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Detailed Study of Formulation and Evaluation of Capsule Dosage Form: A Review

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ABSTRACT:
Polymeric film forming materials and manufacturing technologies used in the production of capsule shells have been developed to offer additional consumer acceptability, to improve the dosage form physical and chemical stability, and to modify release of the encapsulated contents from the dosage form. These developments resulted in the use of hypromellose and starch based polymeric materials as alternate to the animal source gelatin in the manufacture of capsule shells. Hypromellose capsule shells have lower moisture content and hygroscopicity than gelatin capsule shells. As a result, moisture transfer from the hypromellose capsule shells into the encapsulated fill material is lower and thus the physical and chemical stability of hypromellose shell based products containing compounds prone to water induced precipitation and hydrolysis is improved. Gelatin and non-gelatin capsule shells can also be formulated to modify the release of their fill contents in a site-specific manner in the GIT either by coating the filled capsules with a modified release polymer or by incorporating the polymer within the capsule shell before filling. These modified release capsule shells are soluble in or disintegrated by the intestinal secretions but resistant to the acid secretions of the stomach.

KEYWORDS: Capsule, Rotary process, Plasticising agents, soft gelatin capsule, Hard gelatin capsule

I. INTRODUCTION

Capsule: Capsules are defined as unit solid dosage form of medicaments available as small containers (shells) made up of gelatin enclosing accurately measured drug substances. The term capsule is derived from the Latin word capsula, meaning a small container. Capsule occupy a significant position in the drug development. They are often believed as the primary oral dosage form because of their manufacturing process compared to other dosage forms. medicament completely. Instead, of gelatin, denatured gelatin, methyl cellulose and polyvinyl alcohol can also be used to make the capsule shells" There are mainly two types of capsules which areHard-shelled capsules, which contain dry, powdered ingredients or miniature pellets made by e.g. processes of extrusion or spheronization. These are made in two halves: a smaller-diameter "body" that is filled and then sealed using a larger-diameter "cap".Both of these classes of capsules are made from aqueous solutions of gelling agents, such as animal protein (mainly gelatin) or plant polysaccharides or their derivatives (such as carrageenans and modified forms of starch and cellulose). Other ingredients can be added to the gelling agent solution including plasticizers such as glycerin or sorbitol to decrease the capsule's hardness."[1-2]

Advantages

- ✓ Fewer developmental problems in capsules, hence allow quicker submission of a new drug for clinical trials.
- ✓ It is easier to vary the dose.
- ✓ Less adjuncts are necessary than for tablets
- ✓ Capsule manufacturing requires fewer steps than tablet manufacturing.
- ✓ Easy to swallow hence improves patient compliance
- ✓ Simple separation of two incompatible products (combination)
- ✓ More possibilities for product identification (printing) Drug with high dose and low compressibility can be incorporated in capsules.[3]

Disadvantage [3]

- ✓ Capsules are not suitable for liquids that dissolve gelatin, such as aqueous or hydro alcoholic solution
- ✓ The concentrated solution which require previous dilution are unsuitable for capsule

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because if administered as such lead to irritation into stomach.

- ✓ Not useful for efflorescent or deliquescent material. Efflorescent cause capsule soften & Deliquescent may dry the capsule shell to brittleness.

Types of capsule[4]

1. Hard gelatin capsule.
2. Soft gelatin capsule.

Fig 1: Types of capsule

1.soft gelatin

Originally developed in the 19th century to mask unpleasant taste and odour of drug substances, soft gelatin capsules are used in many applications, for pharmaceutical, health and nutrition products, cosmetic applications and even recreational products such as paint balls.gelatin capsules are used in many applications, for pharmaceutical, health and nutrition products, cosmetic applications and even recreational products such as paint balls[5-6]

Basic components of soft gelatin capsule shell

The various components of the soft gelatin capsule shell are as follows:

a. Gelatin

Similar to hard gelatin capsule shells, the basic component of soft gelatin capsule shell is gelatin. A large number of different gelatin shell formulations are available depending on the nature of the liquid fillmatrix. Most commonly, the gelatin is alkali- (or base-) processed (type B) gelatin and it normally constitutes 40% of the wet molten gel mass. Type A acid-processed gelatin can also be used. **b.Plasticising agents**

Plasticizing agents are added in a soft gelatin capsule formulation to ensure adequate flexibility. The most common plasticizer used for soft gelatin capsules is glycerol. Sorbitol, mannitol, and polypropylene glycol can also be used in combination with glycerol.

c. Water

Water usually accounts for 30-40% of the wet gel formulation and its presence is important both during the manufacturing process (to facilitate manufacture) and in the finished product to ensure that the capsule is flexible. The desirable water content of the gelatin solution used to produce a soft gelatin capsule shell depends on the viscosity of the specific grade of gelatin used. It usually ranges between 0.7 and 1.3 parts of water to each part of dry gelatin.

d. Preservatives

Preservatives are often added to prevent the growth of bacteria and mould in the gelatin solution during storage. Examples of commonly used as preservatives include potassium sorbate, and methyl, ethyl, and propyl hydroxybenzoate.

e. Colorant and/or opacifier

A colourant (soluble dyes, or insoluble pigments or lakes) and/or opacifier (e.g., titanium dioxide) may be added to the shell for visual appeal and/or reducing the penetration of light for the encapsulation of a photosensitive drug. The colour of the capsule shell is generally chosen to be darker than that of its contents.

f. Other excipients

Other, infrequently, used excipients can include flavouring agents and sweeteners to improve palatability.

Manufacture of Soft Gelatin Capsules

Soft gels are manufactured using the following methods

Plate process

This is the oldest commercial process used in the manufacture of soft gelatin capsules. In this process, a warmed sheet of plain or coloured plasticized gelatin is placed over a die plate having a number of depression or moulds or numerous die pockets. By applying vacuum, the sheet is drawn into these depressions or pockets to form capsule wells. The capsule wells are then filled with medication-containing liquid. A second sheet of gelatin is carefully placed on top of the filled wells followed by the top plate of the mould. Pressure is then applied to the combined plate to form, seal and cut the capsules into individual units. This method is used for small scale preparation of soft gelatin capsules and capsules formed generally, had one flat sideThe major problems with this method of manufacturing softgels were the lack of dosage

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uniformity, high manufacturing losses, and its labour-/cost-intensiveness. This equipment is no longer available.[7]

Rotary Die Process

Most soft gelatin capsules are prepared by the rotary die process, a method developed and perfected in 1933 by Robert P. Scherer. This process almost eliminated all the problems associated with the plate process and produced soft gelatin capsules with improved uniformity and high standards of Accuracy .In this process, two plasticized gelatin ribbons (prepared in the rotary-die machine) are continuously and simultaneously fed with the liquid, semiliquid or paste fill between the rollers of the rotary die mechanism. The forced injection of the feed material between the two ribbons causes the gelatin to swell into the left- and right-hand die pockets which govern the size and shape of the softgels as they converge. As the die rolls rotate, the convergence of the matching dies pockets hermetically seals and cuts out the filled capsule.Schematic drawing of a rotary-die soft gelatin capsule filler.

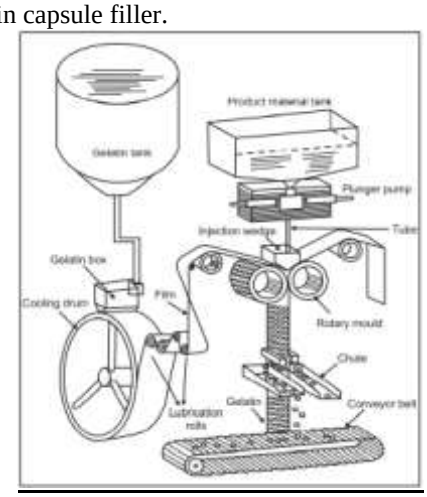

Fig 2: Rotary Die Process

2.Hard gelatin capsule

Hard gelatin capsules are made of two shells: the capsule body and a shorter cap. The cap fits tightly over the end of the capsule body. The basic hard gelatin capsule shells are made from mixtures of gelatin, sugar, and water. They are clear, colourless, and essentially tasteless. Hard gelatin capsule shells are fabricated and supplied empty to the pharmaceutical industry by shell suppliers and are then filled in a separate operation. During the capsule filling unit operation, the body is filled with the drug substances and the shell is closed by bringing the body and the cap together.[8-9]

Basic component of hard gelatin capsules

a. Gelatin

Gelatin is by far the most common and most well known material used to produce hard capsule shells. It is a generic term for a mixture of purified protein fractions obtained from irreversible hydrolytic extraction of collagen obtained from the skin, white connective tissue, and bones of animals. [10-11]

b. Plasticizer

Plasticizers are added to gelatin to reduce the rigidity of the polymer and make it more pliable. Common examples of plasticizers are glycerine and polyhydric alcohol. Water is also a good plasticizer and is naturally present in the gelatin.

Fig 3: Hard gelatin capsules

c. Colourants

Most frequently, hard gelatin capsules are coloured to enhance the aesthetic properties and also to act as a means of identifying the product. Colorants used must meet the regulatory requirements of those countries where the product will be sold. Examples of commonly used capsule colourants include synthetic dyes such as azo dyes and xanthene dyes. Iron oxide pigments are also used.

d. Opacifying agents

Opacifiers (e.g.. titanium dioxide) may be included to make clear gelatin opaque. Opaquse capsules may be employed to provide protection against light or to conceal the contents.

e. Preservatives

Preservatives (often parabens esters) were formerly added to hard capsules as an in-process aid in order to prevent microbiological contamination during manufacture. Manufacturers operating their plants to Good Manufacturing

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Practice (GMP) guidelines no longer use them. In the finished capsules, the moisture levels, 12-16% w/ v, are such that the water activity will not support bacterial growth because the moisture is too strongly bound to the gelatin molecule.

Manufacture of Hard Gelatin

Hard gelatin capsules are manufactured using a dip-coating method and the various stages involved are as follows: [12]

Step 1: Preparation of the gelatin solution (dipping solution)

A concentrated solution of gelatin is prepared by dissolving the gelatin in demineralized water whichhas been heated to 60–70°C in jacketedpressurevessels. This solution contains 30 – 40% w/w of gelatin and is highly viscous, which causes bubbles as a result of air entrapment. The presence of these bubbles in the Final solution would yield capsules of inconsistent weight and would also become problematic during capsule filling and upon storage. To remove the air bubbles, a vacuum is applied to the solution; the duration of this process varies with batch size.

Step 2: Dip-coating the gelatin solution on to metal

pins (moulds)Capsule shells are manufactured under strict climatic conditions by dipping pairs (body and cap) of standardized steel pins arranged in rows on metal bars into an aqueous gelatin solution (25 – 30% w/w) maintained at about 50 ° C in a jacketed heating pan.

Step 3: Rotation of the dip-coated pins

Following adsorption of the gelatin solution on to the surface of the pins, the bar containing the pins is removed and rotated several times to evenly distribute the solution around the pins, correct gelatin distribution being critical to uniform and precise capsule wall thickness and dome strength.

Step 4: Drying of the gelatin-coated pins

Once the gelatin is evenly distributed on the mould, a blast of cool air is used to set the gelatin on the mould. At this point, the gelatin is dried, and the pins are then passed through several drying stages to achieve the target moisture content.

Step 5: Stripping and trimming

After the gelatin is dried, the capsule is stripped off the mould and trimmed to the proper length.

Step 6: Joining of the trimmed capsule shell

Once trimmed, the two halves (the cap and body) are joined to the pre-closed position using a pre lock mechanism. At this point, printing is done if needed before packing in cartons for shipping.

Step 7: Printing

After formation, the capsule shells can be printed to improve identification. Printing can be achieved using one or two colours, containing information such as product name or code number, manufacturer's name or logo and dosage details. Printing reduces the risk of product confusion by the numerous handlers and users of the product including manufacturers, pharmacists, nurses, doctors, caregivers, and patients.

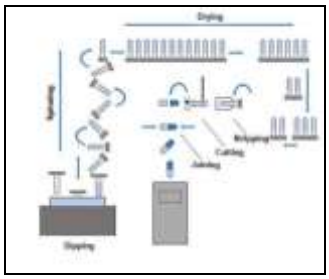

Fig 4:Manufacture of Hard Gelatin Capsule

Filling of hard gelatin capsules

The filling of hard gelatin capsules is an established technology, with equipment available ranging from that for very small-scale manual filling (e.g., Feton capsule filling machine), through intermediate-scale semiautomatic filling to large-scale fully automatic filling. Hard gelatin capsules can also be hand-filled one at a time, as done in a compounding pharmacy.

The basic steps in filling hard gelatin capsules

- Rectification of capsules (placing empty gelatin capsules on the removable plate with bodies facing downward).
- Separation of caps from bodies.
- Dosing of fill material (The body is filled with the formulation manually using a plastic spatula, and the excess powder is removed Hand Operated methods or Semi Automatic Capsules Devices.

Punch Method or Manual Filing.

Automatic Filing ex:Osaka filling machine filing machine,macofar capsule filing machine. [13]

It consist of:

- A bed having 200-300 holes
- A loading tray having 200-300 holes.

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- A powder tray
- A pin plate having a rubber to
- A lever
- A cam handle

Fig 5:Hand Operator Method.

Special types of hard gelatin and soft gelatin capsules

Altered Release capsule [14]

The rate of release of capsule contents can be varied according to the nature of the drug and the capsule excipients. If the drug is water-soluble and a fast release is desired, the excipients should be hydrophilic and neutral. If a slow release of water-soluble drug is desired, hydrophobic excipients will reduce the rate of drug dissolution. If the drug is insoluble in water, hydrophilic excipients will provide a faster release; hydrophobic and neutral excipients will slow its release. A very rapid release of the capsule contents can be obtained by piercing holes in the capsule to allow faster penetration by fluids in the gastrointestinal tract, or by adding a small quantity of sodium bicarbonate and citric acid to assist in opening the capsule by the evolution of carbon dioxide.[15]

Coatingcapsule[(15)]

Coatings have been applied extemporaneously to enhance appearance and conceal taste, as well as to prevent release of the medication in the stomach (enteric coated products). Most coatings of capsules require considerable formulation skill and quality control equipment found in manufacturing facilities. The capsules can be coated to delay the release of the active drug until it reaches a selected portion of the gastrointestinal tract.

Sustained release capsules

The traditional method of taking a dose three or four times a day leads to periods of excess and deficiency in blood concentration of the medicament. One way of correcting this and, at the same time, reducing the number of doses per day, is to administer a capsule containing numerous coated pellets that release the drug successively over a long period.

The finely powdered drug is first converted into pellets, usually by attaching it to sugar granules with an adhesive. The pellets are then treated with protective coatings that delay release of the drug, each batch receiving a different thickness. The batches are mixedthoroughly and suitable doses are filled into capsules. For example, a mixture might contain 30 percent of uncoated pellets, for immediate release of drug, 30 percent each of coated pellets that release at 4 hours and 8 hours, and 10 percent of neutral pellets, used solely to fill the capsule. Each batch may be coloured differently to simplify identification and facilitate control of mixing[16]

Non gelatinous capsule

1.**Hydroxy Propyl Methyl Cellulose (HPMC)**

Hypromellose (INN), short for hydroxypropyl methylcellulose (HPMC), is a semisynthetic, inert, viscoelastic polymer used as an ophthalmic lubricant, as well as an excipient and controlled delivery component in oral medicaments, found in a variety of commercial products[17-19]

Fig 6: Non gelatinous capsule

Appearance: HPMC is white or similar to white fiber or granular powder, Odourless, Properties: Almost insoluble in ethanol, ether and acetone: Quickly dispersed in 80-90 centigrade water, Aqueous solution is very stable in room temperature; Has good wetting dispersing / adhesive thickening emulsifying water preserving/film-forming properties;

Dissolving process

HPMC will agglomerate when directly added towater and then dissolve. In this way it dissolves very slow and hard. Suggested methods as followers: 1. in hot waterHPMC does not

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Manufacturing of (HPMC) capsules

Hard gelatin and HPMC capsules are manufactured using similar equipment developed by Eli Lilly. hard gelatin capsule manufacturing, pins (moulds for making the capsules) at 22°C are dipped in a dip pan or pot that holds a fixed quantity of gelatin at a constant temperature, between 45 and 55°C. The level of solution is maintained automatically by a feed from the holding hopper. Once the molds are dipped a film will be formed on them by gelling since they are at lower temperature. The slowly withdrawn pins from the dipping pan are rotated to. maintain uniform film thickness, where they arepassed through a series of drying kilns at controlled temperature and humidity. The dried films (shells) are stripped of the pins, cut to the correct length and the two pieces (cap and body) are joined together. The pins are then cleaned and lubricated to start the next cycle.

The manufacture of HPMC based capsules. necessitates some modification to the molding machine or to the formulation of the shell material Because HPMC shell walls are much HPMC gelling from solution occurs when the temperature is raised while it is converted to its original solution as the temperature is lowered,

2) Starch Capsules

Properties of starch

Moisture content: Moisture content in starch capsule lies between 12% to 14% w/w, with more than 50% being tightly bound to starch. The presence of this bound moistureindicates that starch capsules lmay provide betterstability properties and reduces susceptibilities to change on storage[20-22]

Dissolution -Similar to that of gelatine capsules.

Advantages

-Ready for filling immediately following manufacturing

-Offer greater resistance to humidity and heat than gelatin and allow easy filling as they are non-static.

-Dissolution is independent of pH.

-Good surface finish.

-Coating of hard gelatine capsule with aqueous spray formulations can lead to softening of gelatin shell or gelatin shell may become brittle due to water evaporation and drying. Especially at the onset of coating. On the contrary, the coating of starch capsules seems to be less problematic because of smooth seal of the filled unit, together with the higher bulk density of the capsules, which provide a more uniform coating bed.

Manufacturing of starch hard capsules

-Hard gelatin capsules have been used most widely. Recently, however, starch capsules have been used in various controlled-release products as well as in general use as demands for non-animal based products increase. Starch capsules are more easily coated than gelatin capsules. Gelatin shells may soften and solubilise when sprayed with aqueous dispersion of coatings and can become brittle during the drying stage. The higher bulk density of the starch capsule provides for a more uniform coating bed.

-Starch capsules are manufactured by an injection molding process that yields exact dimensions and provides an excellent seal between "top" and "bottom." The filling and sealing process is simultaneous, resulting in a finished product that is well-sealed, secure and relatively resistant to further

3)PVA Copoylmer Capsules

Hard capsules have been developed as an edible container to mask the taste and odour of medicines. Traditionally used for powder or granulated formulations, capsules have also been adapted to contain oily liquids, tablets and even powders for inhalation. They are popular because of their relative ease of manufacture (compared with other dosage forms such as tablets) and theirflexibility to accommodate a range of fill weights. Additionally, capsules readily demonstrate bioequivalence between different strengths of the same formulation. The solubility of many

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compounds used in potential new drugs is very low because they are selected for their affinity to receptors, which increases as the lipophilicity of a compound increases. Although these compounds are expected to have a high clinical performance, they often fail to become new drug entities because of their low absorption in the gastro intestinal (GI) tract - a result of poor dissolution. [23-25]

Manufacturing of PVA Capsule

Capsules made only of PVA are available, although they are easily softened by surrounding moisture. In the PVA copolymer, MMA was used to increase the hardness of the capsule shell; however, increasing the amount of MMA decreases the polymer solubility. Thus, AA was copolymerized to increase the solubility at neutral pH. The composition ratios of PVA, AA and MMA in the PVA copolymer can be modified; the best copolymer is formed when the levels of PVA, AA and MMA are 70-80%, 2.5 5.0% and 15-25%, respectively.

Drug capsules should dissolve in purified water, as well as in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8) of the disintegration test method listed in the Japanese Pharmacopoeia (JP). The dissolution of PVA copolymer cast film in the above media was examined. The result showed that the film was soluble in all three fluids, indicating that the copolymer has suitable dissolution characteristics. The film showed no erosion, swelling or dissolution in macrogol 400.

Evaluation parameter of capsule[26]

1.Disintegration test
2.Content uniformity test
3 Weight variation test
4. Dissolution test
5 Moisture permeation test
6. Stability testing

1) Disintegration test:

Disintegration of hard and soft gelatin capsules isevaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. The compendial disintegration test for hard and soft gelatin capsules follows the same procedure and uses the same apparatus described in the article "Quality Control Tests for Tablets"

The capsules are placed in the basket-rack assembly, which is repeatedly lowered 30 times per minute into a thermostatically controlled bath of fluid at 37 +2°C and observed over the time described in the individual monograph.

Fig 7:Disintegration Appratus

2) Content uniformity test:

This test is performed only when the content is specified in the individual monographs and when capsules fail weight variation test. If the weight of capules is completely filled no need of this test. Unless otherwise stated in the monograph for an individual capsule, the amount of drug substance, determined by assay, is within the range of 85.0% to 115.0% of the label claim for nine (9) of ten (10) dosageunits assayed, with no unit outside the range of 75.0% to 125.0% of the labelled drug content. Additional tests areprescribed when two or three dosage units are outside ofthe desired range but within the stated extremes.

3) Weight variation test:

- 20 capsules are selected or taken at randomly and weighed individually, take average and compare each capsule weight with average.
- Then test passes if none of the individual weights are less than 90% and more than 110% of average.
- If test requirements are not met we have to remove the powder, net content of powder can beweighed individually. They have to be averaged.
- Test requirements are met if not more than 2 of the individual's difference is not greater than10 of average. In any case difference should not be more than or equal to 25% .
- If more than 2 and less than 6 net weights determined, they deviates 10% Then we go foradditional 40 capsules.
- The average of 60 capsules is determined by weighing capsules individually and comparedwith average

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- Test requirements are met if the difference does not exceed more than of the 60 Capsule
- Deviation should not be more than 25% in any case
- Then particular batch passes weight variation test
- To weigh capsules we use Rotoweigh and Varicap 1200

4) Dissolution test:

Dissolution test for capsules Drug absorption and physiological availability depend on the drug substance being in the dissolved state at the site of drug absorption. The rate and extent of dissolution of the drug from the capsule dosage form is tested by a dissolution test. This test provides means of quality control in ensuring that, different hatches of the drug product have similar drug release characteristics and also, a given batch has similar dissolution as the batch of capsales that was shown initially to be clinically effective.

Fig 8:Dissolution Appratus

5) Moisture permeation test:

The USP requires determination of the moisture permeation characteristics of single-unit and unit dose containers to assure their suitability for packaging capsules. The degree and rate of moisture penetration is determined by packaging the dosage unit together with a colour revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for colour change (indicating absorption of moisture) and comparing the pre-test and post-test weight of the packaged unit

6) Stability testing:

- Stability tests for capsules are performed to known the integrity of gelatin capsule shell but not
- to know the stability of therapeutically active agent and for determining the shelf life of capsules The test helps in improving thequality of contents of capsule shell and for choosing the appropriate retail package
- The capsule shells are to be stabilized to know atmospheric condition with relative humidity

Packaging and storage of capsule

Finished hard gelatin capsules normally contain an equilibrium moisture content of 13 to 16%. This moisture is critical to the physical properties of the shells since at lower moisture contents (<12%), shells become too brittle and may crack when exposed to the appropriate stress. At higher moisture contents (>18%) they become too soft and may lose shape. It is therefore important to avoid extremes of temperature and to maintain a relative humidity of 40 to 60% when handling and storing capsules. [27]

Hard gelatin capsules can be individually protected by enclosure in strip or blister packs. In the former, the units are hermetically sealed in strips of aluminium foil or plastic film. In the latter one of the films enclosing the units is formed into blisters. An ideal foil or film forthese packs should be:

- Heat stable
- Impermeable to moisture, water vapour, air, andodours
- Strong enough for machine handling
- Reasonably easy for patients to tear and open

Fig 9:Packaging of Capsule

Future perspective[29]

• The study of recent advancement of Solid dosage form capsule is studying for better kind of dosage. forms.

There are two way approach for capsule dosage form innovation in capsule shell and innovation incapsule system. The present review focuses on innovation in capsule system.

• This review includes newer trends related to capsule shell, capsule fill material, capsule

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sealingtechnique, and different capsule systems to achieve modified drug release.encapsulation of various kind of materials and for modifiedapplication like mapping of the drug forclinical evaluation.

1. To reduce the frequency of dosing or to increase effectiveness of the drug bylocalization at the site of action, reducing the dose required, or providing uniform drug delivery.
2. To Enhanced bioavailability, reduced side effects, improved patient compliance, reduced peak to trough ratio of drug in systemic circulation4 Modifications in conventional capsule delivery system are needed to overcome the disadvantages associated with them and to provide products of higher selectivity for medical treatment.

II. CONCLUSION

Polymeric film forming materials and manufacturing technologies used in the production of capsule shells have been developed to offer additional consumer acceptability, to improve the dosage form physical and chemical stability, and to modify release of the encapsulated contents from the dosage form. These developments resulted in the use of hypromellose and starch based polymeric materials as alternate to the animal source gelatin in the manufacture of capsule shells. Hypromellose capsule shells have lower moisture content and hygroscopicity than gelatin capsule shells. As a result, moisture transfer from the hypromellose capsule shells into the encapsulated fill material is lower and thus the physical and chemical stability of hypromellose shell based products containing compounds prone to water induced precipitation and hydrolysis is improved. Gelatin and non-gelatin capsule shells can also be formulated to modify the release of their fill contents in a site-specific manner in the GIT either by coating the filled capsules with a modified release polymer or by incorporating the polymer within the capsule shell before filling. These modified release capsule shells are soluble in or disintegrated by the intestinal secretions but resistant to the acid secretions of the stomach.

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