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CAPSULE TECHNOLOGY: INNOVATIONS AND APPLICATIONS IN DRUG DELIVERY

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Abstract: The composition of the gelatin capsule shell determines whether it is soft or rigid. The patient is supposed to consume the capsules whole. When patients, particularly youngsters, are unable to swallow capsules, the contents can be taken out and put to soft food—for example, by sprinkling it on top—right before it is consumed. Encapsulation, as used in pharmaceutical manufacturing, describes a variety of methods used to encapsulate medications in a somewhat stable capsule so that they may be consumed orally or used as suppositories, for example. Hard-shelled capsules: these are often used for small pellets or dry, powdered materials. They are both manufactured from aqueous gelling agent solutions, such as: Primarily composed of gelatin, animal protein also includes non-gelatinous substances including plant polysaccharides and their derivatives, such as carrageenan's and modified starch and cellulose. Even while gelatin capsules have many benefits, there are a few disadvantages that restrict the material's application in capsule form. particular customers, including vegetarians and vegans, as well as members of particular religious or cultural groups, may find the animal source of gelatin to be problematic. Additionally, because unmodified gelatin is prone to cross-linking when it comes into contact with aldehydes, solubility issues may be anticipated with specific fill formulations. The components of the non-gelatin capsule shells include starch, HPMC, PVA, and alginate.

Key words: Gelatin/Non-Gelatin Material, capsule shell, Starch, HPMC, PVA, Alginate.

Introduction

Soft gelatin capsules1 (referred to as soft elastic gelatin capsules, liquid gels or soft gels) are a unique drug delivery system that can provide distinct advantages over traditional dosage forms such as tablets, hard gelatin capsules and liquids. However due to economic, technical and patent constraints there are relatively a few manufacturers of soft gels in the world. Soft gel is a hermetically sealed, one-piece capsule with a liquid or semisolid fill. The soft gel consists of two major components, the gelatin shell and the fill. In the

finished product gelatin shell is primarily composed of gelatin, plasticizer and water. The fill material can include a wide variety of vehicles and can either be a solution or a suspension. Soft gels may be coated with suitable exterior coating agents such as Cellulose acetate phthalate (CAP) to obtain enteric release of encapsulated material. The standard soft gel shape of oral pharmaceutical products is oval, oblong and round, though soft gels can be manufactured in many shapes. Soft gelatin capsules generally contain the drug in a non-aqueous solution or suspension. The vehicle may be water immiscible liquid, such as PEG, and non-ionic surface-active agent, such as Polysorbate 80. Hydrophobic drugs dissolved in a lipophilic solvent such as vegetable oil would generally demonstrate poor bioavailability compared to the same drug given as a powdered

solid, suspension or hard gelatin capsules. However, a drug dissolved or dispersed in a water miscible solvent may have better bioavailability than a compressed tablet of the same drug.

Since the introduction of Soft Capsule Making Machine in the 1970s, formulations have continually become more popular with rapid developments in recent years. This could be illustrated by emergency of a more than 560 sets of Soft Capsule Making Machine with transfer mode having a production rate of up to 60 billion pills/year (i.e. more than 3600 kinds of drugs) in the world.

Up to now, there are more than 30 manufacturers producing more than 40 kinds of soft capsules by using over 60 sets of advanced machines.

TYPES OF CAPSULES

- **Gelatin capsules**, informally called **gel caps** or **gel caps**, are composed of gelatin manufactured from the collagen of animal skin or bone. (Gelatin is not derivable from ungulate hooves, which are composed of a different protein, keratin.)
- **Vegetable capsules** are composed of Hypromellose, a polymer formulated from cellulose. There are two types of capsules, “hard” and “soft”. The hard capsule is also called “two pieces” as it consists of two pieces in the form of small cylinders closed at one end, the shorter piece is called the “cap” which fits over the open end of the longer piece, called the “body”. The soft gelatin capsule is also called as “one piece”. Capsules are available in many sizes to provide dosing flexibility. Unpleasant drug tastes and odors can be masked by the tasteless gelatin shell. The administration of liquid and solid drugs enclosed in hard gelatin capsules is one of the most frequently utilized dosage forms.

Advantages of Capsules

- Capsules mask the taste and odor of unpleasant drugs and can be easily administered.
- They are attractive in appearance
- They are slippery when moist and, hence, easy to swallow with a draught of water.
- As compared to tablets less adjuncts are required.
- The shells are physiologically inert and easily and quickly digested in the gastrointestinal tract.
- They are economical
- They are easy to handle and carry.
- The shells can be opacified (with titanium dioxide) or colored, to give protection from light.

Disadvantages of Capsules

- 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.

GELATIN CAPSULE SHELL[2]

Development of capsule shell by Gelatin

Gelatin is the major component of the capsules and has been the material from which they have traditionally been made. Gelatin has been the raw material of choice because of the ability of a solution to gel to form a solid at a temperature just above ambient temperate conditions, which enables a homogeneous film to be formed rapidly on a mould pin.

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

- ✓ It is non-toxic, widely used in foodstuffs and acceptable for use worldwide.
- ✓ It is readily 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 gives them strength.

Some of the disadvantages with using gelatin for hard capsules include: it has a high moisture content, which is essential because this is the plasticizer for the film and, under International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) conditions for accelerated storage testing, gelatin undergoes a cross linking reaction that reduces its solubility. Gelatin is a translucent brittle solid substance, colorless or slightly yellow, nearly tasteless and odorless, which is created by prolonged boiling of animal skin connective tissue or bones. Type A gelatin is derived from an acid-treated precursor and exhibits an isoelectric point in the region of pH 9, whereas type B gelatin is from an alkali-treated precursor and has its isoelectric zone in the region of pH 4.7. Capsules may be made from either type of gelatin, but mostly a mixture of both types is used considering availability and cost. Difference in the physical properties of finished capsules as a function of the type of gelatin used is slight. Blends of bone and pork skin gelatins of relatively high strength are normally used for hard capsule production. The bone gelatin produces a tough, firm film, but tends to be hazy and brittle. The pork skin gelatin contributes plasticity and clarity to the blend, thereby reducing haze or cloudiness in the finished capsule.[3]

HARD GELATIN CAPSULES

The majority of capsule products are made of hard gelatin capsules. Hard gelatin capsules are made of two shells: the capsule body and a shorter cap. The cap fits snugly over the open end of the capsule body. The basic hard gelatin capsule shells are made from mixtures of gelatin, sugar, and water. They are clear, colorless, and essentially tasteless.

Gelatin is a product obtained by partial hydrolysis of collagen acquired from the skin, white connective tissue, and bones of animals. Gelatin is a protein which is soluble in warm (or hot) water, but insoluble in cold water. At low temperatures, gelatin dissolved in water becomes a gel (which is insoluble in water). This property is used to prepare Jello and other gelatin deserts. Gelatin capsules become dissolved in warm gastric fluid and release the contents. Normally, hard gelatin capsules contain 13–16% of moisture. If additional moisture is absorbed when stored in a high relative humidity environment, hard gelatin capsule shell may lose their rigid shape and become distorted. In an opposite environment of extreme dryness,

capsules may become too brittle and may crumble during handling. Since moisture can be absorbed or released by the gelatin capsules, capsules containing moisture-sensitive drugs are usually packaged in containers. Gelatin for making hard shells is of bone origin and has 220–280 bloom strength (the weight required to depress a standard plunger 4 mm into the gel

Manufacturing of Hard Capsules

Some of the major suppliers of empty gelatin capsules are: Eli Lilly and Company, Warner

Lambert's Caps gel (formerly Park Davis) and R. P.Scherer Corporation.

The metal moulds at room temperature are dipped into a hot gelatin solution, which gels to form a film. This is dried, cut to length, removed from the moulds and the two parts are joined together, these processes are carried out as a continuous process in large machines.

The completely automatic machine most commonly used for capsule production consists of mechanisms for automatically dipping, spinning, drying, stripping, trimming, and joining the capsules.

- Stainless steel pins are used on which the capsule is formed and controls some of the final critical dimensions of the capsule.
- One hundred and fifty pairs of these pins are dipped in to gelatin sol of carefully controlled viscosity to form caps and bodies simultaneously. The pins are usually rotated to distribute the gelatin uniformly, during which time the gelatin may be set or gelled by a blast of cool air.
- The pins are moved through a series of controlled air-drying kilns for the gradual and precisely controlled removal of water. The capsules are striped from the pins by bronze jaws and trimmed to length by stationary knives while the capsule halves are being spun in chucks or collets. After being trimmed to exact length, the cap and body sections are joined and ejected from the machine. The entire cycle of the machine lasts approximately 45 min.
- Thickness of the capsule wall is controlled by the viscosity of the gelatin solution and the speed and time of dipping. Mold pin dimensions, precise drying, and machine control relating to cut lengths are matters that are critical to the final dimensions. Precise control of drying conditions is essential to the ultimate quality of the cast film.

The in-process quality controls include periodic monitoring, and adjustment when required, of film thickness, cut lengths of cap and body, color, and moisture content.

Inspection processes to remove imperfect capsules were previously done visually, have recently been automated following the development and patenting of a practical electronic sorting mechanism by Eli Lilly and Company. This equipment mechanically orients the capsules and transports them past a series of optical scanners, at which time those having detectable visual imperfections are automatically rejected. [5]

SOFT GELATIN CAPSULES

Soft gelatin (also called soft gel or soft elastic) capsules consist of one-piece hermetically-sealed soft shells. Soft gelatin capsules are prepared by adding a plasticizer, such as glycerin or polyhydric alcohol (e.g., sorbitol), to gelatin. The plasticizer makes gelatin elastic. Soft gelatin capsules come in various shapes such as spherical, elliptical, oblong, and special tube shapes with and without twist off. They can contain non-aqueous liquids, suspensions, pasty materials, or dry powders. They are especially important to contain volatile drug substances or drug materials susceptible to deterioration in the presence of air.

MANUFACTURING OF SOFT CAPSULES

There are several procedures to prepare soft gelatin capsules, such as the plate process, the rotary die process, and reciprocating die process. Most soft gelatin capsules produced in industry are prepared by the rotary-die process. In this process, two continuous gelatin ribbons are brought together between twin rotating dies. At the moment that the dies form pockets of the gelatin ribbons, metered-fill material is injected between the ribbons. Then the pockets of fill-containing gelatin are sealed by pressure and heat. The capsules are subsequently severed from the ribbon. As the capsules are cut from the ribbons, they may be collected in a refrigerated tank to prevent capsules from adhering to one another and from getting dull.

Soft gelatin capsules contain more moisture than the hard capsules. Since gelatin is subject to microbic decomposition when it becomes moist, soft gelatin capsules may be prepared with preservatives to prevent the growth of fungi. Gelatin used for making soft capsules is usually of bone and skin origin and has 150–175 g bloom strength.[6]

NON-GELATIN CAPSULE SHELL

Development of Non-gelatin capsules

Traditionally, gelatin has been used almost exclusively as shell-forming material of soft capsules. This is due to its legal status and its unique physicochemical properties, namely its oxygen impermeability and the combination of film forming capability and thermo reversible sol/gel formation that favor its use for the industrial capsule production especially in the rotary die process. Despite these great advantages, which have been described in detail in the section above on ‘Soft gelatin capsules’, gelatin has several drawbacks that limit its use. Mainly,

- The animal source of gelatin can be a problem for certain consumers such as vegetarians or vegans and religious or ethnic groups (Jews, Muslims, Hindus, etc.) who observe dietary laws that forbid the use of certain animal products Since unmodified gelatin is prone to cross linking when in contact with aldehydes, solubility problems might be expected with certain fill formulations.
- Transparent low-color capsules are difficult to produce owing to the effect of the intrinsic Maillard reaction on gelatin color.
- The temperature and moisture sensitivity of gelatin- based soft capsules is an issue that complicates the use of soft gelatin capsules in very hot and humid regions and requires special packaging and storage conditions to ensure product stability.
- For low-price health and nutrition products, pricing of commercially available gelatin might be an additional problem.

To address these concerns, there has been a great interest in the soft capsule industry in looking for gelatin substitutes. Indeed, several concepts based on synthetic polymers and/or plant-derived hydrocolloids have been described in the patent literature. [7]

A) DEVELOPMENT OF STARCH CAPSULES [8]

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 moisture indicates that starch capsules may provide better stability properties and reduces susceptibilities to change on storage.

- **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.

The advantages of soft gelatin capsule:

- ✓ Soft gels are easy to swallow, once swallowed, release their contents very quickly.
- ✓ have the ability to mask odors and unpleasant tastes
- ✓ have an elegant appearance
- ✓ readily dissolve in the gastric juices of the digestive tract
- ✓ they may enhance the bioavailability of the active ingredient
- ✓ In specialized dosage form, soft gel can be made into chewable, extended release, cap tabs, etc. It can also be used for ophthalmic preparations, e.g. aplicaps, vaginal/rectal suppositories.
- ✓ Dosage Accuracy. Uniformity and precision dosage
- ✓ Product Security. Dosage and formulation are tamper-resistant (a punctured or tampered soft gels will leak or become discolored). Protection against counterfeit
- ✓ Product Stability. Sealed container, Protection from light for photosensitive formulations, Protects drug from oxidation and degradation

Soft gel also had some disadvantages point :[9,10]

- ➢ water soluble material is difficult to incorporate
- ➢ Highly moisture sensitive. Gelatin is extremely water soluble, which helps it dissolve in the body. The downside is that soft gelatin capsules are very sensitive to heat and humidity. In hot or humid climates, soft gel caps may stick together or even break open before you have a chance to use them. Keeping your soft capsules in the bathroom may also decrease their life expectancy, since showers create a hot, humid climate that may not dissipate quickly.
- ➢ Efflorescent material cannot be incorporated, they may cause softening/leaching
- ➢ Deliquescent materials cannot be incorporated. They may cause hardening or brittle capsule.
- ➢ More Costly. Many pharmaceutical companies do not have the equipment necessary to fill soft gelatin capsules and have to transport the drugs to have them processed, adding to the cost. This cost can

increase the price the consumer pays. Certain health supplements, such as cod liver oil, come in liquid and soft gel cap form. In most cases, the price is greater for the soft capsules than for the liquid.

- Dietary Restrictions. Gelatin is traditionally made out of the bones and skins of pigs and cows. Many groups, however, have dietary proscriptions that prevent them from consuming animal products found in soft gelatin capsules. Soft gel caps violate the religious dietary restrictions of observant Jews, Muslims, Buddhists and Hindus. Because soft capsules are made out of animal parts, many vegetarians also opt not to use them. There are animal-free substitute gelatin capsules made out of seaweed extract or other sources, but they are generally more expensive and harder to find.

Ideal characteristics of soft capsules:

- ✓ To optimize the chemical stability of the active compound.
- ✓ To improve bioavailability of the active compound
- ✓ To allow for an efficient and safe filling process
- ✓ To achieve a physically stable capsule product.
- ✓ Final product stability is related to shell compatibility

New Soft gel Variants:

The following new dosage forms have been developed:

1. Enteric Soft gel:

In contrast to existing enteric dosage forms, Banner's new enteric soft gel is not coated. The enteric features of the dosage form reside in the shell itself. The result is a clear enteric dosage form with the exact same appeal and patient benefits that the standard soft gel offers. Banner's enteric soft gel meets all Pharmacopeial (American, European, Japanese and British) standards for enteric delivery. Banner's enteric soft gel technology is unique in that it offers a one-step process to manufacture enteric soft gels. Traditionally, enteric soft gels were prepared by coating with enteric polymers using traditional coating technology. Coating has its own disadvantages such as unsuccessful adhesion of the enteric polymer onto the soft gelatin shell due to the shell's inherent flexible nature. This can lead to chipping and peeling of the coat. Enteric coating also results in a hazy and opaque appearance of the capsule and is an additional step of manufacturing.

Advantages of the enteric soft gel over other enteric dosage forms can be summarized as follows:

- Enteric soft gel technology provides enteric properties more consistently than other products because the enteric system is built into the gelatin shell, not just as a coating on top;
- Clear, transparent dosage form, as opposed to coated enteric dosage forms;
- offers the exact same advantages as standard soft gels, including improved 'swallow ability', taste-masking and protection against light or oxygen degradation; and
- No leaking problems, as opposed to regular two-piece hard shell capsules.

Candidates for enteric delivery include:[11]

- Compounds those are unstable in gastric acid, For Example: proton pumps inhibitors, certain antibiotics, triptans and dideoxy inosine (ddI);
- Compounds that is irritating or damaging to the gastric mucosa, for example bisphosphonates, non-steroidal anti-inflammatory drugs, certain antibiotics and carbamazepine;

- compounds targeted at the small intestine, e.g. drugs for the treatment of Crohn's disease or other intestinal disorders, and drugs that are preferentially being absorbed in the small intestine; and
- Compounds that may cause belching, regurgitation or other goitrogenic discomfort.

Banner has comprehensively designed and optimized the new enteric technology to suit a wide variety of products. We have applied the new technology on different drugs and have generated accelerated stability data. Banner is currently working on an existing drug for scale-up purposes. For this compound, the enteric softgel formulation has successfully passed accelerated stability testing as well.

2. Controlled Release Soft gel:

Banner's scientists have developed a controlled release technology that is able to achieve a large variety of release patterns. The controlled release soft gel can be applied to a wide range of active molecules. Banner's controlled release soft gel technology uses a lipid matrix in a standard soft gel shell. Depending on the physicochemical properties of the active molecule, an emulsion or a suspension is chosen as a matrix. By applying these, or combinations of these, almost any release profile can be engineered simply by varying the formulation. The result is an oral dosage form offering controlled release of the active moiety, combined with all the benefits that the soft gel dosage form offers. Its release properties, combined with the advantages of a soft gel, make the CR-soft gel a preferred form for those insoluble compounds that require enhanced absorption as well as a prolonged and controlled release.

3. Chewable Soft gels:

The chewable gelatin dosage form offers excellent mouth feel and chewing experience as compared with other chewable dosage forms. Chewable soft gels are particularly suitable for pediatric populations, where swallowing whole tablets or capsules is often a problem and chewable tablet are often rejected. Consumer preference testing with Banner's new chewable gels showed that three out of four parents would buy this product for their children (Trigon Research, data on file). In the adult population, chewable gels are convenient because they can be taken easily on the run, without the need for water. Lipid-coating of the active ingredient has been used and tested as a means to mask the taste of bitter active ingredients. This approach has resulted in a highly acceptable end-product. Other taste-masking technologies can be combined with the chewable soft gel.

1. Gelatin-free Soft Capsule:[12]

Gelatin-free soft capsules are made from vegetable ingredients. They have all the advantages of standard soft gels, but do not contain gelatin. Gelatin-free soft capsules are particularly suitable for vegetarians or other populations that prefer non-animal products.

1. Soflet ®Gel caps

Soflet® Gel caps represent a patented technology whereby tablets are enrobed with gelatin. Soflet® Gelcaps are a dosage form preferred by consumers because of the ease of swallowing as well as the taste and odour-masking properties imparted by the gelatin coating. The unique, patented manufacturing process of Soflet® Gel caps results in a single or two-toned colour dosage form that can be imprinted upon. These features offer distinctive opportunities for product branding. Soflet® Gel cap technology is therefore widely used in over the-counter products, both branded and private label. In addition, Soflet® Gel caps are ideal for clinical trial blinding. Banner now also has the capability of manufacturing gelatin-free Soflet® Gel caps.

2. 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 mixed thoroughly 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 colored differently to simplify identification and facilitate control of mixing.

- **Liquid filled hard gelatin capsules:**

It is generally accepted that many of today's NCE's (New Chemical Entities) are poorly water soluble and the classical methods, such as reduction in particle size are no longer adequate to achieve satisfactory drug adsorption from a solid oral dosage form. One of the most promising strategies to deliver these insoluble compounds is using dissolved systems like using lipids, liquids or semi-solids to formulate new products. Twp piece hard shell capsules are one of the most logical approaches when choosing the best dosage form to deliver these new liquid formulations.

The new technology of packaging liquids in hard gelatin capsules is considered a major breakthrough. It can make a significant contribution to the development of efficacious pharmaceutical products by providing the flexibility to rapidly develop and test in-house formulations when only small quantities of drug substance is available. The process can be scaled-up and also kept in-house similar to the operations of tabletting or powder/pellet filling of hard gelatin capsules.

3. Rectal capsules:

Soft gelatin capsules may be used as substitutes for rectal and vaginal suppositories. Various shapes and sizes are used for this purpose. They are generally wider at one end which is inserted first; the movement of the sphincter muscles forces the capsules forward into the rectum. Liquids or solids can be filled into rectal capsules but the base in which the medicaments have been incorporated must be non-toxic, non-irritant and compatible with the capsule shell

4. Capsules for packing of ophthalmic ointments:

It is very important that the ophthalmic ointments should be sterile and free from irritant effect. Therefore they must be packed in such a manner that the product remains sterile until whole of it is used up. The best method to keep the preparation free from contamination during use is to pack it in single dose containers. Now a days soft gelatin capsules are very commonly used for filling ophthalmic ointments. These capsules are meant for single application to the eye. Just before application, the capsule is punctured with a sterile needle, the contents instilled into the eye and the shell discarded.

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