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Soft gelatin capsules for encapsulation of Pharmaceuticals, Cosmeceuticals and Nutraceuticals

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Abstract:

Soft gelatin capsules are single-unit solid dosage forms, consisting of a liquid or semi-solid fill enveloped by a one-piece sealed elastic outer shell. Technologically with softgel, content uniformity of low-dose drugs has been achieved and also has consumer preference as is easy to swallow. Various oils, vitamins are unstable and susceptible to degradation when exposed to environmental stresses like oxygen, temperature, and light. Vitamins and oils encapsulated in soft gelatin capsules show promise as anti-microbial, antifungal, antiviral agents and can provide therapeutic benefits. Due to the dynamic nature of the softgel dosage form, its development and shelf-life stability optimization are fraught with several challenges. The review article focuses on applications of soft gelatin capsules in the pharmaceutical, chemical, food and cosmetic industry.

Keywords: *Cosmeceuticals, Encapsulation, Nutraceuticals, Pharmaceuticals, Softgel and Soft Gelatin Capsule*

Introduction:

The term "Pharmaceuticals" is associated with medicine which covers various aspects of drug development; formulation designing and evaluation for their in vitro and in vivo performance. Pharmaceuticals are products of scientific research that supports their claims for health benefits. Cosmeceuticals are cosmetic-pharmaceutical hybrids intended to enhance beauty through ingredients that provide additional benefits to the consumer's health[1,2]. Topically, they are applied as cosmetics, but contain ingredients that influence the skin's biological function[3]. Nutraceuticals are products, which provide nutrition and also have medicinal/therapeutic values and can provide protection against chronic disease. The term "nutraceutical' is intended to describe specific chemical compounds found in foods that may prevent disease[1]. Both pharmaceutical and nutraceutical compounds might be used to cure or prevent diseases, but only pharmaceuticals are approved for their medicinal uses by the regulatory authorities[1,2,4].

Various essential oils, oils of animal origin such as fish oils and oil-soluble vitamins constitute a significant percentage of the ingredients of pharmaceutical, cosmeceutical or nutraceutical preparations which provide multitudeof health-promoting effects[5,6]. Fish oil is used as nutritional supplement due to presence of omega 3 fatty acids and is reported to exert neurological benefits, anti-depressive effects and cardiovascular benefits[5,7]. SachaInchi oil possesses nutritional value owing to its high polyunsaturated fatty acid (PUFA) and monounsaturated fatty acid (MUFA) content and exhibits antithrombotic, anti-dyslipidemic and anticancer effects[8]. Vitamin D is known to modulate atherothrombosis i.e. modulate inflammatory processes, endothelium and smooth muscle cell proliferation and even platelet function. Secosteroids can enhance intestinal absorption of essential minerals, such as calcium, iron, magnesium and zinc[9].

Essential oils are compounds formed as a result of specialized metabolism in plants[10]. When essential oils are the active ingredients or serve as important excipients, they are difficult to handle because of their volatility, other stability issues and because of their low concentration requirement in formulations. The efficacy of active principles of the essential oils can be affected by environmental factors such as temperature, light and oxygen. Therefore, encapsulation may be regarded as an alternative for the protection and preservation of these substances. In addition, encapsulation can also maintain the effect of these oils as antimicrobial agents and antioxidants[10,11]. The encapsulated essential oils also showed enhanced antimicrobial, antifungal, antioxidant, antiviral and pesticidal activities. The use of encapsulated essential oils in food, cosmetic and pharmaceutics could be an economic benefit and also fulfill the consumer concern regarding safety[12]. Fortifying foods with fish oil containing EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) is a standard approach to deliver these oils as part of diet. However, these polyunsaturated fatty acids are unstable and readily oxidize in the presence of light and oxygen with the formation of a variety of degradation products. Some of these degradation products are aldehydes that have an unpleasant smell and taste, leading to off-flavors in food products fortified with fish oil. To overcome this problem and to keep fish oil well-protected against oxidation throughout the shelf-life of a food product, the fish oil should better be encapsulated [5,7].

The purpose of the present review is to focus on the advancements in the field of soft gelatin capsules especially in the area of encapsulation of oily ingredients, essential oils etc. to be employed as pharmaceutical, cosmeceutical or nutraceuticals. The encapsulation technique reduces the rate of evaporation or transfer of the core compounds into the environment, increases

the ease of handling the encapsulated substance, allows for release control, reduces odors and strange flavors and permits homogeneous distribution of the encapsulated compound in any product for human use and consumption.

Soft Gelatin Capsules for Pharmaceuticals, Cosmeceuticals and Nutraceuticals[5,8,13-16]

Soft gelatin capsules are very easy to swallow and unlike chewable or liquids that are also easily swallowable. Various soft gelatin capsules are available in the market for delivery of multivitamins like Vitamin A (from beta carotene, fish liver oil), C (as ascorbic acid), vitamin D-3, E, B1, B2, niacin, B6, folic acid, B12, biotin, pantothenic acid, etc. Vitamin C softgel capsules are available in combination with multivitamins and minerals. They support immune system, protect against damaging free radicals, help to support collagen production and iron absorption. Calcium combined with vitamin D has maximized effect for bones. Green tea soft gelatin capsule forms a part of healthy diet. Ferrous fumarate softgel capsule is used to treat iron deficiency anaemia. Encapsulated high DHA fish oil incorporated in wide range of food products[17]. Essential fatty acids like omega-3 help to maintain healthy skin, joints and cell membrane and supports nervous system. Coenzyme Q10 (ubiquinol) capsules are employed as antioxidants. They have no unpleasant taste and are also free of bad odor. Soft gelatin capsules for cosmetic skin care products are very popular and are high selling products owing to their attractive appearance in varying shapes and colours and aesthetic appeal. Moreover, they are convenient, portable and are more stable[18].

Other examples of soft gelatin capsules include conjugated linoleic acid softgels, lycopene (10%) + lutein (8%) + β-carotene(10%)+ zinc sulphate + selenium dioxide + grape seed extract softgels, myo-inositol + L-methyl molate(500µg) + Vit D3 (1000 I.U) + N-acetyl cysteine + L-arginine softgels, pregabalin + methylcobalamin softgels, curcumin + piperinesoftgels, Co enzyme + L-carnitine softgels, lutein softgels, Aloe vera extract softgels, dried extract of *Ginkgo biloba* softgels.

Soft Gelatin Capsules: Brief theory and manufacturing process

Soft gelatin capsules are a single-unit solid dosage form, consisting of a liquid or semi-solid fill enveloped by a one-piece sealed elastic outer shell. The amount of drug or extract together with adjuvant is enclosed within a globular, oval or other shape of a soft shell[19]. Soft gelatin capsules (softgels) offer the possibility of delivering a liquid (solution, suspension or emulsion) in a solid oral dosage form which will inherently lead to better absorption of the active ingredient as compared with delivery in a tablet or as a powder[20].

The softgel dosage form offers several advantages over other oral dosage forms, such as [21, 22]

i. delivering a liquid matrix designed to solubilize and improve the oral bioavailability of a poorly soluble compound as a unit dose solid dosage form,
ii. delivering low and ultra-low doses of a compound,
iii. delivering a low melting compound,
iv. minimizing potential generation of dust during manufacturing and thereby improving the safety of production personnel.

Manufacturing process of soft gelatin capsule

Manufacturing process of soft gelatin capsule is divided into the following steps:

1. Gelatin Preparation
2. Material (Fill) Preparation
3. Encapsulation
4. Drying
5. Inspection
6. Polishing
7. Packaging

The various methods that are adopted for manufacture of soft gelatin capsules are described briefly[23-25].

I. Plate Process

This is the oldest process for manufacture of soft gelatin capsules. In this process, a warmed sheet of plain or coloured plasticized gelatin is placed over die plate which has a number of depressionsor moulds or numerous die pockets. By applying vacuum, the sheet is drawn into these depressions to form capsule wells. Then capsule wells are filled with liquid medication. A second sheet of gelatin is placed on top of the filled wells followed by the top plate of the mould. Pressure is then applied to the combined plate to form, seal and cut the capsules into individual units. This method is used in small scale preparation of soft gelatin capsules.

II. Rotary Die Process

Two ribbons of gelatin are fed continuously into a rotating die assembly and are simultaneously formed into the two halves of a capsule. The ribbons converge adjacent to a fill injector. The fill injector is actuated by a pump which measures and dispenses the appropriate volume of fill material into the capsules. The filled capsules are subsequently sealed as the die assembly rotates. This process permits accurate and reproducible fill uniformity. Pump heads are available for fill weights as low as 100 mg. For oral dosage forms, the fill weight ranges from 100 mg up to about 1 gram.

III. Reciprocating Die Process

This process is similar to rotary process in that ribbons of gelatin are formed and used to encapsulate the fill. The gelatin ribbons are fed between a set of vertical dies that continually open and close to form rows of pockets in the gelatin ribbons. These pockets are filled with the medication and are sealed, shaped, and cut out of the film so that they progress through the machinery. As the capsules are cut from the ribbons, they fall into a cooled solvent bath and prevents the capsules from adhering to one another.

IV. Acogel Process

The process involves a measuring roll that holds the fill formulation in its cavities under the vacuum and rotates directly above the elasticized sheet of the gelatin ribbon. The ribbon is drawn into the capsule cavities of the capsule die roll by vacuum. The measuring rolls empty the fill material into the capsule-shaped gelatin cavities on the die roll. The die roll then converges with

the rotating sealing roll covered with another sheet of elasticized gelatin. The convergence of two rotary rolls creates pressure to seal and cut the formed capsules.

V. Seamless Process (Bubble Method)

The seamless technique produces one-piece soft gelatin capsules without the use of dies. The process is often referred to as a bubble method that creates seamless, spherical soft gelatin capsules called pearls. In this process, a molten gelatin stream is blown through the outer nozzle of a concentric tube at a constant rate. Then the medicated liquid formulation is dispensed through the inner orifice by means of a precision metering pump. The emerging stream is broken up into an intermittent but steady flow of uniform-size droplets enveloped in molten gelatin.by a pulsating mechanism. The formed capsules are quickly removed from the nozzle, slowly congealed, and automatically ejected from the system.

Reported studies on soft gelatin capsules for pharmaceuticals, cosmeceuticals and nutraceuticals

In a study on soft gel encapsulation of coenzyme Q-10 or an analog thereof, a sufficient quantity of a monoterpene like limonene was used to solubilize the coenzyme Q-10. Generally, about 30 to about 45% of the CoQ-10 (by weight) was solubilized in the monoterpene. L-carnitine was also included in soft gel formulations in combination with CoQ10. Suitable ratios of limonene, CoQ-10 and L-carnitine in softgel formulations are of importance as dietary supplements or as nutraceuticals. Softgels contained about 20-70% gelatin, generally a plasticizer and about 5 to about 60% by weight sorbitol. The filling of the soft gelatin capsule involved liquid formulation in combination with rice bran oil or beeswax and included, apart from the antioxidant actives, a hydrophilic matrix e.g. polyethylene glycol.[7]. Comparative studies on intestinal absorption data, collected in basal conditions from soft gelatin capsules of COQ10 with dry powder formulation demonstrated higher basal blood CoQ10 levels (167%) and the 273% greater absorption rate from the capsules and established that soft gel formulation is a superior product to the dry powder formulations. This may be especially beneficial for those individuals where daily CoQ10 requirement is elevated due to high physical activity or there is a need for CoQ10 as an antioxidant; or are suffering from active disease associated with known CoQ10 deficiencies.[7,15].

A novel method of forming a softgel dosage form has been reported of suspending micronized anhydrous magnesium powder in an emulsion forming a fill composition, disposing the fill composition between two sheets of a gelatin composition, and sealing edges of the two sheets together forming a seam having cross-linked gelatin across the seam to form the soft gel[16].

Sacha inchi (*Plukenetia volubilis*) seed oil is a rich source of polyunsaturated fatty acids (PUFAs) that are beneficial for human health, whose nutritional efficacy is limited because of its low water solubility and labile bioaccessibility (compositional integrity). The work reported on the encapsulation effect using blended softgels of gelatin (G) and cactus mucilage (CM) biopolymers, on thePUFAs' bioaccessibility of *P. volubilis* seed oil during in vitro simulated digestive processes (mouth, gastric, and intestinal). The bioaccessibility of linolenic, linoleic, and oleic acid was found to be 1.70%, 1.46%, and 35.8%, respectively, along with the presence of some oxidation products. G/CM soft capsules are capable of limiting the in vitro bioaccessibility of PUFAs because of the low mucilage ratio in their matrix, that influences the enzymatic

hydrolysis of gelatin and increasing the release of the polyunsaturated content during the simulated digestion[8].

Pharmacokinetic study confirmed that softgel capsules containing lipophilic *Echinacea* extract are anattractive option to improve bioavailability of tetraene. It was estimated that 3.5-fold improvement was observed compared with previous studies on other tetraene formulations.The study also demonstrated the effect on the innate and adaptive immune system of *Echinacea angustifolia* lipophilic extract in healthy subjects, supporting at least in part its use as health promoting supplement. Indeed this treatment has potentially a strong anti-inflammatory effect reducing the synthesis and plasma levels of powerful pro-inflammatory cytokines such as IL-6, TNF-α and IL-8 and up-regulating the expression of anti-inflammatory molecules as IL-10[13].

Encapsulation of vegetable oils (essential oils and non essential oils) in different formulations was proved to be successful in improving their benefits (antibacterial, antifungal and antiviral properties). Controlled release of the bioactive agents from the vegetable oils was made possible by improving the preservative effect in food, pharmaceutical and cosmetic applications. The material filling the inventive capsules may also contain, if so desired, variable quantities of one or several vegetable oils, for instance borage oil, soya oil, sunflower oil, safflower oil, avocado oil, peanut oil etc. the material filling the inventive capsule contains between 0.2 and 10% by weight over the total filler material of borage oil. Borage oil is the source of omega 6 gamma linolenic acid. It supports in inflammatory response, platelets function, and healthy skin[14].

Olive oil, obtained by crushing olives, the fruit of the olive tree (*Olea europaea*), approximately consists of an 84% mixture of several glycerides of unsaturated fatty acids, mainly oleic acid (between 70 and 80% of the total) and is commonly used for foods purposes. Oleic acid [*cis*-9-octadecenoic acid] is a monounsaturated fatty acid which is seemingly responsible for many beneficial effects of olive oil. soft gelatin capsules containing variable quantities of a filler material containing olive oil along with other oils selected from a group consisting of borage oil, fish oils with EPA, soya oil, sunflower oil, safflower oil, avocado oil, peanut oil and mixtures thereof, were prepared and improving blood clotting and for preventing cardiovascular diseases. Soft gelatin capsules containing 300 mg of a filler material comprising olive oil, fat-soluble and water-soluble vitamins, oils and vegetable proteins, per capsule, were prepared. Specifically, the filler material comprised olive oil, 2.5% of vitamin C, 5% of silk protein, 5% of nut oils, 3% of essential oils, 3% of paraffin, 0.5% of polyethylene glycol and 0.3% of castor oil, colorants and perfumes in sufficient quantities suitable for the hair and skin. Soft gelatin capsules containing 300 mg of a filler material based on several quantities of olive oil and fat-soluble and water-soluble vitamins per capsule to fill one of the compartments with olive oil, 0.5-1% of vitamin A, and 0.5-1% of vitamin E, and the other compartment with 0-5-1% of vitamin B5 and 2.5-10% of vitamin C for nutrients. This has led to an increasing demand for softgel capsules across different applications in the nutraceutical sector. Softgel capsules also find wide adoption in sports nutrition. A growing health awareness among consumers has led to a surge in adoption of nutraceuticals and sports supplements, eventually fueling the demand for softgel capsules from manufacturers of nutraceuticals and sports nutrition product [7,10,12].

Conclusion:

By comparing the soft gelatin and hard gelatin capsules softgel capsules and other dosages form shows more bioavailability than that of other ones. Although the softgel capsules have many

advantages like Increased the rate of absorption of drugs, Increased bioavailability of drugs, Decreased variability of plasmatic drugs, Patient compliance and consumer preference, Safety for potent and cytotoxic drug, Dose uniformity of low-dose drugs, Product stability. The specificity of the encapsulation process ensures the microbiological safety of the product without the use of preservatives. This is particularly important in case of products intended for children, pregnant women and people with sensitive skin. Twist-off softgels are unit-dose preparation - no risk of contamination of the product during application –important in case of products for sensitive skin with dermatological problems. Now a days soft gelatin capsules used as neutraceuticals i.e. dietary supplements, cosmetic purposes and disease purposes.

Reference:

1. Bellad AK, Nanjwade KB, Kamble SM, Srichana T. Development of Cosmeceuticals. World J P Pharm Sci 2017; 6: 643-691.
2. Lang PD. Softgel Capsules with Iridescent Appearance and Containing Dietary Supplement. Lang Pharma Nutrition, Inc 2013.
3. Wu Y, Choi HM, Li J, Yang H, Shin JH. Mushroom Cosmetics: The Present and Future. MDPI 2016; 3(22): 2-13.
4. 4.Mahale D, Gondkar S, Saudager R. Neutricosmetics: Review Article. Int J Uni Phram Bio Sci 2017; 6(2).
5. Barrow JC, Nolan C, Holub JB. Bioequivalence of Encapsulated and Microencapsulated Fish-Oil Supplementation. J Func Foods 2009;1: 39-43.
6. McDanie CJ, Belury M, Ahijevych K, Blakely W. ω-3 Fatty Acids Effect on Wound Healing. Wound Repair Regen 2008; 16(3): 337-345.
7. Ramakrishnan S. Encapsulation Of Omega-3 Fatty Acids by Premix Membrane Emulsification. Tesis Doctoral Xaraxa 2014.
8. Otalora CM, Camelo R, Torres WA, Chaparro CA, Castano JAG. Encapsulation Effect on the In Vitro Bioaccessibility of Sacha Inchi Oil (*Plukenetia volubilis* L.) by Soft Capsules Composed of Gelatin and Cactus Mucilage Biopolymers. MDPI 2020; 2-10.
9. Derohanes E, Rayl K, Siwek M, Williams J. Co - Q10 , Krill Oil And Vitamin D. United States. Patent Application Publication 2018; Pub. No.: US 2018 / 0084813 A1.
10. Radunz M, Helbig E, Borzes CD, Gandra TKV, Gandra EA. A Mini-Review on Encapsulation of Essential Oils. J Analytical Pharm Res 2018; 7(1): 00205.
11. Maes C, Bouquillon S, Fauconnier ML. Encapsulation of Essential oil for the Development of Biosourced Pesticides with Controlled Release: A Review. MDPI 2019; 24(14): 2539.
12. Majeed H, Bian YY, Ali B, Fang Z, Majeed U, Jamil A, Khan FQ, et. al. Essential oil encapsulations: uses, procedures, and trends, Royal Society of Chemistry 2015; 5: 58449-58463.
13. Djilani A, Dicko A. The Therapeutic Benefits of Essential Oils. Nutrition, Well-Being and Health 2012; 154-178.
14. Sagiri SS, Anis A, Pal K. A Review on Encapsulation of Vegetable Oils: Strategies, Preparation Methods and Applications. Polymer-Plastics Technology and Engineering 2015.
15. Udell RG, Beverly H, Naguib YMA, Hari PS. Formulation and Manufacturing Process For Coenzyme Q10 Soft Gel Capsules. United States. Patent Application Publication 2005; Pub. No.: US 2005/0031681 A1.

16. Shuai F, Zhang N, Zhang W, Zhang J. Mixing and Extruding Method For Preparing Starch Soft Gel Capsules. United States. Patent Application Publication 2015; Pub. No.: US 2015/0119472 A1.

17. Fard GS, Loh PS, Turchini MG, Elliott G, Wang B, Sinclair JA. Microencapsulated Tuna Oil Results in Higher Absorption of DHA in Toddlers. MDPI 2020.
18. Kowalski ER, Sheu SS, Rashid A, Brons C, Nascimento E. Encapsulation Of Heat And Moisture Sensitive Substances. United States. Patent Application Publication 2010; Pub. No.: US2010/0055083 A1.
19. Cole TE, Cade D, Benameur H. Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration. Adv Drug Deliv Rev 2008; 60(6): 747-56.
20. Hulmajage SB, Chavan SS, Khurde SS, Shetkar SL. A Review On: Soft Gelatin Capsule, Int J Inn Pharm Sci Res 2018; 6(06): 59-71.
21. Guruva RR, Krishnomurti B. Soft Gelatin Capsules-Present and Future Prospective as a Pharmaceutical Dosage Forms - A Review. Int J Adv Pharm Gen Res 2013; 1(1): 20-29.
22. Benza HI, Munyendo LLW. A Review of Progress And Challenges In Soft Gelatin Capsules Formulations For Oral Administration. Int J Pharm Sci Res Rev 2011; 10(4): 20-25.
23. Jaffe R. Soft Gel Encapsulation. United States. Patent Application Publication 2016; Pub. No.: US 2016/0022594 A1.
24. Jain AK, Mishra DK, Jain PK. A Review on Various Techniques of Microencapsulation, Int J Pharm Chem Sci 2013; 2(2): 963-977.
25. Mahato R, Narang A. Pharmaceutical Dosages form and Drug Delivery. 3rd ed. New York: Taylor &Francis Group; 2018. P. 521-526.