Recent Trends In Nutraceuticals : As A Softgel Capsule

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Abstract

The term Nutraceuticals was coined from “nutrition” and “pharmaceutical” by Stephen Defelice. According to Defelice “Nutraceuticals are food or part of a food that provides medical or health benefits including the prevention and/or treatment of a disease.” Nowadays people are shifting towards Nutraceuticals from pharmaceuticals because of their benefits over the pharmaceuticals. Softgel capsules are the unique type of delivery system in nutraceuticals which is preferred due to its unique characteristics. A softgel capsule is a one-piece hermetically sealed soft gelatin shell containing a liquid, a suspension or a semi solid, referred to as a fill material. Soft gelatin capsules were developed within the 19th century to mask unpleasant taste of drug substances. The 1st capsule prepared from gelatin was a one piece capsule patented in France by MOTHES and DU BLANC in 1834. There are several processes used for manufacturing of the softgel capsules i.e., Plate Process, Rotary die Process, Reciprocating die Process, Accogel Process, Seamless Process. They are available in a large variety of shapes and sizes which provides us with drug dose flexibility. They are highly suitable for liquid and volatile substances. Softgels are used as absorption enhancing technique. They also provide increased solubility. It masks the unpleasant taste of the active ingredients as they are completely sealed inside the softgel capsule.
INTRODUCTION:
The term Nutraceuticals was coined from “nutrition” and “pharmaceutical” by Stephen Defelice MD, founder and chairman of the foundation for innovation in medicine (FIM) Cranford, New Jersey, in 1989. According to Defelice “Nutraceuticals are food or part of a food that provides medical or health benefits including the prevention and/or treatment of a disease.” The bureau of Nutritional science, of the Food Directorate of Health Canada, has proposed the following definitions; A Nutraceutical is a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food. A Nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease. Greek physician HIPPOCRATES (known as father of medicines) said “Let food be your medicine” The philosophy behind is “focus on prevention” Other words used in the context are Dietary supplements, functional food, multi-functional food, etc.

CONCEPT OF NUTRACEUTICALS:
Simply, Nutraceuticals means, NUTRITIVE + PHARMACEUTICAL: A food stuff (as a fortified food or dietary supplement) that provides health benefits.

THE REASONS FOR SHIFT TOWARDS NUTRACEUTICALS:
- Nutraceuticals cover most of the therapeutic areas, such as anti-arthritis, cold and cough, sleeping disorders, digestion and prevention of certain cancers, osteoporosis, blood pressure, cholesterol control, pain killers, depression and diabetes.
- Dissatisfied with pharmaceutical agents in promoting health, are turning to nutraceuticals to improve their health and prevent chronic disease.
- Health care provider recognize the fact that our heavily processed food supply coming from crops grown with chemical fertilizers, pesticides, herbicides, and often genetically modified seeds, lacks sufficient nutrients necessary for optimum Health.
- Nutraceuticals show an ample scope to flourish in future as therapeutic agents with preventive and curative properties.
- People who have chronic diseases and have found no solution in allopathic medicines.
- Nutraceuticals are quickly replacing pharmaceuticals in prevention and management of acute and chronic health problems.
- Economically challenged patients, People believing more in prevention than a cure.
- Increasing numbers of consumers, concerned about healthcare costs.

SOFT GELATIN CAPSULE:-
Soft gelatin capsules were developed within the 19th century to mask unpleasant taste of drug substances. The 1st capsule prepared from gelatin was a one piece capsule patented in France by MOThES and DU BLANC in 1834. Latin word CAPSULA means...
“THE SMALL BOX” Capsules are unit solid dosage form in which one or more medicinal and or inert substances are enclosed in either a hard or soft soluble container or shell of suitable form of gelatin. A softgel capsule is a one-piece hermetically sealed soft gelatin shell containing a liquid, a suspension or a semi solid, referred to as a fill material. Capsules are solid dosage form in which one or more medicinal and inert ingredients are enclosed in a small shell or container usually made of gelatin. Soft gelatin capsules are also referred to as soft elastic gelatin capsules, liquid gels or softgels. They are unique drug delivery system that can provide distinct advantages over traditional dosage form such as tablets, hard gelatin capsules and liquids. The softgel consists of two major components, the GELATIN SHELL and the FILL. The fill material can include wide variety of vehicles and can either be a solution or a suspension.

CONCEPT OF SOFT GELATIN CAPSULE :-

FILL MATRIX

GELATIN SHELL

- A softgel is an oral dosage form for medicine in the form of a specialized capsule.
- Soft gelatin capsules are a completely sealed dosage form and cannot be opened without destroying the capsules.
- They are consisting of gelatin based shell (outer shell) surrounding a liquid fill or semi-solid centre (inner fill). Softgel shells are a combination of gelatin, water, opacifier and a plasticizer such as asglycerin or sorbitol. The shell may be transparent or opaque and can be colored and flavoured if desired.
- Gelatin shells generally derived from hydrolysis of collagen.

SIZE AND SHAPE OF SOFT GELATIN CAPSULE:-

The capsules are available in a wide range of sizes and shapes. Such as

- Oval
- Round
- Oblong
- Tubs
- Suppository
- Special shapes

Best size and shape for convenient oral use in humans is 9 minim round, 16 minim oval and 20 minim oblong. (1 minim = 0.0616 millilitre)

APPLICATION:-

- Easy to swallow, no taste, unit dose delivery, temper-proof, wide variety of colors, shapes and size.
- Accommodates a wide variety of compounds filled as semi-solid, liquid, gel or paste.
- Immediate or delayed drug delivery.
- Can be used to improve bioavailability by delivering drug in solution or other absorption enhancing media.
- As an oral dosage form for human or veterinary use.
- As a suppository dosage form for rectal or vaginal use.
- As a speciality package in the tube shape for human or veterinary use of Topical, Ophthalmic, Otic preparation.
- In the cosmetic industry, this can be formulated as a speciality package for Breath fresheners, Perfumes, Bath oil, various skins creams etc.
- Capsule formulation had a reduced ulcerogenic potential when compared to the tablet formulation.
- Improve Drug Stability by resist gaseous diffusion and contain no water, thus protect drug sensitive to oxidation or hydrolysis on long term storage.
- Higher degree of reproducibility is achieved during the manufacturing of soft gelatin capsule.
Dose uniformity is optimized because the drug is dissolved or dispersed in liquid which is then dosed volumetrically into the capsule accurately.

Delivery of low and ultra-low doses of a compound using Softgel also ensures decrease Plasma variability.

Soft gelatin capsules provide a patient friendly dosage form for peroral administration of non-palatable and for oily liquids.

**Manufacturing Technique of Soft Gelatin Capsule:**

Process:

Formulation of Gelatin.

**FORMULATION OF SOFT GELATIN CAPSULES [13,14]**

1. **Gelatin** [15]
   The highest proportion of components in the soft capsule shells is gelatin, its origin is natural, and it is obtained from animal collagen (skin, tendons, bones, and cartilage) through acid hydrolysis and alkaline hydrolysis. This way, two types of gelatin are obtained, known as type A (acidic) and type B (alkaline) [16,17,18]. However, the extraction of gelatin from other animal sources, mainly fish skin, has recently been investigated.[19]

2. **Plasticizers:**
   These are used to make the softgel shell elastic and pliable. They usually account for 20-30%. The most common plasticizers used in softgel is glycerol although sorbitol and propylene glycon-400 are used frequently often in combination with glycerol. The amount and choice of the plasticizer contribute to the hardness of the final product and may even affect its dissolution or disintegration characteristics, as well as its physical and chemical stability. One of the most important aspect of softgel formulation is to ensure that there is minimum interaction or migration between the liquid matrix and the softgel shell. The choice of Plasticizer type and concentration is important in ensuring optimum compatibility of the shell with the liquid fill matrix.[19]

   Plasticizer concentration can be expressed as part of dry plasticizer to 1 Part of dry gelatin. In practice this ratio vary widely between 0.3 and 1.0. This wide range encompass the diversity of plasticizer and fill material. More specifically low ratio 0.3 and 0.5 are used for oily liquid fill, between 0.4 and 0.6 for oily fills with added surfactants and between 0.6 and 1.0 for water miscible fills and chewable capsules. [20]

**Water:**
   The other essential component of the softgel shell is water. Water usually accounts for 30-40% of the wet gel formulation and its presence is important to ensure proper processing during gel preparation and softgel encapsulation. In dry gels the equilibrium water content is typically in the range 5-8% w/w, which represents the proportion of water that is bound to the gelatin in the soft gel shell. This level of water is important for good physical stability, because in harsh storage conditions softgels will become either too soft and fuse together, or too hard embrittled. [21]

**Colorants/Opacifiers:**
   Colorants can be either synthetic or natural, and are used to impart the desired shell color for the product identification. An opacifier, usually titanium dioxide may be added to produce an opaque shell when the fill formulation is a suspension, or to prevent photo degradation of the light sensitive fill ingredients. Titanium dioxide can either be used alone to produce a white opaque shell or in combination with pigments to produce a colored opaque shell.[18]

**Preservatives:**
   Preservatives are sued to preserve the drug medicament from the microbes. It is used about 0.2% concentration of total drug medicament. Methly Paraben and propyl Paraben is mainly used as preservative.

**Flavouring Agents:**
   Flavouring agents are used for the taste masking. Ethyl Vanillin, essential oils and different sugar mainly sucrose is also as flavouring agent. [18]

**MANUFACTURING OF SOFT GELATIN CAPSULE** [22,23,24]

Following methods are used:

1. Plate process
2. Rotary die process
3. Reciprocating die process
4. Accogel process
5. Seamless gelatin capsules
1. **Plate process:**
In this process a warmed sheet of gelatin sheet is placed over a die plate having a number of depression or moulds or numerous die pockets. The sheet is drawn into these depression or pockets by applying vacuum. A measured quantity of liquid medicament is pour over it. Over this another plate of the mould is placed and the pressure is then applied to thew combine plate. The capsules are then simultaneously shaped, filled, sealed, and cut into individual units. This methods is used for small scale preparation of the soft gelatin capsules. It has 20-40% of net moisture content. [20]

2. **Rotary Die Process:**
Before encapsulation process thakes place there are two basic process.
Production of gel mass which provide the soft gel shell: The gel mass is prepared by dissolving the gelatin in water approximately at 80ºc and under vaccum folloowd by addition of plasticizer once the gelatin is fully dissolved other components such as color, opacifier, flavours and preservatives may be added. The color is compared with the standard then the temperature is maintained at 57º- 60ºc in melting tank. The hot gel mass is then supplied to the encapsulation machine through heat transfer pipes by a casting method that forms two separate gelatin ribbons. The gelatin mass is fed by gravity to a metering device which controls the flow of mass on to air heated(13º-14º) rotating drums. Gelatin ribbons are produced . During the casting process the gelatin passed through sol gel transformer and the thickness of each ribbon is controlled ton ±0.1mm. The thickness is checked regularly during the process. The ribbon of 0.022-0.45 inches but for most capsules it is between 0.025-0.032 inches. The two gel ribbons are the carried through rollers (at which a small quantity of vegetable oil lubricant is applied) and onwards to the rotator die encapsulation. Each ribbon provides one-half of the soft gel. [17]

**Fill Matrix:**
The liquid fill matrix containing the active drug is manufactured separately from preparation of molten gel. Manufacture of the active fill matrix involves dispersing or dissolving the drug substances in the non-aqueous liquid vehicle using conventional mixer homogenizers. They also break up the agglomerates of solids. Oxygen sensitive drugs are protected by mixing under vacuum and or inert gas or by addition of antioxidant.

**Rotatory Die:**
This machine has two, side-by-side cylinders in each of which half-moulds are cut. These cylinders, like the rollers of a mangle, rotate in contrary direction and as they are mirror image the moulds come together precisely during rotation. Two ribbons of soft gelatin are fed between rollers and just before the opposing rollers meet, jets of medicament press the gelatin ribbon into moulds, filling each half. The moment of pressure follows, immediately sealing the two halves together to form a capsule. These rotary machines are capable of producing between 25000 and 30000 capsules an hour with an accuracy of dosage of approximately ±1 percent.

**Encapsulation:**
Liquid gelatin flowing from an overhead tank is forward into continuous ribbon by the rotating drum and brought together between twin rotating dies. The injection of liquid between the ribbons, force the gel to expand and into the packets dies, which govern the size and shape of the softgels. The sealing of the capsules is done by mechanical pressure on the die rolls and the heating of ribbons by the wedge. After manufacture, it is subjected to IR drying and then they are separated on the tray and stacked in funnel drier that supplies air at 20% relative humidity. [20]

3. **Reciprocating Die Process:**
This is similar to rotary process, but is differ in the actual encapsulating process. The gelatin ribbons are fed fed between a set of vertical dies that continuously open and close to form the rows of the pockets in the gelatin ribbons. These pockets are filled with the medication and are sealed, shaped and cut out of the film as they progress through the machinery. [20]

4. **Accogel Process (Stern Machine):**
This is another rotary process involving the measuring roll, a die roll and a sealing roll. The measuring roll rotates directly over the die roll, and the pockets in the two rolls are aligned with each other. The powder or granular fill material is held in the pockets of the measuring roll under vacuum. A plasticized sheet is drawn in to the die pockets of the die roll under vacuum. As the measuring roll and the die roll rotate, the measured doses are transferred to the gelatin lined pockets of the die roll. The continue rotation of the filled die converges with the rotating sealing roll where second gelatin sheet is applied to form the other half of
capsule. The pressure developed between the both rolls seals and cut out of the capsules.\[20\]

5. Seamless gelatin capsules:
It is a modern method for making soft gelatin capsules takes advantage of the phenomenon of drop formation. The essential part of the apparatus consists of two concentric tubes. Through the inner tube flows the medicament and, through the surrounding outer tube, the gelatin solution. The medicament, therefore, issues from the tube surrounded by gelatin and forming a spherical drop. This is ensured by allowing the drop to form in liquid paraffin in which the gelatin is insoluble. Regular induced pulsations cause drops of the correct size to be formed, and a temperature of 4\(^\circ\)C ensures that the gelatin shell is rapidly congealed. The capsules are subsequently degreased and dried. \[17\]

EVALUATION OF SOFT GELATIN CAPSULES:
The Soft gelatin capsules should be subjected to following tests for their standardization.

Disintegration Test: \[19,25\]
For performing disintegration test on capsules the tablet disintegration test apparatus is used but the guiding disc may not be used except that the capsules float on top of the water. If hard capsules float on the surface of the water, the discs may be added. One capsule is placed in each tube which is then suspended in the beakers to move up and down for 30 minutes. The beaker containing 600 ml water and temperature is 37 \(^\circ\)C. Unless otherwise stated in the monograph. The capsules pass the test if no residue of drug or other than fragments of shell remains on No. 10 mesh screen of the tubes. If the disc is used, any residue remaining on its lower surface should only consist of fragments of shell.

Dissolution\[19,25\]
It is done if capsules contain drug which have limited solubility in gel fluid. The dissolution test is carried out using the dissolution apparatus official in both the U.S.P. and N.F. The capsule is placed in a basket formed from 40-mesh stainless steel fabric. A stirrer is attached to the basket, and the basket is immersed in the dissolution medium and caused to rotate at a specified speed. The dissolution medium is held in a covered 1000 ml glass vessel and maintained at 37\(^\circ\)C \(\pm\) 0.5\(^\circ\)C by means of a suitable constant temperature water bath. The stirrer speed and type of dissolution medium are specified in the individual monograph.\[13\]

Weight Variation Test\[19,25\]
Twenty capsules are taken at random and weighed. Their average weight is calculated, then each capsule is weighed individually and their weight noted. The capsule passes the test if the weight of individual capsule falls within 90-110\% of the average weight. If this requirement is not met, then the weight of the contents for each individual capsule is determined and compared with the average weight of the contents. The contents from the shells can be removed just by emptying or with the help of small brush. The remainder contents are removed by washing with a suitable solvent. After drying the shells, they are weighed and the content weights of the individual capsules are calculated. The requirements are met if not more than 2 of the differences are greater than 10\% of the average net content and in no case the difference is greater than 25\% . \[7\]

Content Uniformity Test \[19, 25\]
This test is applicable to all capsules which are meant for oral administration. For this test a sample of the contents is assayed as described in individual monographs and the values calculated which must comply with the prescribed standards. 30 capsules are selected and 10 of these are assayed individually. At least 9 of these contain 85–115 \% of drug and none contain below 75–125\% of drug. If 1 to 3 of them falls outside of 85 – 115\% limits, the remaining 20 capsules are individually assayed and the requirements are met if no fewer than 27 contain 85 – 115 \% of drug and none contain less than 75 – 125 \% of drug. \[20\]

Moisture Permeation Test\[19, 26\]
By packing the dosage unit together with color revealing desiccant pellet; exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for color change and comparing the pre and post weight of the packaged unit, moisture permeation can be determined.\[7\]

Capsule Stability\[19,26\]
This inherent characteristic warrants a brief discussion of the effects of temperature and humidity on these products, and points to the necessity of proper storage and packaging conditions and to the necessity of choosing an appropriate retail package. The variety of materials capsulated, which may have an effect on the gelatin shell, together with the many gelatin
formulations that can be used, makes it imperative that physical standards are established for each product.[7]

CONCLUSION:
Nutraceuticals is very rapidly growing sector as people nowadays preferring more towards remaining healthy rather than just treating the disease. The demand for nutritional supplements is growing at a fast pace as working people are unable get those nutrients due to their hectic work life and high workload. Softgels are more preferred by the consumers as they are easy to digest and convenient to swallow. The efficacy and fast-acting properties of drug get enhanced by Softgels. As the average level of education regarding supplement rise the superior and unique qualities of Softgels in specific solutions will become more appealing. The tasteless property of softgel is very appealing for the consumers. Softgel capsules are very efficient in improving the bioavailability by delivering the nutrient in solution or other absorption enhancing media. The nutrients are always protected in the Softgels as they are sealed and prevent oxidation and degradation. The shelf life of the medicament gets increased because of softgel. As the shapes and sizes of softgel can vary the most consumers appealing shape, size and color can be selected. Softgels are hermetically sealed due to which it becomes more suitable for liquid and volatile substance.

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