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A REVIEW ON CAPSULE TECHNOLOGY

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ABSTRACT

Capsule market size in India is calculable at Rs. 2,380 crore accounting for about 11% of the total domestic pharmaceutical industry. The capsules are consumed in around twelve major therapeutic segments in India. Capsule is one of the most preferable drug delivery system. This review article is intended to get comprehensive information about the capsule, its advantages and disadvantages over other dosage form, the brief manufacturing process of capsule and methods of evaluation.

KEY WORDS: capsule, duo cap, capsule manufacturing, hard and soft capsule

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INTRODUCTION

The word capsule originated from the diminutive of the Latin word "capsa" that means "box", a capsule is basically "a little box" and may refer to any encompassing structure or tiny container[1]. Capsules are a solid dosage form of medication within which the drug is closed in either a hard or soft soluble container or shell made of gelatin. It is additionally defined as dosage forms within which one or more medicinal or inert substances are enclosed inside a small gelatin shell. Most are meant to be swallowed whole, however sometimes the contents could also be removed from the gelatin shell and used as a premeasured medicinal powder[2].

Advantages of capsules *(3, 9)*

Capsules mask the taste and odor of unpleasant medicine and can be easily administered. Unique mixes and ingredients are possible. They're slippery when wet and, hence, easy to swallow with a small amount of water. As compared to tablets fewer adjuncts are needed. The shells are physiologically inert and easily and quickly digestible within the GI tract. Sealed hard gelatin caps can be good oxygen barriers. If produced in massive quantities it is economic, attractive and available in wide range of colors. They're easy to handle and carry. Protection for sensitive ingredients. The Shell usually breaks down/opens in four minutes Shells which can be opacified (with titanium dioxide) or colored, to provide protection from light. Easily filled either extemporaneously or in big scale. They're attractive in appearance. Permits medical practitioner to advise the exact medication required by the patient. Oil and fat-soluble nutrient delivery. Eliminate the presence of various additives, as in the case of tablets which can influence the absorption of the drug and so the clinical absorption obtained. Most popular technique for administering new therapeutics for analysis in initial clinical trials. Reduced gastrointestinal irritation. Fewer developmental issues in capsules, hence enable quick submission of a brand new drug for clinical trials. Capsule manufacturing needs fewer steps than tablet manufacturing. Easy to swallow therefore improves patient compliance easy separation of two incompatible products (combination) Offers medical practitioner a larger flexibility in dosages and drug combinations. Little pressure needed to compact the material as unit dose form. Easy to store and transport. Drug with high dose and low compressibility are often incorporated in capsules.

Disadvantages of capsules *(3, 9)*

The drugs which are hygroscopic absorb water from the capsule shell making it brittle and hence are not suitable for filling into capsules. The concentrated solutions which require previous dilution are unsuitable for capsules because if administered as such lead to irritation of stomach. Bulky materials can result in large capsule size Can be susceptible to Moisture. Ingredients can interact with capsule shell. More difficult to fill accurately. It's Costly. Capsule or lubricant allergies/sensitivities are possible. Softgel contents restricted to a tight pH range. Not suitable for highly soluble substances like potassium chloride, potassium bromide, ammonium chloride, etc. Not suitable for aqueous or hydro alcoholic solutions. Not suitable for highly efflorescent or deliquescent materials. Special conditions are required for storage.

Types of capsule

There are many types of capsules and they are divided into two broad classes i.e. hard and soft capsules (fig.1). Capsules are available in various sizes to provide dosing flexibility. Unpleasant medicinal tastes and odors are often masked by the tasteless gelatin cover. The administration of liquid and solid medicine encapsulate in hard gelatin capsules is one of the most often utilized dosage forms.[4]

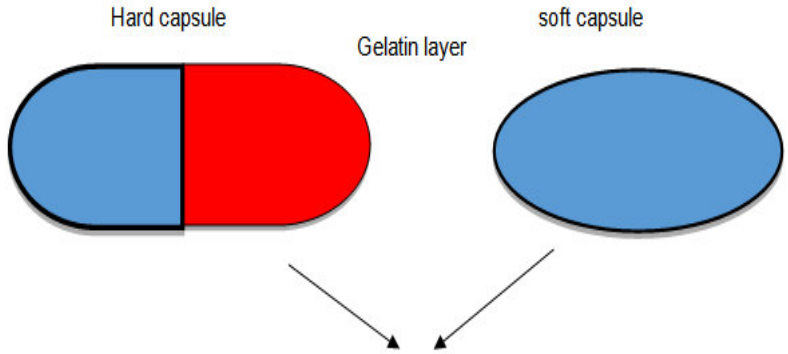


Figure 1
Types of capsule hard and soft capsule

Hard capsule

The hard capsule consist of two separate parts, each one is of semi closed cylindrical in shape. One part 'the cap' has a slightly larger diameter than the other, which is called the 'body' and is longer. The cap fits closely over the body to form a sealed unit.

Soft capsule

The soft capsule is a one- piece container, which has a variable shape and owing to its method of manufacture, may be either seamed, along its axis, or seamless[5].

Table 1
Difference between hard and soft gelatin capsule [6, 9]

	HARD GELATIN CAPSULE	SOFT GELATIN CAPSULE
Advantages		
1	High Accuracy/precision and hermetically sealed	Rapid drug release
2	Reduced dustiness in manufacturing process	Unique mixed fills possible
3	Reduced gastric irritancy	Good barriers to atmospheric oxygen
Disadvantages		
4	Costly to produce	Not suitable for bulky materials andstrongly hygroscopic drugs
5	product manufacturer is contracted out to a limited number of speciality houses	Maintenance of proper shell moisture content essential, therefore storage at 45-65% RH required
6	Intimate contact between the shell and contents hence stability is a concern	Cross-linking can affect hard gelatin capsules
7	Mixed fills not adaptable	
Manufacturing		
8	Contains 4-5 times less gelatin	Requires 4-5 times more gelatin
9	Requires only water and gelatin	Requires additional additives like glycerin for softening purpose.
10	Allow step by step filling of 2 different formulations (two stage release)	Filling and sealing are one and the same process.
11	Heat resistant:- allow filling thermo- stable substances up to 75^0 c	Filling temperature s about 35^0 c
12	Are stable in hot climate	Tends to stick together and become gluey
13	Disintegrates faster	Disintegrates slower
14	Constant external dimensions	Dimensions vary according to filling, weight and batch wise.

Manufacturing process of capsule[7]

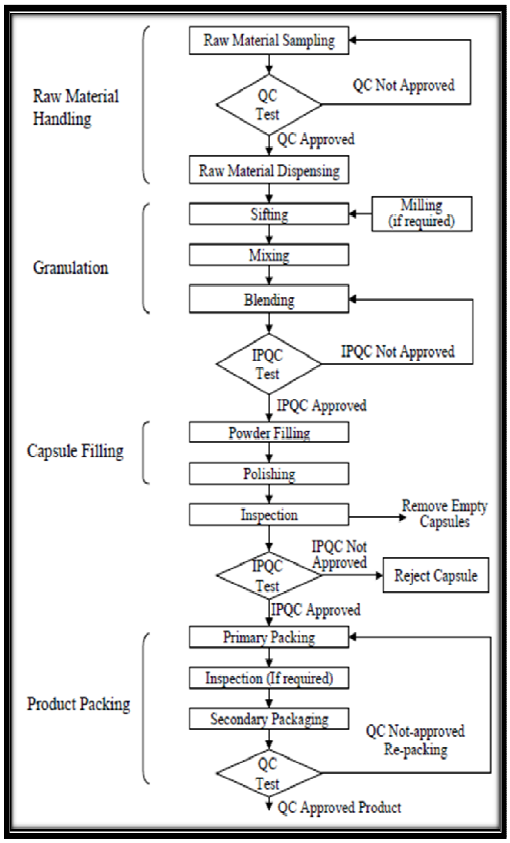


Figure 2
Flow chart of capsule manufacturing process

The capsule manufacturing process is a batch process[8] ***(fig.2)***

- Initially, the raw material goes through a quality Check (QC) and if approved numerous Active Pharmaceutical Ingredients (API) and Excipients are dispensed for processing.
- The raw material is undergone the sifter machine for sifting to achieve uniform granule size.

- Additionally, the residual raw material from sifter that's of the larger size is milled in a Multi mill to the requisite granule size.
- The output of the dryer is taken into the blender for blending the material and the output of the blender machine is processed for Intermediate process Quality Check (IPQC).
- If approved, the blended materials are taken to the power filling section.
- Within the powder filling section, the blended powder is filled in the empty capsules.
- The capsules are filled they proceed to polishing section where the capsules are polished to get rid of the surplus powder on the outer side of the filled capsule

Raw materials and excipients for capsules[9]

The raw materials used in the manufacturing process of both hard and soft gelatin capsules are similar. Both contain gelatin, water, colorants and optional materials such as process aids and preservatives.

1. Gelatin

Gelatin is that the very important a part of the capsules and has been the fabric from that they need historically been created. Gelatin could be a clear brittle solid substance, colorless or slightly yellow, nearly tasteless and scentless, that is created by prolonged boiling of animal product animal tissue or bones. Gelatin has been the fabric of alternative because of the potential of an answer to form a gel at a temperature simply beyond close temperate conditions that permits a homogenized film to be fashioned apace to solid on a mould pin[9].

The reason for this is that gelatin possesses the following basic properties

•It is non-toxic, widely used in foodstuffs and acceptable to be used worldwide.
•It is instantly soluble in biological fluids at body temperature.
•It is good film-forming material, producing a strong flexible film
•The gelatin films are homogeneous in structure, which provides them strength.

2. Colorants

The color of pharmaceutical product plays a vital role in their use. Color given primarily to identify a product in all stages of its manufacture and use in the manufacturing company it assists in complying with GMP norms by helping the operators differentiate between products [10].

3. Process aids

Preservatives and surfactants were added to the gelatin solution during capsule manufacture to help in processing. Gelatin solutions are an ideal medium for microorganism growth at temperatures below 55^0C. Preservatives are added to the gelatin and colorant solutions to reduce the growth of microorganisms till the moisture content of the gelatin film is below 16 pf w/v. at moisture content below that value, the bacterial population will decline in numbers with time. The materials used as preservatives include: sulfur dioxide which is more because the sodium salts bisulfite or metabisulfite, sorbic acid or the methyl propyl esters of para hydroxy-benzoic acid, and the organic acids, benzoic and propanoic acids. Some hard gelatin capsules may contain 0.15 % w/w of sodium lauryl sulphate which functions as wetting agent, to make sure that the lubricated metal moulds are uniformly coated when dipped into the gelatin solution.[11]

- ***Excipients of Hard gelatin capsule***[12]
  - Gelatin
  - Colour & Opecifying agent
  - Preservatives (methyl paraben, propyl paraben, butylated hy-droxyaniline, EDTA, sodium benzoate)
  - Dyes, pigments,
  - pH-adjusting additive
  - Flavors and fragrance

- ***Excipients of Soft gelatin capsule***[13]
  - Gelatin
  - Softener (plasticizer): sorbitol, xylose, maltitol, glycerin, PEG, wa-ter)
  - Preservatives (methyl paraben, propyl paraben, butylated hy-droxyaniline, EDTA, sodium benzoate)
  - Dyes, pigments,
  - Solvent
  - Polar: glycerin, PEG, PEG 400, PEG 3350, ethanol, PPG, water
  - Nonpolar: beeswax, coconut oil, triglyceride , corn oil, mineral oil, soybean oil, D,L-α tocopherol
  - pH-adjusting additive
  - flavor and fragrance
  - Pigment: titanium oxide, ferric oxide
  - Anticaking agent: Silicone dioxide
  - Humectant: polyol

Capsule shell filling

Types of materials for filling into hard gelatin capsules:

Dry solids – powders, pellets, granules or tablets
Semisolids – suspensions or pastes
Liquids – non-aqueous liquids

Hand operated hard gelatin capsule filling machines

Hand operated and electrically operated machines are in practice for filling the capsules but for small and quick dispensing hand operated machines are quite economical.

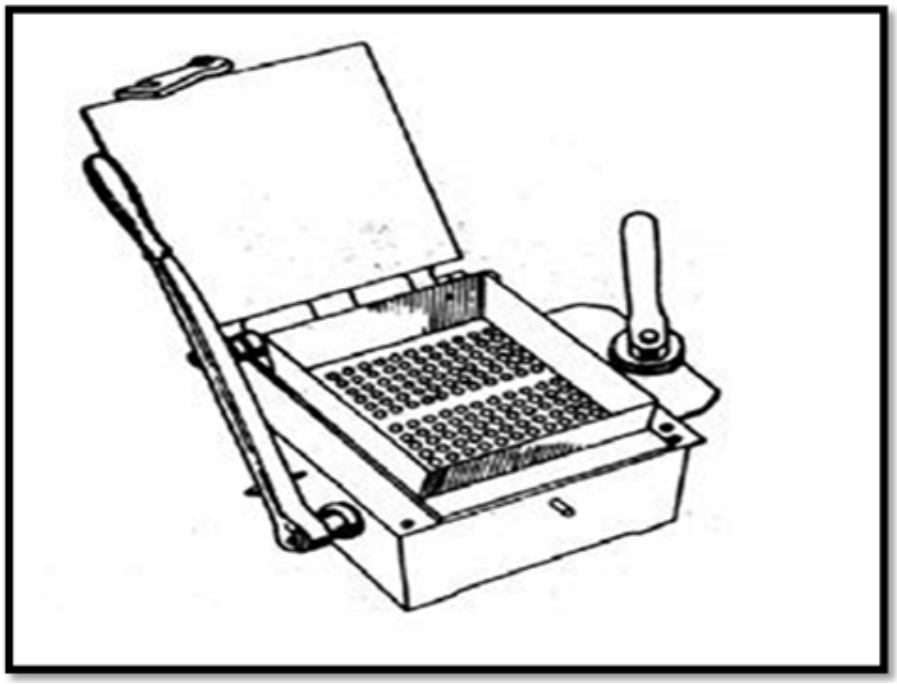


Figure 3
Hand operated hard gelatin capsule filling machines

Capsule filling devices
Machine can be "tapped" to spread the powder and drop it down into the capsule bases. A small device consists of many "pegs" on a handle can be used to tamp the powder into the capsule bases gently and evenly. Any remaining powder then is unfold equally over and into the capsule bases and tamped. These procedures are repeated until all of the powder is within the capsules. The capsule caps are then fitted over the machine, fixed in place, and the filled capsules removed, dusted using a clean cloth, and packaged.

Filling capsules with a semisolid mass
If the material to be placed into hard gelatin capsules is a semisolid, it can be encapsulated by either forming a pipe or pouring a melt.[14]

1. Pipe
If the material is sufficiently plastic, it can be rolled into a pipe with a diameter slightlyless than that of the inner diameter of the capsule in which it will be enclosed. The desired quantity of material is cut using a spatula or knife, the length determining the weight of the material enclosed. The pieces may be dusted with corn starch (check patient allergies) prior to individual insertion into the capsules. If a material is too fluid to be worked as described, it may be necessary to add cornstarch or some similar material to yield a more firm consistency. The quantity to be added can be determined empirically.

2. Semisolid pour
If the material is too firm to roll into a pipe but its melting point is satisfactory, it can be melted and poured into the capsule bases, cooled, and the caps replaced. A stand to hold the capsule bodies may be fashioned from a block of wood into which a series of holes the diameter of the capsule caps is drilled. When capsule caps are glued into these holes, capsule bases may be inserted for filling without scratching or marking by the wood. This method also can be used to enhance the bioavailability of drugs, which are poorly soluble and exhibit bioavailability problems. For this purpose, the drug is added to a melt of a material such as polyethylene glycol (PEG). The mixture is heated and stirred until the powder is either melted or thoroughly mixed in the PEG. The melt is cooled to just above the melting point of the PEG and poured into the capsule shells as described. When this method is used, the desired quantities can be measured using a pipe, syringe, or calibrated dropper to deliver the volume to the individual capsules[15].

Liquids in Hard Gelatin Capsules
Liquids can be prepared in hard gelatin capsules if the gelatin is not soluble in the liquid to be encapsulated; alcoholic solutions and fixed and volatile oils work well. It may be necessary to determine the solubility of gelatin in the liquid by experimentation. The liquid can be measured accurately using a pipette (micropipet) or a calibrated dropper and dropped into the gelatin base, taking care not to touch the opening. The gelatin caps can be touched, open end down, on a moist towel to soften the gelatin at the opening of the caps or a cotton swab dipped in warm water can be rubbed around the edge of the capsule cap to soften. The cap is placed over the base containing the liquid with a slight twist and the softened edge of the cap should form a seal with the base to prevent leakage. Prior to packaging, these capsules should be placed on a clean, dry sheet of paper and observed for leakage. Another method of sealing makes use of a warm gelatin solution that is painted around the capsules and the inside of the caps prior to placing on the base[16].

Cleaning and packaging
It is imperative that every precaution to minimize traces of moisture or body oils on capsules be taken to reduce powders sticking to the surface, which would create a

disagreeable appearance and taste. Cleaning capsules is difficult if they have become moist or sticky. The capsules should be handled so that they retain their dryness and shiny appearance. Use of gloves provides a more hygienic environment and helps preserve the dry, shiny capsule appearance. Another method of cleaning capsules is to place them in a container that is filled with sodium bicarbonate, sugar or salt then gently to roll the container. The contents then can be poured into a 10 mesh sieve and the "cleaning salt" allowed to pass through the screen, which collects the capsules. It must be emphasized that these cleaning methods are only effective if the capsules have been kept clean and dry. Once capsules become soiled and dull, they cannot be cleaned effectively. ROTOSORT is a new filled capsule-sorting machine sold by Eli Lilly and Company. It is a mechanical sorting device that removes loose powder, unfilled joined capsules, filled or unfilled bodies, and loose caps. It can handle up to 150,000 capsules per hour, and it can run directly off a filling machine or be used separately[17].

Alternative material for Hard-shell capsules

Several materials have been examined as a substitute for the gelatin in two-piece hard capsules. Hydroxypropylmethyl cellulose (HPMC) has become a successful alternative material for two-piece capsules and is actually on the market in the world**.** HPMC capsules have been developed for both pharmaceutical products and dietary supplements. QUALI-V, developed by Shionogi Qualicaps, is the first HPMC capsule developed for eventual use in pharmaceutical products [18].

Soft gelatin capsules

A soft gel (a soft gelatin capsule) is a solid capsule (outer shell) surrounding a liquid or semi-solid center (inner fill), as shown in figure 6. An active ingredient can be incorporated into the outer shell, the inner fill, or both. The formulation of drugs into soft gelatin capsules has gained popularity throughout the past decade due to the many advantages of this dosage form. The bioavailability of hydrophobic drugs can be significantly increased when formulated into soft gelatin capsules. Many problems associated with tableting, including poor compaction and lack of content or weight uniformity, can be eliminated when a drug is incorporated into this dosage form. Improved stability of drugs that are highly susceptible to oxidation can be achieved when formulated into a soft gelatin capsule[19]. Gelatin soft capsules are made from gelatin and water but with the addition of a polyhydric alcohol, such as glycerol or sorbitol, to make them flexible. Sorbitol is less hygroscopic than glycerol. They usually contain a preservative, such as beta-naphthol. They are available in variety of shapes and sizes as shown in figure 4.

- Spherical – 0.05 -5 ml
- Ovoid – 0.05 - 7 ml
- Cylindrical – 0.15- 25 ml
- Tubes – 0.5 - 0 ml
- Pear shaped – 0.3 - 5ml

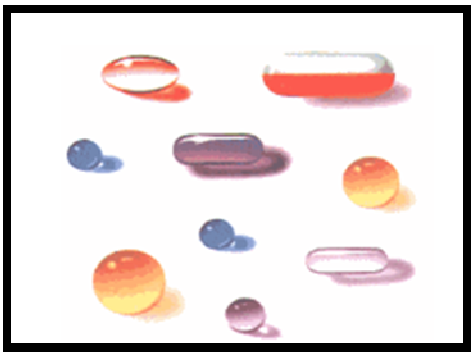


Figure 4
Different shapes of soft gelatin capsule

They are most suitable for liquids and semisolids and are widely used, in spherical and ovoid forms for vitamin preparations such as cod liver oil, vitamins A and D and multiple vitamins.[20]

There are three primary types of inner fill materials[21]

1) Neat Substance, especially oily liquids eg. Cod liver oil capsules

2) ***Solution Fills***

Active dissolved in a carrier

- Oils such as soybean oil and Miglyol 812 (neutral oil, triglycerides of medium chain fatty acids)
- Polyethylene Glycols: especially PEG 400 -600
- Other solvents: Any other solvent, which doesnot degrade or solubilize the gelatin shell, i.e., dimethyl isosorbide, surfactants, diethylene glycol monoethly ether.

Optional Ingredients for solution fills

1. Water or alcohol: up to 10% w/w (if needed for solubility).

2. Glycerin: 1 to 4% w/w (to retard the migration of the glycerin out of the shell into the fill).
3. Polyvinylpyrrolidone: Up to 10% w/w used in combination with PEG (can increase drug solubility, and also improve stability by inhibiting drug recrystallization).

***3) Suspension Fills**:*

Active dispersed in a carrier.

- Suspensions can accommodate about 30% solids before viscosity and filling become a problem
- Suspensions can be heated up to 35ºC to decrease viscosity during the filling process
- Suspended solids must be smaller than 80 mesh -- mill or homogenize before filling to prevent needles from clogging during filling.

Example of suspension fills include drug suspended in the following carriers

1. Oily mixtures

a) Soybean Oil with beeswax (4-10% w/w) and lecithin (2-4% w/w). The lecithin improves material flow, and imparts some lubrication during filling. Add enough beeswax to get a good suspension, but avoid creating a non-dispersible plug.
b) **Gelified Oil** (e.g. Geloil® SC), a ready to use system composed of soybean oil, asuspending agent, and a wetting agent.

2. Polyethylene glycol

- PEG 800 -1000 for semi-solid fills
- PEG 10,000 -100,000 for solid fills
- Or mixtures of the above. (Heat up to 35ºC to make fluid enough for filling)

Optional Ingredients that can be added in the suspension fill

Surfactant: sorbitan derivatives such as polysorbate 80 or lecithin.
For hydrophobic drugs dissolved or dispersed in an oily matrix, a surfactant of HLB 10 will increase the dispersibility of the product in aqueous fluids and also may improve bioavailability.

Recent updates in Capsule technology

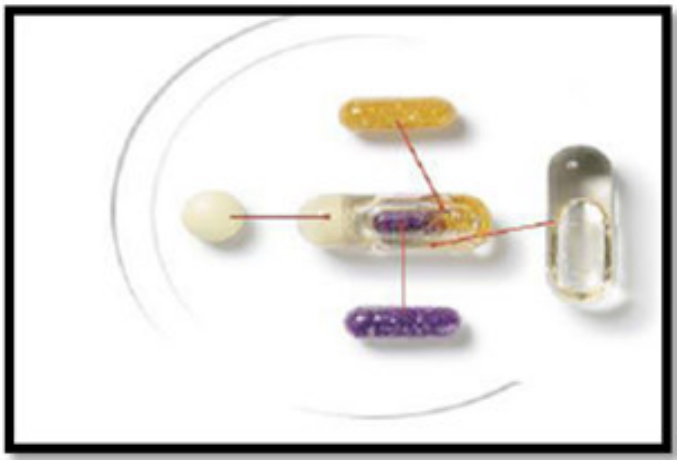
a) Capsugel has introduced Ocean caps capsules, these capsules made from all natural fish gelatin derived from farm-raised fish, they have the same characteristics as traditional gelatin capsules, including appearance, machinability, mechanical properties, hygroscopic and oxygen properties, chemical stability, and versatility. Plus, they are odourless and tasteless.
b) Licaps new 000 size capsules are ideal for maximising liquid dosage with a fill capacity of 1000 mg to 1400mg depending on th e density of the liquid fill material. This two-piece capsules has been specially designed to be sealed for secure containment of liquids and semi-solids without banding. Available in both gelatin and HPMC (Hydroxypropyl Methylcellulose) capsules they are available in a variety of colors to meet your specific needs.
c) Capsule in capsule: - Capsule in capsule formulation consists of two phases A) Immediate releasing phases B) Sustained releasing phases. The approach is well suited to formulating and filling formulations with various functions: •Specific in vitro release requirements (pulsatile or bimodal); •Avoidance of site-specific degradation in the gastrointestinal tract; •Improvement of patient compliance; •Compatibility issues for multi component products; and •Marketing needs for line extensions [22]

Figure 5
Capsule in capsule technology.

d) Innercap Technology

The photo to the above shows how four individual compounds are combined into one single dosage form. The combination example consists of a high potency insoluble active in a lipid emulsion, sustained release tablet and a cocktail of two crystalline active materials. A combination of release

Figure 6
Innercap technology.



e) Chewcaps

Encap Drug Delivery has explored various formulations for „chewable" capsules containing a range of flavours. The mouthfeel is agreeable as the capsule body is crushed and folded into the flavoured matrix by chewing. Gelatin capsules simply fracture, creating a very uncomfortable sensation. Several other issues arise during formulation work

- The suitability of the matrix for the mechanics of chewing (hardness/brittleness/ chewability)
- The duration of residence in the mouth;
- The ability to mask taste; and the taste of the shell.

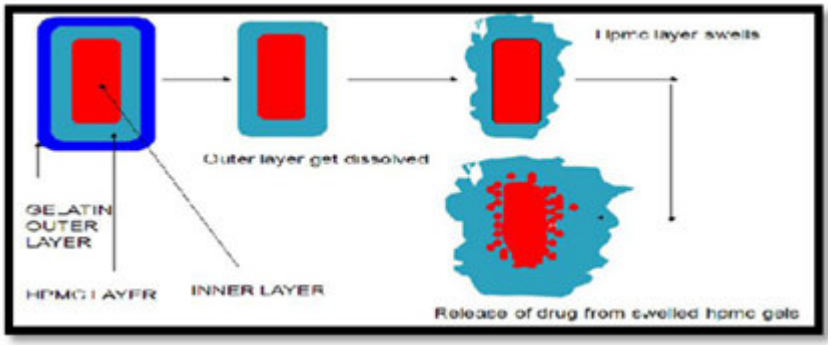
Here, the permeability of the HPMC product is an advantage. Typically, gelatin capsules do not transmit odour. For chewable, where taste is significant to user acceptability, the perceived flavour may enhanced by perception of product odor on opening the (bulk) pack. Profiles can be incorporated in the system[23].

f) Hydrophilic sandwich(HS) capsules

It is a simple and time delayed probe capsule. Based on a capsule within a capsule, in which the intercapsular space was filled with a layer of hydrophilic polymer (HPMC). This effectively created a "Hydrophilic Sandwich "between two gelatin capsules. When the outer capsule dissolved, the sandwich of HPMC formed a gel barrier layer that provided a time delay before fluid could enter the inner capsule and cause drug release. The time delay was controlled by-

- Molecular weight of polymer
- Inclusion of soluble filler. eg. Lactose

Figure 7
Hydrophilic Sandwich (Hs) Capsules



g) Duo caps

Their preparation is often complex at bench level and proportionately difficult at manufacturing scale. Using its liquid fill technology for hard capsules, encap Drug Delivery has developed a practicable and convenient formulation system that is well suited to such multiphase products (DuoCap™). It has also designed and built machine modules that enable full- scale manufacturing on the Bosch-based equipment. It enables a capsule (wide range of formats, including coated) to be filled into a larger liquid-filled capsule, which may, in turn, be coated. The approach is well suited to formulating and filling formulations with various functions: •Specific in vitro release requirements (pulsatile or bimodal); •Avoidance of site-specific degradation in the gastrointestinal tract; •Improvement of patient compliance; •Compatibility issues for multi component products; and •Marketing needs for line extensions.

Figure 8
Duo cap technology

PACKAGING AND STORAGE OF CAPSULES

Capsules should be packed in a well-closed glass or plastic containers and stored in a cool place. These type of containers have an advantage over cardboard boxes that they are more convenient to handle and transport and protect the capsules from moisture and dust. To prevent the capsules from rattling a tuft of cotton is placed over and under the capsules in the vials. In vials containing very hygroscopic capsules a packet-containing desiccant like silica gel or anhydrous calcium chloride may be placed to prevent the absorption of excessive moisture by the capsules. Now a days capsules are strip packaged which provide sanitary handling of medicines, ease in counting and identification[24]. Empty gelatin capsules should be stored at room temperature at constant humidity. High humidity may cause softening of the capsules and low humidity may cause drying and cracking of the capsules. Storage of capsules in glass containers will provide protection not only from extreme humidity but also from dust. Storage of filled capsules is dependent on the characteristics of the drugs they contain. Semisolid filled hard gelatin capsules should be stored away from excessive heat, which may cause a softening or melting of the contents.

EVLUATION OF CAPSULES

Weight Variation test

Ten capsules were individually weighted and the content were removed. The emptied capsule were individually weighed and the net weight of the contents was calculated by subtraction and the percent weight variation was calculated by using the following formula.
Weight variation= (weight of capsule-Average weight)/Average weight of capsule x 100 Weight variation should not be more than 7.5%.[25]

(1) Lock length

Ten individual capsule were taken from formulation trial batch and lock length was measured manually by using Vernier calipers and average of ten capsule was noted.

(2) Disintegration

The capsules were placed in the basket rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37^0 C. To fully satisfy the test, the capsules should disintegrate completely into a soft mass having no palpably firm core without any fragments of the gelatin shell. If one or two capsules fail the test should be repeated for additional of 12 capsules. Then not fewer than 16 of the total 18 capsules tested should disintegrate completely.

(3) Dissolution studies

Dissolution is a process by which the disintegrated solid solute converted into solution. The test determines the time required for a definite percentage of the drug in capsules to dissolve under specified conditions. The release of drug was determined using a dissolution apparatus of USP type II paddle at 50 rpm 900 ml of 0.1 N HCL solution was used as a dissolution media and maintained at temp 37.5^{0} C

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