

Duocapsule and alternative shell material to gelatin: Advancement in capsule formulation

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Abstract

Owing to broad advantages like self-medication, unit dosage form, and patient compliance, cost effective, limited interaction with the excipients and possibility of mask the unpleasant taste, capsules are the most extensively recognized conventional solid dosage form after Tablet. In the world of Novel drug delivery system to overcome the disadvantages of conventional delivery system modifications are made in the capsule to develop a product of higher selectivity for medical treatment like the capsules that facilitates the controlled drug delivery, sustained and targeted release profiles with its own benefits as conventional dosage form. The advancement in capsules has led to the formation of different types of capsule formulations such as tablets in capsules, pellets in capsule and the capsule in another capsule, liquid in capsule products and pellets in capsule formulations.

This article aims to highlights the advancement in the capsule system, particularly Duocapsules and capsules with capsule shell prepared with alternative shell material to gelatin. The Duo capsule is also called as capsule in capsule formulation as it contains two capsules one with the bigger size containing the smaller sized capsule inside it with different or same formulations in various forms such as liquids, solids, powders, tablets, pellets etc. The article mainly focuses on the different applications, advantages, formulation consideration, and applicable drugs of duo capsules.

Considering the challenges involved in manufacturing the gelatin shell and instability of in different climatic conditions, the present article also emphasizes on the formulation development in capsule system with alternative polymers to the gelatin like HPMC, starch and PVA copolymer capsule shells.

Keywords: Duocapsule; Dual release profile; HPMC; Starch capsule shell; PVA copolymer capsule shell

1. Introduction

Capsules are the most widely accepted conventional solid dosage form after Tablet. Owing to broad advantages like self-medication, unit dosage form, and patient compliance, cost effective, limited interaction with the excipients and possibility of mask the unpleasant taste of the contents present in it the capsule remains preferred dosage form though number of novel product is coming up. Capsules are dosage form designed to enclose the medicament in shell. They can be divided in main two categories, hard capsule (two pieces) and soft capsule (one piece) according to the presence of glycerol or another plasticizer which make it soft and elastic.

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Gelatin is the most widely used capsule shell material because of its tremendous benefits like non-toxicity, solubility in biological fluids at body temperature, ability to undergo thermal gelation and form a strong, flexible and homogeneous film [1].

In the world of Novel drug delivery system to overcome the drawbacks of conventional dosage form like immediate release, fluctuation in plasma concentration, the evolution in capsule system have led to develop the capsules that facilitates the controlled drug delivery, sustained and targeted release profiles with its own benefits as conventional dosage form. The advancement in capsules has led to the formation of different types of capsule formulations such as tablets in capsules, pellets in capsule and the capsule in another capsule, liquid in capsule products and pellets in capsule formulations.



Figure 1 Different types of Capsules

Moreover, the need of novelty has driven the marked advancement in capsule system is Capsule in capsule technology; it is also called as Duo caps, where one capsule is inserted into another capsule. The inner capsule of this system can contain liquid, semi-solid, powder or pellets, while the outer capsule can either be a liquid or semi-solid. Development of such capsules provides different benefits like change in the release pattern of drugs from fast release to delay / controlled release or combination of both, administration of combination of two incompatible drugs together in one formulation, insertion of drugs two different phases like liquid, solid or semisolid and delivery at different region of the GI tract to meet targeted delivery system. Capsules are the solid dosage forms in which the medicament is contained within gelatine shells. The current review article emphasizes on Duocapsule, benefits, its application and technology here.[2]

2. DUOCAP capsule technology facilitates

- Formulating of combinational products or dual release of a single ingredient
- Providing multiple release profiles
- Unique finished product presentation for brand recognition
- Which makes the duocapsule ideal for brands seeking differentiated products featuring two complementary ingredients or two incompatible ingredients in one, easy to use capsule.

2.1. Benefits

- Delivers multiple benefits of two or more drugs in a single capsule
- Accurate, pre-measured dosing for a 'perfect dose' is possible
- Maintains potency, freshness, and effectiveness
- Sustainable and Biodegradable
- Attractive and Convenient with ease of swallowing

2.2. Technical advantages

- Ability to combine two active ingredients that are :
 - Are typically not stable together
 - Have shortened shelf life when combined
 - Are complementary to enhance benefits
- Protects and preserves sensitive actives
- Advanced range of applications in nutraceuticals, skin care, hair care, fragrances, etc.
- Flexibility for custom shapes, sizes, and colours.

2.3. Disadvantages

- If a toxic dose is given, it will stay toxic for a long time ·
- Takes a long time to titrate patient ·
- Strong first pass effect by staying below the metabolizing enzymes saturation point
- Risk of Dose Dumping a large immediate dose ·
- Inflexible dosing schedule,
- Sensitive to heat and moisture and Dietary restrictions.[1]



Figure 2 Capsule in Capsule Formation



Figure 3 Duocapsules

3. Applications of duo capsules

3.1. Providing combined release or multiple release profiles

For example solubilized prebiotics in the outer capsule and probiotics in the inner capsule. The prebiotic releases immediately and the probiotic release later of Probiotics and prebiotics in one dosage form to improve patient compliance.

3.2. For diabetes

Capsule-in-capsule technology also allows to formulate antidiabetic drug with combine release pattern where the inner capsule containing optimized sustained release tablet of Glimepiride can be filled into a bigger capsule body size 00 which will further fill with the liquid of Glimepiride as loading dose using medicine droppers. Various conditions like diabetes hypertension needs a combination of delivery system of immediate release and controlled release in order to give immediate as well as prolong effect of medicament. This single oral dosage delivery system, which involves inserting a smaller pre-filled capsule into a larger liquid-filled capsule, offers numerous possibilities and a broad range of formulation and design options.[3]

3.3. Protection of nutraceutical formulations

Nutritional supplements, like flavonoids, carotenoids, hydroxycinnamoyl acid or vitamin C, can also be highly degraded (80–91%) during gastrointestinal digestion, while bioactives like proteins and peptides can be damaged by the action of pepsin and trypsin degradation, thus significantly reducing their activity (Bao et al., 2019). Different strategies, including tablet coating or bioactive encapsulation, have been developed for acid-sensitive products to provide an adequate delivery systems. (Varum et al., 2020a, Varum et al., 2020b). Tablets have some disadvantages such as low compressibility, slow dissolution or bitter taste (Al-Tabakha, 2010). In addition, during the early stages of drug development, the limited amount of drug availability can hinder the development of a coated pellet or tablet formulation (Cole et al., 2002). Therefore, some of the capsule polymers, like cellulose derivatives or acrylic/methacrylic acid derivatives may offer a better solid dosage form and also provide possibility to deliver liquids or semi-solid formulations to the small or large intestine (Cole et al., 2002, Barbosa et al., 2019). Thus, capsule technology has made a significant progress, offering economically convenient alternatives for drug and nutraceutical formulation as well as functionality for targeted release. To achieve the controlled release and optimal performance or product bioactivity, modification in the capsule polymers or capsule-in-capsule (DUOCAP®) technology has been developed.[4]

Magnetic localization of chemotherapeutics at the site of GI tumors, which are simultaneously identifiable on X-ray following intravenous administration of radio opaque contrast, would enable localized dosing while minimizing side effects associated with systemic administration.[1]

3.4. Treatment of H. Pylori

The H. pylori bacteria enter into the stomach and attach to the lining of the stomach and produce poisonous substances which increase the secretion of water and electrolytes in the stomach and cause cell death of the stomach lining. This causes damage to the tissues resulting in ulcers of stomach lining. There are different therapies for treating H. Pylori. The standard triple therapy is a proton pump inhibitor (PPI) and 2 or 3 antibiotics, levofloxacin containing triple therapy, Bismuth containing quadruple therapy, sequential therapy and Concomitant therapy. The first line treatment is the PPI based triple therapy (Lansoprazole + Clarithromycin + Amoxicillin) which is approved by the US-FDA. The current therapy includes different dosage forms in high doses, which may cause inconvenience to the patient and can cause dose dumping and toxicity. There is no combination dosage form available for the same, which can help in patient compliance and convenience to patient.

FDA approved medication for treatment of H.pylori includes Amoxicillin, Lansoprazole Clarithromycin taken individually which may be inconvenient for patient to take. An attempt was made to prepare combination dosage form (Amoxicillin + Clarithromycin + Lansoprazole) for the treatment of H.pylori infection. The approach selected was capsule in capsule with inner enteric coated capsule of Lansoprazole and outer capsule was of mini tablets of amoxicillin and Clarithromycin.[2]

3.5. Combinational therapy

Rifampicin and isoniazid are widely prescribed as a combination product in the treatment of tuberculosis, these are the drugs majorly used in the therapy. But when given in combination rifampicin interacts with isoniazid in the acidic media of stomach to form inactive 3-formyl rifamycin isonicotinyl hydrazone, thus results in the emergence of drug resistant tuberculosis and hence treatment failure. Whereas it is observed that rifampicin is highly soluble between 1-2 pH and well absorbed from the stomach and isoniazid is well absorbed from all the three sections of small intestine. Thus, the capsule in capsule formulation is used to combine incompatible active pharmaceutical ingredients and to deliver compounds to two different regions of gastro-intestinal tract. To overcome this both the drugs are given in combination in the form of duo capsule, where rifampicin is placed in the outer capsule and is released in the stomach media and isoniazid in the inner capsule targeting the release in the small intestine. The formulation is developed by filling the outer capsule with rifampicin liquid dispersion or floating mini tablets and inner small capsule with intestinal targeted isoniazid mini -tablets.[5]

3.6. Micro- flora guard

It is a unique DuoCap - capsule in a capsule providing plant oils in the outer capsule and probiotic bacteria with garlic in the inner capsule, the ingredients which normally would not be able to taken together. It helps to promote the health of the gastrointestinal system. This design enhances the product stability by protecting the probiotic inner capsule in an HPMC capsule, creating an effective barrier to moisture, which helps the probiotic remain inactive until it is consumed. Resolving the problem in probiotic stability.[6]

4. Formulation consideration of duocapsules

As involvement of two different sizes capsules one in another in duocapsule, selection of size of capsule shell is an important parameter in case of duo. Generally the inner hard capsule should be two sizes smaller than the outer is optimum (e.g., a size 2 capsule would fit in a size 0 outer capsule). Size considerations may be affected by the introduction of coatings (e.g., enteric or colon-targeted for either or both capsules). The inner capsule of this unique delivery system contains liquid, semi-solids, powder or pellets, while the outer capsule can be either a liquid or semi-solid formulated capsule and should be leak proof.

Other parameters remains same as that of the conventional dosage form including the basic steps for formulation. Fig. 3 depicts here the steps involved in the development of Capsule similar to that of the capsule in capsule.

4.1. Evaluation parameters

Evaluation parameters like Weight variation, Lock length with the help of Vernier calliper, Disintegration, Dissolution, Stability studies etc.

For Duo are also remained same as conventional dosage form with extensive studies on release pattern is desirable in duo.

4.2. Drugs candidates for duo capsules

- Drugs having Poor bioavailability i.e. Digoxin
- Drugs that have Low melting point i.e. Ibuprofen
- Drugs which are having Low dose / High potency.
- Drugs which are having Critical stability i.e. the antibiotic Vancomycin hydrochloride
- Drugs which are having Sustained release and require large doses.
- Drugs which are having Short half-life & Short long life. Eg. penicillin G, Diazepam
- Drugs which are having extensive plasma protein binding. [1]

4.3. Alternative shell material to gelatin

The challenges while preparing capsule shell with traditional way of using gelatin has compelled to search for an alternative material of choice. Considering the drawback of gelatin like its non-vegetarian source, unstability with fluctuation in climatic conditions like humid and high temperature at the time of production and storage, ability of crosslinking reactions with many excipients

4.4. HPMC

HPMC is found to be an alternative material of choice with all beneficial properties of Gelatin. HPMC is proved as standard with more advantageous effect like its suitability to incorporate the hygroscopic substances, and liquid filling. Though liquid can be filled in soft gelatin capsule shells, the selection of solvents on the basis of non-solvency for gelatin is important, while in case of HPMC can encapsulate the liquid filled without affecting shell property. Moreover, HPMC also helped in solving the problem of gelation shell and some medicaments where undesirable effect seen, for example, with Ascorbic acid and salicylic acid.[8]



Figure 4 HPMC Capsule Shells

4.5. Starch capsule shell

Recently starch capsules have been used in various controlled release formulations due to the increasing demand for non-animal based products. The gelatin shells may solubilise or get soften on spraying with coating material and can become brittle on drying. Whereas starch capsules can easily be coated than the gelatin capsules, such as a redox sensitive material or pH- sensitive material can be used for the delivery into the small intestine. These capsules can also be coated using a material that can be broken down by specific enzymes or bacteria present in colon to get a targeted delivery approach. More uniform coating is found due to higher bulk density if starch capsules. Starch capsules are prepared using injection molding process which yields exact dimensions and proper sealing. The filling and sealing process is simultaneous resulting in well-sealed, secure and resistant to manipulation finished product. It offers greater resistance to heat and humidity than gelatin and also allows easy filling as these are non-static. The dissolution is independent of pH and it is ready for filling immediately after manufacturing. [6][10]

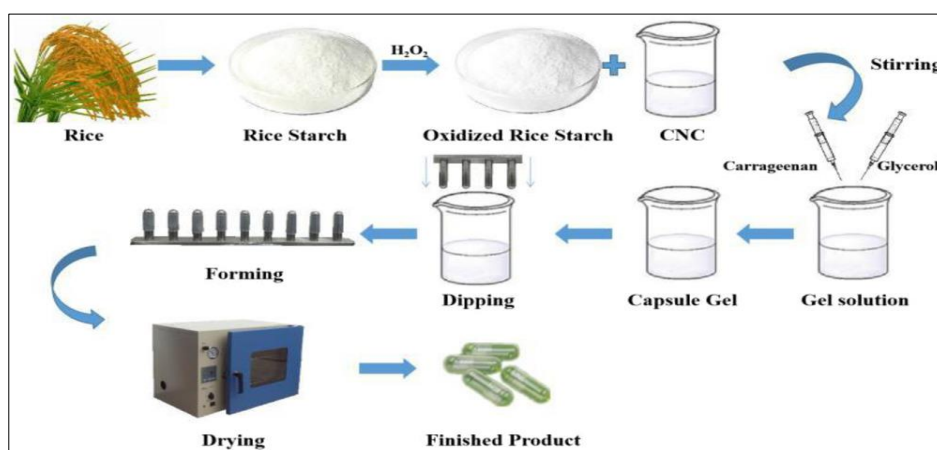


Figure 5 Preparation of Capsule Shells from Starch

4.6. PVA copolymer capsule shell

Hard capsules are traditionally used for powder or granulated formulations and are also adapted to contain oily liquids, tablets and inhaling powders. The solubility of some compounds having potential drugs is very low as they are selected due to their affinity to receptor, which increases its lipophilicity. Such insoluble drugs are combined with macrogol 400, owing to increase in its solubility. Due to its large potential it is difficult for the conventional capsules to hold them as a result capsules that can hold macrogol 400 are synthesized. They are developed by copolymerizing acrylic acid (AA) and methyl methacrylate (MMA) on PVA as a skeleton and then the obtained PVA copolymer is used as a capsule shell. These shells are water soluble and less hygroscopic than gelatin. It has a unique property of having very low oxygen permeability and has the ability to contain macrogol 400. [9][10].

5. Conclusion

The approach for formulating capsules in a double liquid-filled capsule format is adaptable for various formulation aims and market sectors. In particular, it is suited to the delivery, of a selected pharmaceutical actives of different purpose or release pattern in a single dosage unit, (e.g., a prompt and a slow-release combination suited to oral analgesics).

Furthermore, the second-phase delivery of the active ingredient in the duocapsule can be targeted by appropriately coating the inner capsule for local delivery to a specific intestinal site (e.g., the colon). In addition to use for single-drug formulations, the system is applicable for combination of products, as stated above. In its simplest form, the system could deliver two active ingredients, each one of which could be formulated for its specific optimized delivery and stability profiles. Complex combinations may be conceived in the formulated according to compound, delivery, and market needs. The system may be used for gelatine and HPMC capsule formats.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

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