effects the mouldability of the formulated polymer base into capsule.

Hypromellose also decides the mechanical characteristics of the capsules. Hypromellose layers with high viscosity have a greater capability to withstand the diffusion of gastric fluids into the encapsulated material thus help in extended release of the drug (Nellore et al., 1998). Higher viscosity hypromellose will reduce the swelling properties of the capsule thus resolve the capsule separation problem.

Hypromellose ($C_{32}H_{60}O_{19}$)

Gelling agent:

Gelling agent like gellan gum is used in this formulation. Gellan gum is of very high importance in pharmaceutical industry in producing oral dosage forms like gels and capsules (Kubo W, Miyazaki S et al., 2003). Gellan gum shows effect on the release of the drug so it is used for controlled or sustained release (Alhaique F et al., 1995). Hypromellose in the presence of a secondary polysaccharide like gellan gum have the capability to forma strong structure and retain the structure during mouliding of capsule. The compounds containing aldehyde groups can combine with gelling agent like gellan gum to form cross links making the capsule insoluble (Digenis GA et al., 1994). Gellan gum is categorized based on the proportions of polysaccharide, the percent of o-acetyl substitution of polysaccharide and protein content. Gellan gum with high acyl condition has to selected for this formulation because gellan gum with high acyl content is capable of formation of soft, elastic and non brittle gels. On the other hand gellan gums with low acyl forms brittle and non elastic gels (Kelco Biopolymers, Gellan Gum for Pharmaceutical Applications rev. 10/99, 2004.). Gellan gum induces

temperature dependent gelation. This gelation is caused due to series of activities in the order of formation of double helical junction zones and then gellan gum aggregation of these segments resulting in formation of three-dimensional structures by complexation and hydrogen bonding.

The structure of deacetylated Gellan Gum

The variation of amount of gellan gum in the formulation effects the gelating nature of the polymer base. The hypromellose and gellan gum has a biphasic nature. The percentage of gellan gum will result in phase change.

Stabilizing agent:

Sodium alginate is used as the stabilizing agent in these formulations. Sodium alginate acts as the tertiary polysaccharide. Sodium alginate imparts its acid insoluble properties to the hypromellose formulation thus making it enteric. Sodium alginate also acts as gelling agent. The amount of sodium alginate effects the gelation and acid solubility properties of the capsule.

Sodium alginate

Addition of plasticizer:

Addition of plasticizer to the formulation decreased the water absorbing nature of the capsule. The major obstacle is the capsule separation due to the swelling of the capsule by absorbing water. Poly ethylene glycol (PEG) is used as the plasticizer to decrease the water absorbing nature of the capsule. Excess of PEG resulted in formation of brittle capsules and also effects the dissolution properties of the capsule.

Addition of lubricating agent:

Lubricating agent is added inorder to facilitate the dipping process. Addition of lubricating agent like PEG helped in easy removal of the capsule from the dipping pin. In absence of lubricating agent the capsules deformed while inverting from the dipping pin resulting in irregular shaped capsules.

Addition of swelling agent:

Addition of swelling agent is done inorder to achieve differential swelling between cap and body of the capsule to prevent capsule separation. Swelling agents are added in such a manner that swelling of body of the capsule is more when compared to that of cap. This will result in tightening of the capsule and can restrict the capsule separation.

Process variables:

Capsule size:

Capsule size has a major effect on the release rate. For different capsule sizes with same aspect ratio and constant volume, the release rate decreases with increase in size of the capsule. This is due to the change in the surface area. The diffusion pathways are longer in longer capsules when compared with that of smaller ones. So the drug release with respect to time is much larger in smaller capsules when compared to longer ones (Siepman et al., 1999b)

Capsule shape:

The surface area of a capsule depends on the shape of the capsule. The capsule which have high surface area for a constant volume has potential exposure to the acidic environment in the stomach and the drug release rate is high. Capsules with near spherical shape have less surface area compared to other shape (Rekhi et al., 1999) These kinds of capsules are recommended for controlled release characteristics. Variation in the aspect ratio of the capsules can effect the drug release. By varying the aspect ratio of the hypromellose capsule the drug relase can be modified (Siepman et al., 1999b).

Moulding temperature:

Viscosity of the polymer base changes with temperature. At higher temperatures, the viscosity of the polymer base is less, so when the dipping pin is dipped in the polymer base at higher temperatures the thickness of the polymer attached to the pin is less due to the lower viscosity. So by altering the moulding temperature the thickness of the capsule can be controlled.

Capsule Thickness:

The generally assumption is that the encapsulated material release is through the capsule wall. So a thicker wall can control the release and slow the drug release. Thicker wall can also withstand drastic acidic condition in the stomach. Apart from the dissolution rate, the capsule thickness also effects the structure of the capsule. Dissolution of the capsule highly depends on the thickness of the capsule. Capsule thickness effects the swelling properties and mechanical properties of the capsules like strength, puncture force etc. The capsule thickness is controlled during the moulding

of the capsules by proper attention to viscosity and temperature of the hypromellose polymer base. The dipping can be dipped twice or thrice according to the target thickness if required.

Mechanism of drug release in hypromellose and gelatin capsules:

The solubility of gelatin and hypromellose capsules in aqueous media is different due to difference in their permeability characteristics. This has a great effect on disintegration and drug release mechanism in both the materials (Nagata, 2002). The drug delivery is due to absorbance of water and hydration of the capsules by which the capsules dissolve and release the encapsulated contents. Gelatin dissolves in the fluids at body temperature. Further decrease of temperature (<36oC) the solubility decreases. SO dissolution testing for gelatin capsules is generally done in the temperature range of 36oC â€" 37oC. The capsule effects the solubility characteristics of gelatin (Jones and Cole, 1971). Different visualization techniques revealed the non uniformity of gelatin layers in capsule.

Comparative studies of dissolution of hypromellose and gelatin capsules revealed that the dissolution of HPMC is independent of temperature but gelatin dissolution is highly dependent on temperature of solution. The release characteristics of HPMC showed that the drug release takes three times the time required for the drug release from gelatin capsules (Chiwele et al., 2000). Hypromellose capsules results in extended release of the drugs. Dissolution is only effected by first breakage of the capsule and start of release of the drug. Once the drug starts to release, the release does not depend on the capsule material. The dissolution studies proved that the

HPMC capsules have longer lag time (Honkanen et al., 2001). The first rupture in case of HPMC takes long time but once the rupture takes place, the capsule disperses uniformly through exposing the drug completely to dissolution media. Gelatin capsules splits near the ends and dissolution takes place through the ends of the capsules for a long time (Podczeck and Jones, 2002). The dissolution characteristics of gelatin capsules are almost same for all the capsules as the sources for gelatin is almost same from all the providers. In case of HPMC, each provider has its own formulations patented and specific characteristics are delivered for their gelling systems. The diffusion of gases through HPMC capsules is more when compared to gelatin capsules. The gas diffusion occurs through the gap between body and cap of the capsule, the sealing between cap and body of the capsule is weak in HPMC capsules when compared to that of gelatin capsules.