Review Article

DUOCAP: THE CAPSULE IN CAPSULE TECHNOLOGY

Kanabar Vishvesh B*, Doshi Sumit M, Patel Vipul P

Department of Pharmaceutics, School of Pharmacy, R.K. University, Kasturbadham, Rajkot-Bhavnagar Highway, Rajkot, Gujarat, India

*Corresponding Author Email: vishveshkanabar@gmail.com

Article Received on: 11/12/14 Revised on: 13/01/15 Approved for publication: 18/02/15

DOI: 10.7897/2230-8407.06220

ABSTRACT

In this article, the study of newer technology of capsule in solid dosage form among all in pharmaceutical dosage forms. This review includes newer trends related to capsule shell, capsule fill material, capsule sealing technique and different capsule systems to achieve modified drug release, encapsulation of various kind of materials and for modified application like mapping of the drug for clinical evaluation Either this done by capsule shell or by dosage filling in capsule dosage forms. This article mostly focuses on advancement of capsule in capsule technology. 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.

Keywords: Capsules, Chew caps, Duo caps, Hard Gelatin Capsule, Soft Gelatin Capsule, Vegetarian capsules.

INTRODUCTION

The word ‘Capsule’ derived from the Latin word “capsula”, which means a small box or container. The word occurs in many scientific disciplines, ranging from anatomy, as an enclosing membrane and in botany, as a descriptive word for fruit, to astrophysics, as a space vehicle.¹ In pharmacy, capsule word has been used to describe a glass ampule and also as a name of protective cap over the stopper of a bottle of medicine. In more recent times, capsule has been used primarily to describe solid dosage forms, which consist of a container, filled with medicinal substance. 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. The soft gel dosage form has been around for many years. The earliest soft gels date back to the 19th century. Since then, many improvements have been made with respect to the production of these soft capsules.² Soft gel manufacturing still requires special skills and equipment that less than a handful of companies can offer to pharmaceutical clients. Notwithstanding the progress that has been made in soft gel manufacturing, the soft gel as a dosage form has remained largely unchanged over the years. As a result, patent protection on the technology was lost, which is a disadvantage in the era of pharmaceutical life-cycle management. For that reason, Banner has developed new soft gel variants that not only offer specific benefits over the standard soft gel, but also provide additional patent protection to the compounds they deliver.

Figure: 1: Capsule in Capsule Formation

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 world.³ 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.⁴ Soft gels 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.

Drug Candidates for Duo Cap

- Drugs which are having Poor bioavailability i.e. Digoxin
- Drugs which are having Low melting point i.e. Ibuprofen and Vitamins
- Drugs which are having Low dose / High potency.
- Drugs which are having Content uniformity.
- Drugs which are having Critical stability i.e. the antibiotic Vancomycin hydrochloride
- Drugs which are having Sustained release. i.e. Gelucire
- Drugs which are having Short half-life. i.e. penicillin G
- Drugs which are having Short long life. i.e. Diazepam.
- Drugs which requires large doses i.e. Sulphonamides.
- Drugs which are having extensive plasma protein binding.⁵

Drug used for Duo Cap

- Digoxin
- Ibuprofen
- Vancomycin
- Gelucire
- Penicillin G
- Diazepam
- Sulphonamides
- Phenytoin
- Furosemide

- Nimesulide
- Paracetamol
- Diclofenac^{5,6}

Figure 2: Duo Caps

Preparation of Duo Cap

Capsule-in-a-capsule formulation consists of two phases; immediate and sustained releasing phases. The immediate and sustained releasing doses were found near about to be 3.24 mg and 8 mg respectively.⁶ Accurately weighed amounts of either PEG 4000 or PEG 6000 were placed in an aluminum pan on water bath and melted with constant stirring with a glass agitator, at 60°C. Fusion was reached in 20 min at this temperature. An accurately weighed amount of drug in 1:1 ratio of drug: carrier was incorporated into the melted carrier with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. The drug: carrier complex melt of drug prepared was solubilized in tetra glycol to give a final drug concentration of 3 % (m/m) and further sonicated for 1 h.⁷ Ionotropic gelation technique was used to prepare the drug alginate sustained releasing beads. Twelve different batches of beads were tried. The batches, BFC-1 to BFC-3 were prepared with sodium alginate alone, BFC-4 to BFC-6 were prepared with HPMC, BFC-7 to BFC-9 were prepared with chitosan and BFC-10 to BFC-12 were prepared with pectin in different proportions. Calcium chloride was used as a cross-linking agent.⁸ The batches, BFC-1 to BFC-3 were prepared as follows: Weighed quantity i.e. 100 mg of drug was uniformly dispersed in 50 mL of sodium alginate solution by using mechanical stirrer at 500 rpm. Bubble free dispersion was roped into 100 mL of aqueous calcium chloride solution through a syringe with a needle of size no.18 and stirred at 100 rpm. After stirring for 15 min the formed beads were separated by filtration, washed with distilled water and dried at 60°C for 6 hours in an oven. Similarly, BFC-4 to BFC-6 were prepared using fixed concentration of sodium alginate and different concentrations of HPMC.⁹ The batches, BFC-7 to BFC-9 were prepared using fixed concentration of sodium alginate and different concentrations of chitosan, as follows: The mixture of drug and sodium alginate dispersion was dropped through a syringe with a needle of size no.18 into 100 mL of chitosan solution containing 5 % calcium chloride (Chitosan dissolved in 10 mL of 5 % (w/v) acetic acid) and stirred at 100 rpm. After stirring for 30 min, the coated beads were separated by filtration, washed with water and dried at 60°C or 6 h in an oven. Similarly, BFC-10 to BFC-12 were prepared using fixed concentration of sodium alginate and different concentrations of pectin.¹⁰

Table 1: Formulation of Duo Cps

Batch code	Sodium alginate % (w/v)	Calcium chloride % (w/v)	HPMC % (w/v)	Chitosan % (w/v)	Pectin % (w/v)
BFC-1	2	3	--	--	--
BFC-2	3	5	--	--	--
BFC-3	4	7	--	--	--
BFC-4	3	5	0.5	--	--
BFC-5	3	5	1.0	--	--
BFC-6	3	5	1.5	--	--
BFC-7	3	5	--	0.5	--
BFC-8	3	5	--	1.0	--
BFC-9	3	5	--	1.5	--
BFC-10	3	5	--	--	0.5
BFC-11	3	5	--	--	1.0
BFC-12	3	5	--	--	1.5

pecial leak proof capsules for both smaller and bigger size was used in this formulation. To prepare a novel capsule in-a-capsule technology the prepared optimized sustained release beads equivalent to 8 mg of drug were filled in size 2 hard gelatin capsule and was sealed with 15 % (m/m) warm gelatin solution.¹¹ This prepared sustained release smaller capsule was filled into a bigger capsule body size 0 which was further filled with the liquid dispersion of drug equivalent to 3.25 mg as loading dose using medicine droppers. After closing with cap the bigger capsule was also sealed with 15 % (m/m) warm gelatin solution. The filled capsules were stored at room temperature until testing.¹²

Advantages

- Increased time within the Therapeutic Window due to lower peak plasma concentration and hollower slope
- Has kinetics similar to IV infusion, with the ease of a tablet
- Reduce dosing frequency
- Improve patient compliance
- Reduce gastric irritation and side effects
- Possible to enhance the bioavailability
- Alleviate the risk of dose dumping
- Reduce fluctuation in circulation drug level
- Avoidance of night time dosing
- More uniform effect
- 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^{13,14}

Figure 3: Caps gel Duo Cap

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 (failed delivery device) a large immediate dose
- Inflexible dosing schedule
- Can't usually split tablets
- High Cost of production
- Sensitive to heat and moisture
- Dietary restrictions^{13,14}

Evaluation of Capsules

Weight variation test

Ten capsules were individually weighed and the contents were removed. The emptied capsules were individually weighed and the net weight of the contents was calculated by subtraction and the percent weight variation was calculated by using the following formula¹⁵:

$$\text{Weight variation} = \frac{(\text{Weight of capsule} - \text{Average weight}) \times 100}{\text{Average weight of capsules}}$$

Weight variation should not be more than 7.5 %

Lock length

Ten individual capsules were taken from formulation trial batch and lock length was measured manually by using vernier calipers and average of ten capsules was noted.

Disintegration

The capsules were placed in the basket rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37°C. To fully satisfy the test, the capsules should disintegrate completely into a soft mass having no palpably firm core without any fragments of the gelatin shell. If one or two capsules fail, the test should be repeated on additional of 12 capsules. Then, not fewer than 16 of the total 18 capsules tested should disintegrate completely.

Dissolution studies

Dissolution is a process by which the disintegrated solid solute converted into solution. The test determines the time required for a definite percentage of the drug in capsules to dissolve under specified conditions. The release of drug was determined using a dissolution apparatus of USP Type II (paddle) at 50 rpm. 900 ml of 0.1N hydrochloric solution acid was used as the dissolution medium and were maintained at the temperature of 37.5 ± 0.5°C. A sinker was used to avoid capsule flotation¹⁴. The samples were drawn at 5, 10, 15 30 and 45 mins and equal amount of fresh medium were replaced to maintain the sink conditions. Samples withdrawn were analyzed to determine the percentage of drug released.

Figure 4: Parts of Duo Caps

Stability Studies

Stability of the drug has been defined as the ability of particular formulations, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity etc. The storage conditions for stability studies were accelerated Condition (40 ± 2°C / 75 ± 5 % RH) and Long term condition (25 ± 2°C / 60 ± 5 % RH). The capsules were packed as 30's count in HDPE containers, induction sealed with adsorbent cotton 26-29.

Uniformity of content

Five capsules were weighed and their contents were removed. An accurately weighed sample equivalent to 100 mg of drug was taken in a volumetric flask (100 ml). The content was dissolved in 0.1N HCl and the volume made up to 100 ml. This solution was filtered through Watt man filter paper No.41. The solution was diluted and the absorbance was measured at 274.0 nm. The drug content was calculated.

Figure 5: Licaps

Application

- This technology is applicable for GI diseases like GI cancers, Crohn's disease and acid reflux. It can even be used in case of diabetes.
- Targeted release by the use of magnet helps the drug's uptake and bioavailability without damaging intestinal tissues.
- 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.
- It provides a fast, cost-effective, and convenient means for the controlled release of drugs to specific sites in the GI tract.
- It can be used to quickly design and complete a study in either a preclinical (animal model) or clinical setting.
- It allows the release profile to be explored, altered and adapted quickly to determine up-front optimal release profile (i.e., before committing resources for solid dosage form development).
- As an oral dosage form of ethical or proprietary products for human or veterinary use.
- As a suppository dosage form for rectal use, or for vaginal use.
- As a specialty package in the tube form, for human and veterinary single dose
- Application of topical, ophthalmic and optic preparations, and rectal ointments¹⁶.

CONCLUSION

From this above study, one can say that capsule in capsule technology named as DUO CAP is newer invention in this time. By one formulation one can get sustained release as well as immediate release pattern. This reduces 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. Drugs which are poorly soluble, having high potency, short life and large doses are very much applicable for same formulation. Capsule-in-a-capsule formulation consists of two phases; immediate and sustained releasing phases. The immediate and sustained releasing doses were found near about to be 3.24 mg and 8 mg respectively. PEG 4000 or 6000 is used in this preparation. Apart from that sodium alginate, calcium chloride and pectin are also used. By this preparation numerous advantages are get such as reducing dose frequency, improve patient compliance and duo effect of controlled and sustained release. Useful in GI's cancer, Chron's diseases and acid reflux widely. Apart from that, it can be used to quickly design and complete a study in either a preclinical (animal model) or clinical setting.

REFERENCES

1. Paresh M, Ansari A, Patel S, Khinchi MP, Agrawal D, Sharma N. A Review on Recent Advancement in Capsule Formulation. American Journal of Pharmtech Research 2013; 3: 1-14.
2. Khan AW, Ahmed MG, Ramesh B. Formulation and Evaluation of Novel Sustained Release Capsules of Terbutaline Sulphate. Int. Res. J. Pharm 2011; 2(1): 249-55.
3. Kathpalia H, Sharma K, Doshi G. Recent trends in Hard Gelatin capsule delivery System. Journal of Advanced Pharmacy Education N Research 2014; 4(2): 165-77.
4. Rabadiya B, Rabadiya P. A Review: Capsule Shell Material from Gelatin to Non Animal Origin Material. International Journal of Pharmaceutical Research and Bio-Science 2013; 2(3): 42-71.
5. Tiwari S, Patil S. Patented Technology in Soft Gelatin Capsule: A Review. International Journal of Research and Reviews in Pharmacy and Applied science 2(3): 491-512.
6. Cole ET. Liquid filled and sealed hard gelatin capsules. Capsugel Library 1999; 92: 1-12.
7. Kumar K, Raveendranath V, Leela M, Dorababu N, Hussain Z. Design and evaluation of pantoprazole Delay release capsules. An International Journal of Advances in Pharmaceutical Sciences 2010; 1(2): 213-20.
8. Rahman AA, Khidr SH, Samy EM, Sayed MA. Enhancement of the Dissolution Rate of Glipizide Capsules Using Fenugreek as Natural Additive. Unique Journal of Pharmaceutical and Biological Sciences 2014; 2(1): 1-8.
9. Vachhani SR, Patel JJ, Patel D, Prajapati ST and Patel CN. Formulation and *in-vitro* evaluation of floating capsules of Loratadine. Journal of Chemical and Pharmaceutical Research 2010; 2(2): 57-64.
10. Srinivas L, Lohithasu D, Madhupriya D, Siddhartha N and Tejaswi N. Formulation and evaluation of ibuprofen pulsing capsule technique for controlled release. Scholar Research Library 2013; 5(1): 60-68.
11. Srividya B, Sowmya CC, Surya, Reddy P. Capsules And It's Technology: An Overview. International Journal of Pharmaceutics and Drug Analysis 2014; 2(9): 727-33.
12. Rao AS, Nayeemuddin M, Hadi MA. Formulation and evaluation of a novel capsule-in-a-capsule technology for biphasic delivery of lornoxicam in the treatment of migraine. International Journal of Pharmaceutical and Biomedical Research 2013; 4(3): 170-76.
13. Chandana N, Gopinath H, Bhowmik D, Williamkeri I, Reddy AT. Modified Release Dosage Forms. Journal of Chemical and Pharmaceutical Sciences 2013; 6(1): 13-21.
14. Benza HI, Munyendo L. A Review of Progress and Challenges in Soft Gelatin Capsules Formulations for Oral Administration. International Journal of Pharmaceutical Sciences Review and Research 2011; 10(1): 20-24.
15. Pandian P, Kannan K, Manikandan M, Manavalan R. Formulation and Evaluation of Oseltamivir Phosphate Capsules. International Journal of Pharmacy and Pharmaceutical Sciences 2012; 4(4): 342-47.
16. Nasreen S, Narayan N. Evaluation of Pre-formulation and Formulation Parameters of an Anti-stress Herbal Capsule. International Journal of Pharma and Bio Sciences 2011; 2(1): 867-77.
17. Gurava Reddy R, Muthukumaran, Krishnamoorthy B. Soft Gelatin Capsules-Present and Future Prospective as a Pharmaceutical Dosage Forms -A Review. International Journal of Advanced Pharmaceutical Genuine Research 2013; 1(1): 20-29.

Cite this article as:

Kanabar Vishvesh B, Doshi Sumit M, Patel Vipul P. Duocap: The capsule in capsule technology. Int. Res. J. Pharm. 2015; 6(2):86-89
<http://dx.doi.org/10.7897/2230-8407.06220>

Source of support: Nil, Conflict of interest: None Declared