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A Review on Recent Advancement in Capsule Formulation

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ABSTRACT

In this article, 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 in capsule system. The present review focuses on innovation in capsule system. In this the study is about to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. By the study of this recent advancement new kind of drug delivery system is developed which is used to Enhanced bioavailability, reduced side effects, improved patient compliance, reduced peak to trough ratio of drug in systemic circulation. The development of new generation of capsules are beneficial for night time dosing and for the drugs having high first pass effect and having specific site of absorption in Gastrointestinal tract.

Keywords: - Hard Gelatin Capsule, Soft Gelatin Capsule, Recent Advancement, Innercap, Chewcaps, Duocaps.

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INTRODUCTION

A capsule is a shell or a container prepared from gelatin containing one or more medicinal and/or inert substances. The gelatin capsule shell may be soft or hard depending on their formulations. Capsules are solid dosage forms in which the medication contained within gelatin shells. The medication may be a powder, a liquid or a semisolid mass. Capsules are intended to be swallowed whole by the patient. In instances where patients (especially children) are unable to swallow capsules, the contents of the capsule can be removed and added (*e.g*., sprinkled) on soft food immediately before ingestion. In this case, capsules are used as a vehicle to deliver premeasured medicinal powder. Capsule dosage forms occupy more than 10% of the total dosage forms on the market. [1]

Capsule sizes:-

Table-1 Physical specification for hard gelatin capsule [2]

S.NO.	Size	Volume (cm^3)
1.	000	1.37
2.	00	0.95
3.	0	0.68
4.	1	0.50
5.	2	0.37
6.	3	0.30
7.	4	0.21
8.	5	0.13

- Capsules are gelatin shells filled with the ingredients that make up an individual dose.
- Dry powders, semi-solids, and liquids that do not dissolve in gelatin may be encapsulated.
- Capsules account for about 20% of all prescriptions dispensed.
- The capsules are present mainly of Two Types:-

1. Soft Gelatin Capsule:-

- One piece hermetically sealed soft gelatin shell containing a liquid, a suspension or semisolid.
- It consists of a continuous gelatin shell surrounding a liquid core. It formed, filled, and sealed in one operation. It is oblong, spherical, elliptical in shape. The capsule shell consists of gelatin, water and plasticizer.
- Soft gelatin capsule are made up of gelatin but differ from hard gelatin capsule in composition that sugar is replaced by plasticizer like glycerin, sorbitol or a similar polyol.
- Plasticizers impart elastic properties to gelatin.

- Single dose application of topical and ophthalmic preparations, rectal ointments and medications for ear and nose can be packed in soft gelatin capsule.
- Soft gelatin capsule are available in oblong, spherical, elliptical and other shapes. They are also available in sizes to contain from 0.1 to 30 ml of volume.

Advantages:-

- Products can be encapsulated in various shapes - various sizes - various colors.
- Products with thick slurry type paste Medicaments to light oils and powders (with inert media) can be encapsulated.
- Lower dose of active ingredients and given as unit dose.
- High accuracy in fill weights.
- Fewer inactive ingredients.
- Improved stability. Longer shelf life.
- Improved bioavailability.
- One piece Capsule - tamper proof.
- One piece Capsule - no problem of microbial contamination, oxidation and evaporation.
- Ease of administration - oral, rectal and vaginal.

Disadvantage

- Highly sensitive to temperature and humidity.
- Additional quality control measures may be required. [1, 3]

Manufacturing Process :-

Composition of Soft Gelatin Capsule Shell:-

1. Gelatin
2. Plasticizer: glycerin, sorbitol
3. Water
4. Preservatives: Methyl Paraben, Propyl Paraben
5. Colorants: F.D & C, Certified lakes
6. Opacifier: Titanium dioxide
7. Flavoring agent: Ethyl vanillin
8. Fumaric acid is added to aid solubility and to reduce aldehydes tanning of gelatin.[4]

Manufacturing Steps of Soft Gelatin Capsule:-

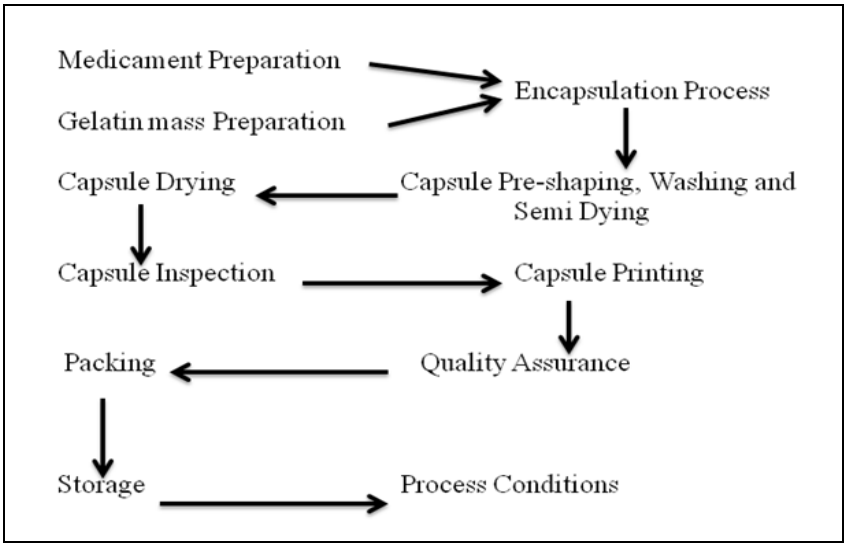

Figure 1 Manufacturing Of Soft Gelatin Capsule [5]

Gelatin Specification For SGC:

Table-2 Gelatin Specification for SGC [6]

Gelatin properties	Acid ossein	Fish
Bloom(g)0	180-210	160-210
Viscosity, 6.67%,600(mpa,s)	2.7-3.2	3.0-3.5
Moisture (%max)	13.0	13.0
Ash (%max)	1.	1.0
PH ,1% solution	5.0-6.0	5.0-6.0
Iso ionic point,ph	6.0-8.0	7.0-9.4
Particle size % passing 4 us #	100	100
SO2 (ppm max)	60	60
H2O2	60	60
Clarity (45% solution in 30% glycerol)	Clear	no precipitate
Microbial standards		
Total count	500	500
E.coli in 10 gm	Absent	Absent
P. Aeruginosa in 10 gm	Absent	Absent

2. Hard Gelatin Capsule

The hard gelatin capsule consists of a base or body and a shorter cap, which fits firmly over the base of the capsule. These types of capsule are economically produced in large quantities and in wide range of colors, and they generally provide ready availability of the contained drug, since minimal excipient and little pressure are required to compact the material.

Advantages:

1. They may be used to mask the unpleasant tastes, aromas, or appearance of a drug.
2. They allow powders to be dispensed in an uncompressed form, thus allowing for quicker

dissolution and absorption of the drug following oral dosing (as compared with tablets).

3. They offer the pharmacist versatility to prepare any dose desired for a variety of administration routes (e.g. oral, inhalation, rectal, or to be diluted for vaginal, rectal, oral or topical use).
4. They may be easier than tablets for some people to swallow.
5. They can be making to alter the release rate of the drug.
6. They are available in various sizes.
7. They can be colored to protect the content (photosensitive) from light and improve the acceptability.
8. Required less excipient than tablets.

Disadvantages:

1. They are easily tampered with (although techniques exist for preventing this).
2. They are subject to the effects of relative humidity and to microbial contamination.
3. More expensive (commercially).
4. Bulk dosage cannot be dispensed in capsule. [7]

Manufacturing Process:-

Shell Composition

Gelatin is the most important constituent of the dipping solutions, but other components may be present are:

Gelatin:-

Gelatin is prepared by the hydrolysis of collagen obtained from animal connective tissue, bone, skin, and sinew. Gelatin is vary in its chemical and its physical properties depending on the source of the collagen and the manner of extraction. There are two basic types of gelatin.

Type A- It is produced by an acid hydrolysis. It is manufactured mainly from pork skin.

Type B- It is produced by alkaline hydrolysis. It is manufactured by mainly from animal bones.

These two types can be differentiated by their isoelectric points (4.8-5.0 for Type B and 7.0-9.0 for Type A) and by their viscosity building and film forming characteristics.

Either type of gelatin may be used, but combination of pork skin and bone gelatin are often used to optimize shell characteristics. Bone gelatin contributes firmness, whereas pork skin gelatin contributes plasticity and clarity. The physicochemical properties of gelatin of most interest to shell manufacturers are the bloom strength and viscosity. The viscosity of gelatin solution is vital to the control of the thickness of the cast film. Viscosity is measured on a standard $6\frac{2}{3}$ % w/w

solution at 60°C in a capillary pipette and generally the range of 30-60 millipose is suitable.

1. Colorants:
    - Colorants are used to identify the product and to improve patient compliance.
    - Commonly soluble synthetic dyes (coaltar) and insoluble pigments are used.
    - Commonly iron-oxide is used.
    - The color of drug will give indication of the disease for which it is used.
    - Ex.:- White - Analgesia Lovander- Hallucinogenic effects
    - Orange- Stimulants Yellow-Antidepressants
2. Opaquing Agents:
    - They are used to make shell opaque.
    - Opaque capsules are used to provide protection against light and to conceal the contents eg. Titanium-dioxide (TiO_2).
3. Preservatives:
    - Preservatives are used to prevent the formulation from detriotions.
    - When preservatives are employed parabens are often selected.
4. Water:
    - Hot demineralized water is used in the preparation of dipping solution.
    - Initially 30-40% w/w solution of gelatin is prepared in large stainless steel tanks, vaccum may be applied to remove the entrapped air from the viscous preparation.
    - Portion of the stock solution is removed and mixed with another ingredients to prepare the dipping solutions.
    - At the point the viscosity of the dipping solution is measured and adjusted. [8, 9]

Manufacturing Steps Of Hard Gelatin Capsule Shell

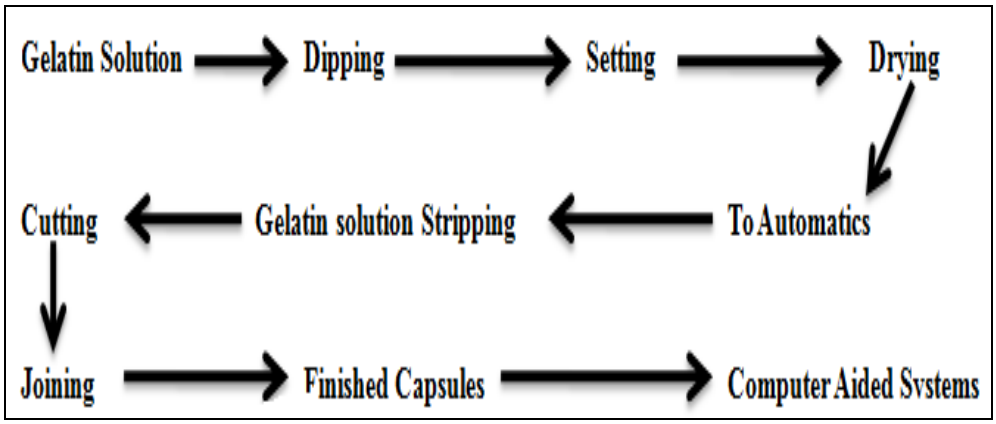

Figure 2:Manufacturing Of Hard Gelatin Capsule Shell [5]

Gelatin Specification for Hard Gelatin Capsule:-

Table-3 Gelatin Specification for Hard Gelatin Capsule [6, 8]

Gelatin properties	Acid pigskin	Fish
Bloom(g)^0	240-255,	220-260
Viscosity, 6.67%,600(mpa,s)	4.2-4.8	3.5-4.5
Moisture (%max)	13.0	13.0
Ash (%max)	1.	1.0
PH ,1% solution	5.2-5.8	5.5-6.0
Iso ionic point,ph	7.0-9.4	7.0-9.4
Particle size % passing 4 us #	100	100
SO2 (ppm max)	40	40
H2O2	Absent	Absent
Microbial standards		
Total count	500	500
E.coli in 10 gm	Absent	Absent
P. Aeruginosa in 10 gm	Absent	Absent

Recent Advancement In Capsule Formulation

Recent Development in Capsules:-

A. **Development in capsule system:** It includes modification of the system to achieve modified release.

B. **Development in capsule shell:** It includes modification of capsule shell to improve shell property.

A. Development in capsule system:

1. 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 profiles can be incorporated in the system.

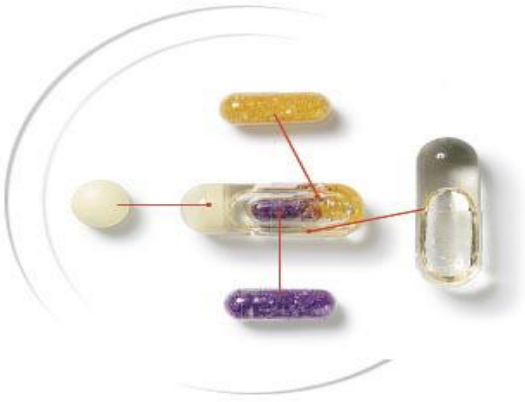

Figure 3 Inner capsule technology

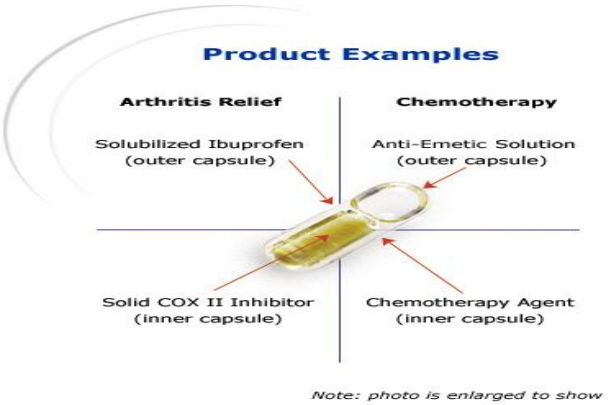

Figure 4 Example of inner capsule technology. [10]

2. Port Capsule Technology : -

Port stands for programmable oral release technologies that use a unique coated in capsulated system with opportunity to provide multiple program release of drug. Port technologies offer significant flexibility in obtaining unique and desirable release profile to maximize pharmacological and therapeutic effect.

There are mainly two dosage forms for port technology. The dosage from consist of a hard gelatin capsule coated with the semi permeable, rate controlling polymer. Inside coated capsule is the osmotic energy source, which normally contains the therapeutic agents to be delivers. The capsule is sealed with the water in soluble lipid separators plug and immediate release dosage can be edit above the plug the to complete the dosing option.

Example of port technologies:-

- Delayed release pseudoephedrine
- Multiple program release of phenylpropanolamine.

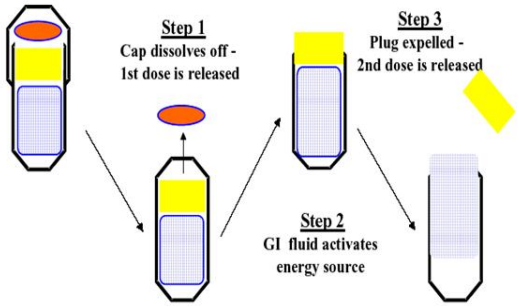

Figure 5 Drug release mechanism from the port capsule.[11, 12]

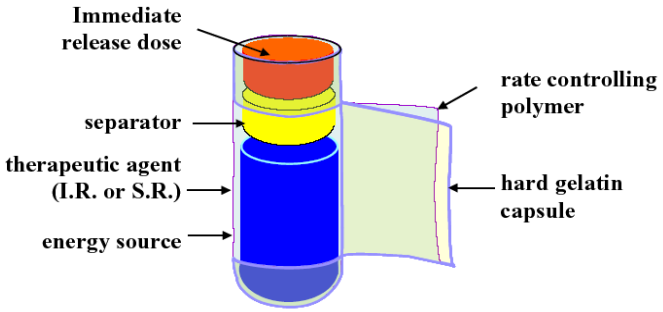

Figure 6 Delayed release pseudoephedrine [11, 12]

3. 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 odour on opening the (bulk) pack.

4. Organic Sachet™

Larger-volume (3-5ml) HPMC capsules are now also becoming available commercially. Although not currently being aimed at use in humans, they may have other applications, for example as a disposable container for, say, single-use toothpaste. Their physical size would preclude them from being used for consumption and this, in itself, opens up other possibilities. They have the advantage that they are cold water-soluble and are therefore suitable for simple (domestic) disposal. The appearance of empty uncolored capsules is amber, cf. bright color less. This is unlikely to be an issue where the shell is being used as a non-consumed container. The capsules may, of course, be colored and printed. [13]

5. Hydrophilic Sandwich(Hs) Capsules

It is a simple and time delayed probe capsule. Based on a capsule within a capsule, in which the inter capsular space was filled with a layer of hydrophilic polymer (HPMC). This effectively created a "Hydrophilic Sandwich " between two gelatin capsule. 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 a soluble filler. eg. Lactose

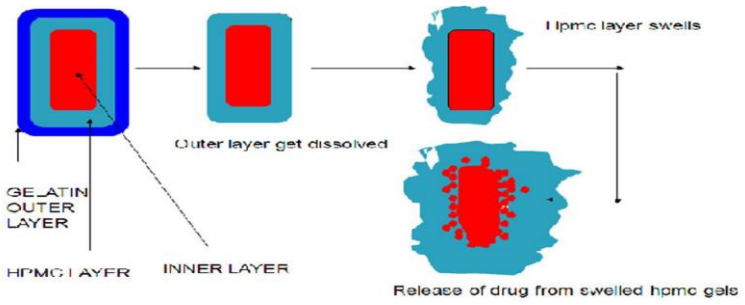

Figure 7 Hydrophilic Sandwich (Hs) Capsules [14]

6. 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 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 ™ [13]

B. **Development in capsule shell**

7. Gelatin/Peg Capsules:

Reduce the brittleness of standard gelatin capsules when exposed to a low-moisture content thus making the capsules more compatible to hygroscopic formulations or moisture-sensitive ingredients.

Gelatin/PEG Features :-

- Less brittle.
- Good for hygroscopic and moisture sensitive ingredients.
- Odorless, tasteless, three-year shelf life.
- Available in sizes from 00 to 4.
- The addition of PEG improves the mechanical strength of the capsule.

- At moisture contents between 8% 12%, gelatin/PEG capsules have equivalent mechanical strength to standard gelatin capsules with moisture between 13% - 16%.

Gelatin/PEG capsules are available in commercial pharmaceutical products-

- Cardiovascular (Tocopherol nicotinate)
- Vasodilators (Nifedipine)
- Antihypertensive (Captopril)
- Digestive Enzyme [15]

8. PRESS-FIT® & XPRESS-FIT™ :-

The Press-Fit® & Xpress-Fit™ Gel caps enrobe caplets with a high-gloss gel cover, that will create a new look and energize sales. Your product will stand out with a distinctive and appealing trade dress, which is a vital part of building a brand. The standard Press-Fit® configuration is completely covered by two flexible gel caps. The Xpress-Fit™ design imparts a gap between the two gel caps, enabling the potential for a fast-release dosage form as well as providing a novel appearance. Consumer's associate gel caps with improved swallow ability, which is perhaps the most critical attribute for and oral dosage form.

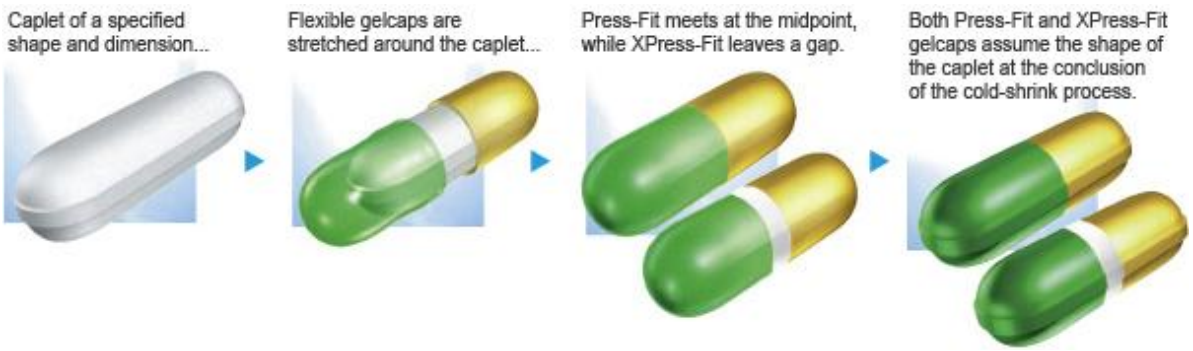

Figure 9 Press-Fit® & Xpress-Fit™ Gel caps [16]

9. STARCH CAPSULES:-

Made from potato starch and represent a direct alternative to hard gelatin capsule. Manufactured by the injection moulding technique developed by Capsugel (Capill®). Offers advantages like-

a. pH independent dissolution
b. Suitable for enteric coating
c. Tamper evident
d. Produced from non-animal derived ingredients.

Consists cap and body; which are sealed together at the time of filling to prevent separation.

Sealing is achieved by applying a hydro alcoholic solution to inner section of the cap, immediately prior to its being placed on to the body. Different size capsules are manufactured (number 0, 1, 2, 3, 4) by changing the mold. Officially recognized in USP 23 and NF 18. [17]

10. HPMC CAPSULES (HYPROMELLOSE):-

QUALI-V®, developed by Shionogi Qualicaps, is the first HPMC capsule developed for eventual use in pharmaceutical products. The features of QUALI-V are summarized as following:-

- Made from non-animal materials.
- Provide physical strength .
- Protection from moisture.
- Protection from microbial contamination.
- Protection from light and oxygen
- Improve compatibility of fill material with capsule shell.

Figure10 HPMC Capsules (Hypromellose), QUALI-V® [18, 19, 20]

CONCLUSION:-

In recent years, interest in using hard gelatin capsules in developing and manufacturing medicines has increased considerably. This is most probably due to rapid advances in dosage forms for hard gelatin capsules. In tandem with this, the structural foundation of a new technology has been developed, and realized in the form of efficient process machinery. It is important for capsule technology development to offer flexibility of materials and delivery system to meet scientific and fast moving commercial markets. In recent years, considerable attention has been focused on the development of Capsule dosage form. These technology not only reduces the side effect but also easy for patient compliance. Thereby increasing its market value competitiveness and life. This development in general, will continue to se significant growth in the pharmaceutical industry. The two piece liquid fill capsule format is well suited to

such approaches and offers the flexibility of design application and manufacturing technology to meet the industry's needs. Quali-V® offer to the formulator a new way of overcoming some of the problems inherent with gelatin capsules. They are made from materials obtained from plant sources, which are an additional bonus in today's regulatory climate. [9, 13, 20]

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