



A REVIEW OF PROGRESS AND CHALLENGES IN SOFT GELATIN CAPSULES FORMULATIONS FOR ORAL ADMINISTRATION

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ABSTRACT

Soft Gelatin Capsules (Softgel) were developed in the 19th century to mask unpleasant taste and odour of drug substances. Since then, many improvements have been made with respect to the production of these soft capsules. In the pharmaceutical field, the softgel dosage forms are increasingly being preferred. Technologically with Softgel, content uniformity of low-dose drugs has been achieved and also has consumer preference as is easy to swallow. Interesting advances have recently been made in the area of developing liquid and semi-solid formulations in a soft gelatin capsule to address particular bio-performance issues. The Softgel dosage form therefore offers several advantages over other oral dosage forms, such as delivering a liquid matrix designed to solubilize rapidly. This improves the oral bioavailability of poorly soluble compounds. Delivery of low and ultra-low doses of a compound using softgel also ensures decreased plasma variability. However, due to the dynamic nature of the softgel dosage form, its development and shelf-life stability optimization are fraught with several challenges. This has led to the commercial pharmaceutical and nutraceutical industries opting for the development of alternative shell forming materials instead of the traditional capsule shell material gelatin. This review discusses establishment and the on-going development of the manufacturing technology for liquid fill capsules with focus on progress and challenges of soft gelatin capsules formulation in oral administration for improved solubility and as an absorption-enhancing technique. This considerations form a basis for new applications in oral drug delivery.

Keywords: Soft gelatin capsules, oral administration, drugs formulation.

INTRODUCTION

Soft 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 shell¹. Soft gelatin capsules (softgel) offer the possibility of delivering a liquid in a solid oral dosage form. The softgel can contain the active ingredient in solution, suspension or emulsion, which will inherently lead to better absorption of the active ingredient as compared with delivery in a tablet or as a powder².

Highly developed soft capsules are currently being applied widely in the pharmaceutical, chemical, food and cosmetic industry. This is attributed to the features of softgels like desirable aesthetic properties and 'swallowability', safety enclosure, precise contents, and pleasing appearance. This has enabled their use as an effective delivery system for hydrophobic drugs, low-melting-point drugs, easy-oxidized drugs, and a variety of health care oil¹.

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 world³. 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.

Softgels' ability to enhance bioavailability not only makes them the preferred dosage form for new chemical entities with poor oral bioavailability, they can also be used for reformulation of existing drugs, with the purpose of life-cycle extension.

Softgel delivery system

The softgel delivery system is a unitary package, formed with gelatin outer layers, which contain between them the active ingredients in solution, suspension or paste form⁴. Hydrophobic drugs do not dissolve readily in water, gastric or intestinal fluid. When they are compounded in solid dosage forms, their dissolution rate is usually low and absorption varies resulting in poor bioavailability. Bioavailability of these drugs can be improved in the presence of fatty acids e.g. mono or diglycerides. Fatty acids do solubilize hydrophobic drugs in the gut and enable more rapid absorption⁵.

The softgel delivers drugs in solution and yet offers solid dosage form. These hydrophobic drugs are dissolved in a hydrophilic solvent, which, when crushed or chewed, releases the drug immediately to produce a solution of the drug in gastric juice ready for absorption from the gastrointestinal tract into the blood stream. This results in rapid onset of desired therapeutic effects⁶. For example, Ibuprofen softgel gives rise to a shorter time to peak plasma concentration and greater peak plasma concentration compared to a marketed tablet



formulation. Cyclosporin does give therapeutic blood levels which are not achievable from tablet form. Similarly oral hypoglycaemic glipizide in softgel is also known to have better bioavailability results compared with tablet form. Softgel delivery systems can also incorporate phospholipids or polymers or natural gums to entrap the drug active in the gelatin layer with an outer coating to give desired delayed/control release effects⁷.

The designs for a specific soft gelatin capsule formulation involve appropriate selection of the shell and fill composition. This is followed by optimization of the two to allow for efficient production of a chemically and physically stable product with the desired biopharmaceutical properties. The shell of a soft gelatin capsule is composed of gelatin, a plasticizer or a combination of plasticizers and water. In addition, it may contain preservatives, colouring and opacifying agents, flavourings and sweeteners, possibly sugars to impart chewable characteristics to the shell, gastroresistant substances and in special cases even active compounds⁸. The formulation of the fill is individually developed to fulfil the requirements for optimum therapeutic action. This entails optimizing the chemical stability of the active compound to improve bioavailability. Emphasis is also put on efficient and safe filling process in order to achieve a physically stable capsule product⁶.

PROGRESS IN SOFT CAPSULE SHELL MATERIALS

Different types of capsule constitutive materials are usually selected for different products. Apart from the traditional gelatin, in recent years new materials have been explored and their application in the development of capsules is progressing rapidly⁵.

Traditionally used gelatine materials

Due to their availability, animal skins and bones have been used extensively as a source of raw material for the formulation of the shell of gelatin capsules. Their excellent film-forming ability and mechanical stability properties of gelatin result in the desired physical properties. Furthermore they can be re-cycled and retain their good performance⁶. The gelatin made from the traditional material like animal skin, bone, tendon and collagen have been noted to meet the necessary pharmaceutical requirements as being quickly hydrolysed by gastrointestinal enzymes. In addition they contain a variety of nutritious amino acids. The purified products obtained therefore are easily swallowed and rapidly absorbed⁵.

Development of news materials

In the recent past a number of new sources of raw materials for the gelatin capsule shell have been reported. This range from natural resources like fish to polymers, the fish gelatin has been obtained from fish skin products and formulated as natural hollow capsules of fish oil, spirulina and cellulose⁹. Natural herbal capsules have been reported as concentrated herbal capsules of

gold *Lippo* plant capsules. The polymer material Hydroxyl Propyl Methyl Cellulose (HPMC) have also been explored, the odorless, milky, fibrous or granular powder, from lint or wood pulp, dissolves completely in cold water but is almost insoluble in ethanol and other organic solvents. FDA has highlighted it as a non-active component that can be used for ophthalmic preparations, oral capsules and suspensions⁵. The gelatin made of hypromellose and pullulan displays chemical stability, friability, low moisture content and oxygen absorption rate¹⁰.

PROGRESS IN SOFT CAPSULES LIQUID-FILL MATERIALS

The formulations of capsule fill have been developed to fulfilling specifications and end-use requirements of the product. Capsulation of liquids that are immiscible with water and non-volatile, such as vegetable oils and vitamin E, have been easily made requiring little or no formulation. However, solids which are not sufficiently soluble in liquids are reported to be capsulated as suspensions having a particle size of 80 mesh or finer¹¹.

A large group of dietary products are reported to have been commonly capsulated in suspensions form. The two suspension formulation gel production equipment widely utilized domestically is the Chatsworth Machine and the GIC Engineering. Basically all these machines produce soft gels in a similar manner, they have rotating dies and an independent wedge with a pump that control the fill⁷. Filling of soft gel capsules with liquid and semi-solid materials has been successful carried out with selected "fillings" that do not dissolve the gelatin¹¹.

Donato and group (2008) showed that the following types of compounds may not be suitable candidates for soft gel encapsulation¹²:

- Liquids that can easily migrate through the gelatin shell, such as water hygroscopic and volatile compounds. Water soluble compounds that may affect the gelatin shell unless they are minor constituents of a formula or combined with a carrier that reduces their effect on the shell.
- Aldehydes, which have the ability to harden the shell and hence affect its dissolution property.
- Acidic or alkaline solutions should be avoided, unless they are adjusted to become neutral; acids and alkalis can cause hydrolysis and leakage of the gelatin shell.

THE SOFT GELATIN CAPSULES AS A DOSAGE FORM

Improved drug absorption is the primary reason for selection of softgel as a dosage form. Nevertheless as a drug delivery system for oral administration of therapeutic agent several advantages as well as disadvantages have been reported with soft gelatin capsules;



Advantages

Increased the rate of absorption of drugs

Major advances have been made in the formulation of softgels to address particular drug absorption issues. One of the best advances is the delivery of the drug into the gastrointestinal tract in the form which it can be rapidly absorbed. This has been achieved by using a drug solution matrix in a softgel formulation whereby absorption is significantly faster than from other solid oral dosage forms, such as compressed tablets. While absorption of a poorly soluble drug from a tablet formulation is rate-limited by the need for disintegration into granules before drug dissolution into gastrointestinal fluid, the solution-softgel approach, the shell ruptures within minutes to release the drug solution; it is usually the rate of absorption⁸.

This has been exploited in the recent past as a valuable attribute for therapeutic reasons, such as the treatment of migraine or acute pain. In a recent clinical trial, the dietary supplement glucosol in a soft gel capsule showed a 30% decrease in blood glucose levels compared to a 20% drop seen with dry-powder filled two-piece hard gelatin capsule formulation, suggesting that soft gel formulation made of glucosol improved its bioavailability¹³. This is further illustrated by Lissy *et al* (2010) in the pharmacokinetic comparison of an oral diclofenac potassium liquid-filled soft gelatin capsule (DPSGC) with a diclofenac potassium tablet, study which showed that, DPSGC, 25mg and 50mg were more rapidly and consistently absorbed than diclofenac potassium 50-mg comparator tablets. The C (max) of DPSGC 25mg was equivalent to the 50-mg diclofenac potassium comparator tablet^{14, 15}.

Increased bioavailability of drugs

As well as increasing the rate of absorption, softgels have also been reported to improve the extent of absorption. This can be particularly effective for hydrophobic drugs with a relatively high molecular weight. An example of such a product is the protease inhibitor saquinavir, which has been formulated as a solution-softgel product. The solution-softgel formulation provided around three times the bioavailability of saquinavir as measured by the area under the plasma-time curve (AUC), compared to a hard-shell capsule formulation¹⁵. The bioavailability of digoxin was reported to have increased significantly when formulated and administered as a liquid in a soft capsule and that dose adjustment were necessary when patients were switched from tablets to liquid-filled capsules¹⁶.

Decreased variability of plasmatic drugs

High variability in drug plasma levels is a common characteristic of drugs with low bioavailability. By dosing drug optimally in solution, the plasma level variability of such drugs has been significantly reduced. The cyclic polypeptide drug cyclosporine (Sandimmun Neoral®) was successfully improved by this approach by using a microemulsion concentrate in a softgel¹⁷.

Patient compliance and consumer preference

A number of self-medicating consumer preference studies have been carried out in an attempt to gauge the relative perception of softgels compared to hard shell capsules and tablets. The results showed consistently that softgels were perceived to be appealing dosage forms to most consumers, and outperformed all other dosage forms in answering patient needs. Consumers expressed their preference for softgels in terms of ease of swallowing, absence of taste and convenience. One further aspect of improved compliance is that if, by using a drug solution in a softgel delivery system, its bioavailability is enhanced, it may be possible to reduce the dose administered in order to achieve therapeutic effectiveness. In this way it may also be possible to reduce the capsule size, which will further improve patient compliance¹⁸.

Safety for potent and cytotoxic drug

The mixing, granulation and compression/filling processes used in preparing tablets and hard-shell capsules has been noted to generate a significant quantity of air-borne powders. By preparing a solution or suspension of drug, where the active component is essentially protected from the environment by the liquid, such safety concerns and associated toxicities have been significantly reduced¹⁹.

Dose uniformity of low-dose drugs

Liquid dosing has been realized to avoid the difficulties of poor powder flow and hence content uniformity. This is an important benefit for formulations containing drug doses in the microgram region. Attempts to produce adequate mixtures of small quantities of a low-dose drug in larger quantities of powdered excipients for tableting or hard-shell filling are often unsatisfactory. In contrast, improved homogeneity has been achieved by dissolving the drug in a liquid and then encapsulating the liquid matrix in a softgel²⁰.

Product stability

Preparations of liquid-filled softgel have proven beneficial to oxidative or hydrolytic degradable drugs. The liquid is prepared and encapsulated under a protective nitrogen atmosphere and the subsequently dried shell has very low oxygen permeability. By formulating in a lipophilic vehicle and packaging in well designed blister packs using materials of low moisture transmission, the drug is protected from moisture. Unlike for formulation in solution, where the drug may be more reactive than in the dry state and hence potentially less stable²¹.

Disadvantages

High Cost of production

Production costs are usually high compared to the other ordinary tablets. This has been accounted for by elaborate machinery involved in production of softgels which also gives rise to high maintenance costs. These costs usually do increase the price the consumer pays. This has been proven by comparison of health



supplements, such as cod liver oil that come in both liquid and soft gel capsules form. In most cases, the price is greater for the soft capsules than for the liquid.³

Sensitive to heat and moisture

The effective dissolution of gelatin in the body has been attributed to its extremely water solubility. On the other hand in regard to shelf stability it has been realized that this is a drawback given 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 and this decreases their life expectancy⁸.

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. Due to this there is an emergence of animal-free substitute gelatin capsules made out of seaweed extract or other sources, but they are generally more expensive and harder to find⁹.

ADVANCES AND CHALLENGES IN SOFTGEL CAPSULES DEVELOPMENT

Advances in development of softgels as a dosage form.

Soft gelatin capsules have received enormous consumer acceptance due to their numerous advantages over other traditional dosage forms such as tablets and even hard capsules²². It has become not uncommon for pharmaceutical companies to reformulate marked solid dosage form in the form of soft gelatin capsules in order improve consumer acceptability owing to dissolution in the gastrointestinal tract of drugs formulated as soft gelatin capsules²³.

Advancement of softgel capsules are traced back to Fuccella *et al* study which showed that, softgel capsules of temazepam ensured a more rapid and complete absorption of the drug and seemed to be an appropriate pharmaceutical form for treatment of sleep disturbances²⁴. This observation led to the development of the soft gel capsules and assessment of bioavailability of the formulation, plasma levels of temazepam determined in healthy volunteers²⁵. Formulation of a hydrophobic amine antimalarial with oleic acid in softgel capsules has been reported as an advancement which resulted in the enhancement of bioavailability²⁶.

Several advances have been made in the development of softgel capsules including;

- Ensuring of suitable physical features. The soft gelatin capsule has been developed to have a tidy and beautiful appearance compared to tablet pills. These features have been reported to ensure faster

disintegration speed, higher bioavailability and convenient ingestion.

- The capsule can cover unpleasant odor of the medicine.
- The capsule has been made into instant-effective, slow-releasing, enteric coated or gastro coated soft gelatin capsule.
- Achievement has been reported in formulation of medicines with dosage form of higher oil concentration that cannot be easily made into tablets or pills and small dosage principle agent that is not water-soluble and hard to be ingested in the digestive.
- Soft capsules technology have facilitated light-sensitive and unstable drugs to be filled into opaque lightproof opaque capsule to improve the stability and prevent the drug from been affected by moisture, oxygen and light in the air.

Advances have enabled soft gelatin capsules to be used to make nutraceuticals, cosmetics and paintball for simulated shooting²⁷.

Challenges in development of soft gelatin capsule

Although the formulation of drugs into softgel capsules has been reported to solve many problem associated with tableting including poor compaction, lack of content or weight uniformity, and other powder flow or mixing problems¹⁰, several problems affecting the development of softgel capsules have been revealed.

Poor differentiation and /or mismatching of gel material added to cross-linking with the drug. The stability of an API in a liquid dosage form, as opposed to a solid dosage form is, in itself, a challenge, as is matching the formulation with the characteristics of the capsule shell and the dosing system of the capsule filling machine. In cases where gelatin as a capsule material is not suitable, alternative polymers for capsule production may be exploited²⁸.

Another phenomenon seen in capsules, especially softgels is extensive cross-linking to the gelatin, which could occur during storage and result in the formation during dissolution testing of swollen, rubbery water-insoluble membranes known as pellicles that have been reported to act as barrier to drug release¹².

The major challenge in the development of the softgel dosage form is that the system is very dynamic in terms of;

- The physical migration of components between the shell and the fill and the shell and the external environment,
- The occurrence of physical and chemical interactions within and between the shell and fill components²¹.

It is critical to understand these interactions to develop a softgel product that is stable and provides desired in vitro and in vivo characteristics.



CONCLUSION

Interesting advances have recently been made in the area of developing liquid and semi-solid formulation in a soft gelatin capsule to address particular bioperformance issues, namely an increase of bioavailability and decrease of plasma variability by improving solubility and absorption-enhancing techniques.

Although the softgel capsules have many advantages, they also face stability problem, mainly for the soft capsules stored for longer than six months. After this time, their soluble products decreased, and the remnants cannot be re-dissolved and/or reabsorbed into the gastrointestinal tract. These problems could be investigated as a research subject.

The proper designs for a specific softgel capsules formulation requires the appropriate selection of shell and fill composition and the optimization of the two to allow for the efficient production of a chemically and physically stable product with the desired biopharmaceutical properties.

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