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Review Article

An overview of microcapsule dosage form

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ABSTRACT

Microcapsules offer a wide variety of convenience in drug delivery when compared with conventional dosage forms. It is a unique carrier system for many pharmaceuticals. Microencapsulation is a potential process which prolongs the efficacy of drug significantly and improves patient compliance. This approach can alleviate the limitations of dose dumping, multiple dose inconvenience, kidney disease. This dosage form has potential advantages for elderly people who have to take multiple drugs. But microcapsule preparation needs method and formulation optimization and proper characterization. In this review paper, we have discussed the advantages, limitation of the microcapsules and microspheres. We have highlighted the applications of microcapsules and microspheres in the pharmaceutical industries. We also discussed the characterization process of microcapsules. Microcapsules open the era of individualized, targeted drug delivery with minimal side effects and greater convenience.

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1. Introduction

Microencapsulation involves making a thin membrane coating of a material over an active agent material. The percentage of coating material with respect to the active material is very minimal.¹⁻⁴ The microcapsules are in the range from 1micron to some 100micron level. Usually the coating is known as cover, shell, film, coating membrane etc. Besides, the active material inside the coating is sometime considered as core element, internal fill, core material etc. Microencapsulation process is applicable for all the phases of the core material named gas, liquid and solid.⁴⁻⁶ This allows easier handling and processing of liquid and gas materials as solids. Microcapsules serve to improve dosage efficiency with minimal side effects.⁷⁻⁹ Microspheres enables better release profiles of active pharmaceutical ingredients (API).¹⁰⁻¹² Examples include quick release formulas, extended release pattern,

targeted release, delayed release etc.^{6,13,14} Many more uses and applications can be explored for obtaining better convenience for patients.^{3,15}

Conventional oral drug administration does not usually provide rate-controlled release or target specificity.¹⁶ In many cases, conventional drug delivery provides sharp increase in drug concentration often achieving toxic level and following a relatively short period at the therapeutic level of the drug concentration eventually drops off until re-administration.^{3,10,17,18} It is necessary to administer an agent to the appropriate tissue in the optimum quantity to be released over the requisite duration of time in order to achieve full therapeutic effectiveness with minimal toxicity and limited side effects.

Microencapsulation is a promising approach that greatly increases the length of the drug effect and promotes patient adherence. Finally, the overall dosage and few side effects may be minimized while the plasma concentration remains stable. There are types of method to achieve target-oriented operation with sustained required period. Among all the

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methods, microsphere is used as drug carrier.^{7,19–21}

2. Structure of Microcapsule^{1,7–9,13,14,19–22}

2.1. Core material

The material to be coated is the core.

2.2. Core material properties

1. It may be liquid or solid
2. Liquid core may be dissolved or dispersed material

2.3. Composition of core material

1. Drug or active constituent
2. Additive like diluents
3. Stabilizers
4. Release rate enhancers

2.4. Coating material

The coating material is usually inert with respect to the core material with a required wall thickness.

2.5. Coating material properties

1. The coating material should be inert and stable.
2. The shell material is non-reactive to the active element.
3. A maintained release of active agent with a fix environment.
4. It should be pliable, taste free, durable membrane coating
5. The shell element is not hygroscopic with low viscosity and cost effective
6. The shell element is soluble in an aqueous solvent
7. The shell membrane can be flimsy, elastic, brittle solid etc.
8. Content of coating material:
9. Inert polymer
10. Plasticizer
11. Colouring agent
12. Coating materials: n
13. Gums: Gum arabic, sodium alginate, carageenan
14. Carbohydrates: Starch, dextran, sucrose
15. Celluloses: Methycellulose, Carboxymethylcellulose
16. Lipids: phospholipids, wax, stearic acid etc.
17. Proteins: Albumin, Gelatin

3. Objectives of the Microcapsule Technology^{6,22,23}

1. Consistent drug release over the required period
2. For the manufacture of powder or suspension, this method is suitable.
3. In cosmetics industries or in injectable drug production, this a proper method.

4. FDA and GRAS authorized coating shell development.

5. For specific drug designing with durable release properties.

6. For cost effective commercial drug manufacturing considering all the expense features of the drug market.

4. Applications in Drug Delivery System^{2,11,19,21,24–26}

Microcapsules, like other medication delivery systems, often help to improve the effectiveness of doses while minimizing possible side effects. Active pharmaceutical ingredient (API) encapsulation helps pharmaceutical firms to build release profiles that are most optimal for a particular therapeutic. Fast release formulas, prolonged release, targeted release, postponed release, etc. are examples.

Microencapsulation processing also requires flavor masking in chewable tablets as well as oral administration without water for bitter compounds.

4.1. Oral route

In conjunction with a sturdy matrix or enteric coating that delays API exposure to the digestive tract, microencapsulated APIs in tablets frequently achieve the required release profile. Tableting technologies for producers, as well as for customers, are proven, stable and inexpensive. In comparison, the intestinal epithelium has a gross surface area of approximately 200sq m, providing the APIs sufficient diffusion surface area. Microcapsules orally delivered are becoming more commoditized than parenteral technology and can generally be manufactured in larger volume batches as such but demands a lower price. Nevertheless, tablet comfort and resistance of injectables and other intrusive treatments generally allow oral distribution the form of option for delivery where necessary. A good candidate for pellets can be correctly formed microspheres.

CIPRO XR is a common example of an orally delivered microencapsulated medication. Bayer has advertised this medicine as an extended release pill once a day to manage urinary tract infections (UTIs). A bilayer matrix of active ingredients is used in this modern 24-hour formulation. Furthermore, with Ranbaxy Laboratories of India, Bayer jointly produced a once-daily formulation of CIPRO-OD.

4.2. Injectables

Injectable treatment has been complex and may stay in the blood for the necessary period of time with limited side effects. Microencapsulation facilitates fewer intense doses, longer-lasting medication half-lives, more advanced targeting of the site, and decreases toxicity. Many peptides and proteins are denatured by the rough environments in the intestine, leaving certain traditional oral distribution routes useless for biologics. Consequently, they must be

injected and they need any form of depot or prolonged release to achieve fair patient enforcement, which can already be achieved using current polymeric encapsulation technologies. The Southern Research Institute was the first to establish depot technologies to expand drug distribution (including Cyanamid microcapsule). Prostate cancer, endometriosis, and precocious puberty are treated with Lupron Depot. The added flexibility of the 4-month dosage form causes TAP pharmaceuticals to charge an extra 100 premium over four single dose forms.

4.3. Dermal route

Transdermal drug distribution has now been formulated to involve microencapsulated medications. However, skin is normally a difficult barrier for pharmaceutical molecules to penetrate, particularly those with high molecular weights, for dermal application.

There is so little active center particle size that it can be consumed by the naked skin. This is another disadvantage of the active agent's microencapsulated medication for transdermal authorization.

If the transdermal permit is very harmful to the skin, the side effect may be improved by the microencapsulation procedure.

An example of a microencapsulated dermal medication is Ortho Neutrogena's Retin-A, which is prescribed to treat extreme acne. The micro sponge technology developed by A.P is used by Retin-A Micro. Pharma to further expand the medication release profile and reduce skin discomfort.

4.4. Inhalation products

A variety of businesses especially for inhalable insulin, are engaged in pulmonary drug delivery. Owing to complications connected with cilia and particle residence duration concerns as excipients are chronically stored in the lungs for a prolonged span, the principle of continuous release in the lungs is especially troublesome. In addition, particle atomization does not necessarily involve microencapsulation.

Microencapsulation provides competitive advantages in the distribution of medicinal molecules, beyond increased efficiency. The output benefits of an NCE will contribute to the market displacement of less sophisticated incumbents. Reengineering with microencapsulation will manufacture different patented versions of a medication for established APIs, build a platform for another NDA, and offer additional patent security to fend off generic competition. In comparison, in commoditized generic markets in which substances are no longer patent secured, microencapsulation may offer a cost-effective means of value addition and product differentiation.

4.5. Multiparticulate delivery system

H.Steckel and F. Mindermann-Nogly used extrusion and spherizationmethode to develop chitosan pellets. Up to 70% concentration of cellulose microcrystal was applied as additive.

The ratio between liquid and water varies during the mixture of powder, water and acetic acid dilutes. production of 50% chitosan pellet mixing happens with demineralized water which act as granulating fluid.

Granulating phase requires 100% rise of chitosan mass fraction in the pallet with acetic acid dilution.

5. Recent Developments in Microencapsulation^{2-4,11,16,18,20,23-27}

Already established and yet to be improved methods are as follows:

1. A high electrostatic with high voltage for Novel microencapsulation of protein
2. Liposome by encapsulated amino glycosides
3. Advanced drug delivery system from microencapsulation method
 - i. *In vitro* release
 - a) Hydrophilic drug
 - i. Doxorubicin
 - ii. Cisplatin
 - iii. 5-Fluorouracil
 - b) Hydrophobic drugs
 - i. Taxol
 - ii. Comptothecin (CPT)
 - iii. *In vivo* release
4. Dispersion
5. Sol-Gel Technology
6. Novel Methods of Microparticulate Production
7. Formulation of Biodegradable Microcapsules
 - i. Calcium alginate microcapsules
 - ii. Chitosan microcapsules
 - iii. Albumin microcapsules
8. Response surface analysis results evaporation of emulsion
9. Novel system based on a poloxamer I PLGA blend as a tetanus toxoid delivery vehicle
10. Development of an oral sustained release delivery system
 - i. Preparation of matrices by direct compression
 - ii. Preparation of Matrices by wet granulation

The development of new microencapsulation technologies and the application of microcapsules are priorities sought globally by several research and development organizations. Technical flaws in existing capsules, unforeseen marketing challenges, and bad product design are concerns that have hindered previous attempts. The growing number of items using microcapsules shows that these problems are being

successfully tackled more and more.

6. Microcapsule Characterization:^{3,15,26}

Microcapsule is a significant technology by which a feasible protein, active agent or antigen medium can be developed. The characterization parameters are:

6.1. Particle size and shape

Scanning electron microscopy and conventional light microscopy is usually used for the morphology of microcapsule. Image quality in Scanning electron microscope is better than the conventional one. Microsphere surface, dual shell system can be visualized by SEM. Besides confocal laser scanning microscope explores the surface morphology and the inner particle image.

6.2. Fourier transform infrared spectroscopy (FTIR)

The polymer arrangement of the carrier and interaction between polymer and carrier can be explored by FTIR.

6.3. Determination of material density

From a pycnometer having multi volume the microcapsule density is measured. A precise weight measured sample cup is present in pycnometer. The chamber is free to be expanded by applied helium. The chamber pressure decreases if the expansion happens. The difference between these two pressures results the microcapsule density.

6.4. The isoelectric point

To determine the microsphere electrophoretic mobility a micro electrophoresis machine is used where we can find the isoelectric point.

Surface charge, ability to form ions, ion absorption behavior has a direct relation to electrophoretic mobility.

6.5. Efficiency of capture

The drug entrap percent is also known as efficiency of capture of microcapsule which is derived from washed microcapsule allowance to lyse. According to the monograph the lysate is obvious to measure from active constituents. The following equation explores about percent encapsulation efficiency.

$$\% \text{ Entrapment} = \frac{\text{Actual content}}{\text{Theoretical content}} \times 100$$

6.6. Contact angle

The angle of contact is measured to determine the wetting property of microcapsule. It determines the nature of microsphere in terms of hydrophilicity or hydrophobicity. The angle of contact is measured at the solid/air/water

surface by placing a droplet in circular cell mounted above the objective of inverted microscope. Contact angle is measured at 20°C within a minute of decomposition of microsphere.

6.7. Release studies for in-vitro operation

There is a need of varying pH situation. For example, for pH value of 1.2 and 7.4 from USP basket rotation or paddle mechanism release rate of the active core material is determined.

The dose is applied for fixed time period and a new medium replace the exact amount.

A monograph requirement and core material release rate are derived from the graphical expression of dose release vs operation time.

7. Mechanism and Kinetics of Drug Release^{24,26}

7.1. Release mechanisms from microspheres

There are four mechanisms of drug release from microspheres as following:

7.1.1. Degradation controlled monolithic system

The medication is dissolved and spread evenly in the matrix. The medication is tightly bound to the matrix and is extracted following matrix deterioration. In relation to the deterioration of the matrix, the diffusion of the substance is sluggish.

7.1.2. Monolithic system from controlled diffusion

The polymer decay is the determining factor for active core release by diffusion.

A homogeneous or heterogeneous decay process of polymer is also deciding factor for core agent release.

7.1.3. Reservoir system with controlled diffusion

A release-controlled film is used to cover the active material as a shell. Through the film the active element diffuses and afterwards the film eliminates when the delivery is finished. The matrix decay doesn't affect the active element release.

Erosion of the coat due to pH and enzymatic hydrolysis causes drug release when certain coating material like glyceryl mono stearate, beeswax and steryl alcohol etc are used.

7.2. Release Kinetics from Microspheres²⁴

Microencapsulation can be used to retard the drug release in the body. This may permit one to control the release of dose to substitute several doses of non-encapsulated drug and also may decrease the bad after effect of drug by controlling large concentration in blood at the initial stage. The active element release mechanism is significant here. In some condition the active element release rate remains

constant.

At the time of drug administration, the amount of drug release remains constant per unit time for a fix efficiency and target. The solid reservoir and dissolved drug are the deciding factor for microcapsule. The release rate remains constant at the initial stage and over time the release rate decreases till the end of the active core. The active element is fix in amount in the microcapsule. There is a concentration difference between the inside and outside region of the capsule. The diffusion process eliminates the difference.

Many investigators have regarded the analytic modeling of drug release as unjustifiably complex and have used more empirical techniques for data analysis. This approach varies from those which provide useful data about the system dynamics to those which one is convinced have been adopted simply to minimize the size of error bars in a graph. Probably the most useful of the former group is the diffusional exponent approach described by Peppas and colleagues, which goes some way to explaining the behavior of hydrating or eroding systems. In such systems, the diffusion coefficient is not constant, and the term anomalous diffusion is often used to indicate that a constant value of the diffusion coefficient does not satisfactorily fit the data. The terms Fickian and non-Fickian are also used to indicate whether or not a material is diffusing with a temporally and especially constant diffusion coefficient; these are somewhat misleading, since, at a particular instant and point in space, diffusion always occurs according to Fick's law. The diffusional exponent method proposes a power law relationship for drug release:

$$\frac{M_1}{M_0} = kt^n$$

The constant n is called the diffusional exponent, and for diffusional (Fickian) release from a planar slab, it should equal 0.5. Values greater than 0.5 suggest anomalous diffusion and are normally representative of a structure that swells until diffusional release. Model study and compared with the precise solutions reveals that n is equivalent to 0.5 for a flat slab and 0.432 for a sphere. However, the n value is 0.45 for swellable spheres. Since simple diffusive release from spheres is often sufficiently equipped when n = 0.5, it is obvious that this method needs correct data to enable a useful value for n to be derived. A corollary of this is that before they can be used to differentiate between the different pathways of opioid release, all of the experimental methods in the literature need refinement.

The definition of release as a biexponential approach is one of the more traditional empirical relationships:

$$\frac{M_1}{M_0} = 1 - [A \exp(-k_1 t) + B \exp(-k_2 t)]$$

The rate constants of the two lifetime components onto which the decay function is decomposed are k₁ and k₂. "The exponentials usually consist of a quick and a slow function, respectively termed as "burst phase" and "sustained release.

8. Conclusion

Microencapsulation technology is very promising to open a new era of drug delivery approach. This approach can alleviate the limitations of dose dumping, multiple dose inconvenience, kidney disease and so on. Drug specific microencapsulation procedures are required to establish suitable method of drug delivery.

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None.

10. Conflict of Interest

The authors declare no conflict of interest.

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