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REVIEW ARTICLE

AN REVIEW OF MICROENCAPSULATION AS NOVEL DRUG DELIVERY

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Abstract:
Microencapsulation products (micro particles) can be defined as small entities that contain an active agent or core material surrounded by a shell or embedded into a matrix structure. Most Microparticle shells or matrices are organic polymers, but lipids and waxes are also used. It is generally accepted that microencapsulation products (micro particles) are larger than 1 micrometer in diameter and can be up to 1000 micrometers. Sustained drug release drug delivery system significantly improve therapeutic efficacy of a drug. Drug release retarding polymers are the key performer in such system. Much of the development in SR drug delivery system is focusing in the preparation and use of polymers with specificity designed macroscopic and microscopic structural and chemical features. Microcapsules continue to be of much interest in controlled release based partly on relative ease of design and formulation and partly on the advantages of micro particulate delivery systems. The latter include sustained release from each individual microcapsule and offer greater uniformity and reproducibility.

Keywords: Microencapsulation, Microcapsule, Sustained release, Controlled release.

Introduction

Microencapsulation is one of the most interesting fields in the area of pharmaceutical technology since its inception many years ago. It is an interdisciplinary field that requires knowledge of polymer science and familiarity with emulsion technology. Starting first as an art than a science, nowadays the topic of microencapsulation is extensively studied inside major pharmaceutical companies and universities as well as research institutes. Polymeric drug delivery devices are focusing on the encapsulation of large molecules, e.g., peptides, proteins, and DNA/RNA for potential use as vaccines or as long-acting release drug formulations. Importantly, some of these initiatives led to important pharmaceutical products and most of them are still on the market (e.g., Lupron Depot®, Zoladex®,Decapeptyl®, Eligard®, Enantone®, Trenantone®, Nutropin Depot®, and Profact®) [1]. In addition, encapsulation for controlling the release of highly water soluble drugs received much attention.

Microencapsulation products (microparticles) can be defined as small entities that contain an active agent or core material surrounded by a shell or embedded into a matrix structure. Most Microparticle shells or matrices are organic polymers, but lipids and waxes are also used. It is generally accepted that microencapsulation products (microparticles) are larger than 1 micrometer in diameter and can be up to 1000 micrometers. Commercial microparticles have a diameter 3 and 800 micrometers and contain 10-90% w/w core. A wide range of core materials has been encapsulated, including adhesives, agrochemicals, live cells, active enzymes, flavors, fragrances, pharmaceuticals and ink. Morphologically, two general structures exist: microcapsules and microspheres. A microcapsule is a reservoir-type system with regular or irregular shapes that contains a well defined core and envelope. The core can be solid, liquid, or gas; the envelope is made of a continuous, porous or nonporous, polymeric phase created by one or more polymers. Alternatively, a microsphere is a homogeneous or monolithic structure made of a continuous phase of one or more miscible polymers in which particulate drug is dispersed throughout the matrix, at either the macroscopic (particulates) or molecular (dissolution) level. However, the difference between the two systems-microcapsules and microspheres- is the nature of the microsphere matrix, in which no well-defined wall or envelope exists. [2-4]

Sustained drug release drug delivery system significantly improve therapeutic efficacy of a drug. Drug release retarding polymers are the key performer in such system. Much of the development in SR drug delivery system is focusing in the preparation and use of polymers with specificity designed macroscopic and microscopic structural and chemical features. Number of

natural, semi synthetic and synthetic polymer material are used in the controlled delivery of drugs. recent trends towards the use of vegetable and nontoxic products demands the replacement of synthetic additives with natural one1. Past research therefore studied and acknowledged various natural gum like agar, guar gum, chatoyant, xanthium, sodium alginate, and lotus bean gum etc. for potential pharmaceutical and bio medical application.

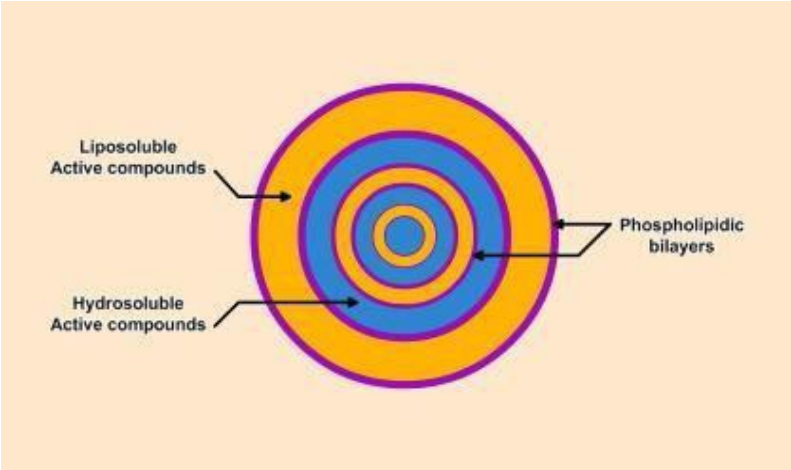
During the past decades, there has been an increasing interest in optimizing the efficiency of existing drugs through the use of better-designed drug delivery systems. Intensive interdisciplinary research efforts have led to a variety of advanced dosage forms. The majority of these systems are based on polymers that differ in their permeability, rate of dissolution, degree of swelling and erodibility [5]. An important class of polymer mediated drug delivery systems that are applied for controlled drug delivery is the microcapsules. Microencap-sulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and controlling release characteristics or availability of coated materials [6]. The recent research has been heavily involved particularly on how the distribution of release controlling parameters among the individual microcapsules of the batch alters the release profile. Microcapsules according to the French Pharmacopoeia are solid material consisting of a solid envelope containing a liquid or solid or a pasty substance. The microcapsules occur in the form of powder with particles less than 1250 μm in diameter.

The scanning electron microscopy (SEM) has revealed the structural features of microcapsules as to be varying and complex. The walled prototype may be mononuclear as shown in Figure 1(a) or may have multiple core structure [7]. Also double or multiple concentric coating may be present [8]. Aggregated microcapsules greatly vary in size and shape [Fig. 1(b)] and may also posses additional external wall. The perfect microcapsules are obtainable by using the liquid cores or forming the microcapsules as a liquid dispersed phase prior to the solidification [9]. Although microstructure of both membrane and interior can be detected by SEM of surfaces or sections [Fig. 1(c)], their physical quality is difficult to characterize quantitatively in microcapsules involving measurements of porosity, tortuousity and crystallinity, though some of progress has been made and efforts are continuing to calculate permeability and porosity from release data, dimensions, densities, and core/wall ratios [10]. The effect of size and shape distribution has only been studied recently [11]

The standard pharmaceutical dosage forms are employed, such as hard gelatin capsules, which also may be enteric coated, soft gelatin capsules, or suspensions in liquids, all of which allow dispersion of individual microcapsules on release.

There has been some recent interest in tableted microcapsules, which will however, only restore the original microcapsules if suitably formulated to undergo complete disintegration. Several publications deals with non-disintegrating tablets, intended to extend release time particularly of soluble drugs and in fact doing so, but to greatly varying extent.[12-13] The release is affected by many factors (excipients, compaction pressure, and usual tableting factors). The advantage of using costlier microcapsules as opposed to conventional mixtures of drug and polymer in sustained release matrix type tablets is no means clear, except when microencapsulation offer additional benefits.

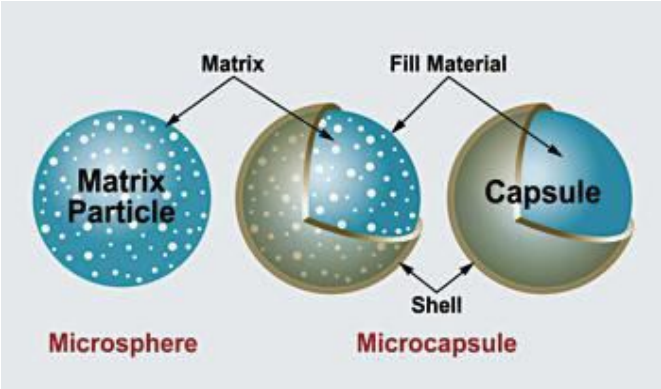
Microcapsules continue to be of much interest in controlled release based partly on relative ease of design and formulation and partly on the advantages of micro particulate delivery systems. The latter include sustained release from each individual microcapsule and offer greater uniformity and reproducibility. Additional advantage over monolithic systems containing multiple doses is the greater safety factor in case of a burst or defective individual in subdivided dosage form. Finally, it has been argued that multiple particle systems are distributed over a great length of gastrointestinal tract, which should result in, (a) lowered local concentrations and hence toxicity or irritancy, and (b) reduced variability in transit time and absorption rate [12].



MICROENCAPSULATION PROCESS

- This technique can be used for converting liquid drugs in a free flowing powder.
- The drugs, which are sensitive to oxygen, moisture or light, can be stabilized by microencapsulation.
- Incompatibility among the drugs can be prevented by microencapsulation.
- Vaporization of many volatile drugs e.g. methyl salicylate and peppermint oil can be prevented by microencapsulation.

- Many drugs have been microencapsulated to reduce toxicity and GI irritation including ferrous sulphate and KCl.
- Alteration in site of absorption can also be achieved by microencapsulation.
- Toxic chemicals such as insecticides may be microencapsulated to reduce the possibility of sensitization of factorial person.
- Bakan and Anderson reported that microencapsulated vitamin A palmitate had enhanced stability



MICROSPEHERE AND MICROCAPSULE

Reasons for Microencapsulation

- The main reason for microencapsulation is for sustained or prolonged relaease of the drug.
- This technique has been widely used for masking the organoleptic properties like taste and odor of many drugs and thus improves patient compliances eg paracetamol, nitrofurantoine for masking the bitter taste.
- By using microencapsulation technique the liquid drugs can be converted in a free flowing powder.
- The drug can be protected by microencapsulation which is sensitive to moisture and oxygen, such as nifidipine is protected from photo instability.
- Microencapsulation techniques also helpful to prevent the incompatibility between drugs.
- The drug which are volatile in nature may vaporize at room temperature like aspirin and peppermint oil can be prevented by microencapsulation.
- Reduction in toxicity and GI irritation including with KCL and ferrous sulphate can be achieved by microencapsulation.

- Microencapsulation has also been employed to change the site of absorption. This application has been used for the those drugs which have toxicity at lower pH.
- Bakan and Anderson were reported that microencapsulated vitamin A palmitate had enhanced stability, as prevent from oxidation.
- Microencapsulation method has also been employed to prepare intrauterine contraceptive devices.[14]

Fundamental considerations

The realization of the potential that microencapsulation offers involves a basic understanding of the general properties of microcapsules, such as the nature of the core and coating materials, the stability and release characteristics of the coated materials and the microencapsulation methods [15, 16].

Release mechanisms

Mechanisms of drug release from microspheres are

1. Degradation controlled monolithic system

The drug is dissolved in matrix and is distributed uniformly throughout. The drug is strongly attached to the matrix and is released on degradation of the matrix. The diffusion of the drug is slow as compared with degradation of the matrix.

2. Diffusion controlled monolithic system

Here the active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Rate of release also depend upon where the polymer degrades by homogeneous or heterogeneous mechanism.

3. Diffusion controlled reservoir system

Here the active agent is encapsulated by a rate controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix.

4. Erosion: Erosion of the coat due to pH and enzymatic hydrolysis causes drug release with certain coat material like glyceryl mono stearate, beeswax and steryl alcohol etc. [17-19]

2.0 TECHNIQUES TO MANUFACTURE MICROCAPSULES

2.1 Physical methods

1) **Pan coating**

The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly. The problem of bitter and

obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. In order to ensure patient compliance bitterness masking becomes essential. Molecule interacts with taste receptor on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva.

2) **Multiple Emulsions**

A novel technique for taste masking of drugs employing multiple emulsions has been prepared by dissolving drug in the inner aqueous phase of w/o/w emulsion under conditions of good shelf stability. The formulation is designed to release the drug through the oil phase in the presence of gastrointestinal fluid. [20,21]

3) **Prodrugs**

A prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent drug. Examples of drug with improved taste are given below.2

Table no.1: Prodrugs with improved taste

Sr. no.	Parent drug	Prodrug with improved taste
1	Chloramphenicol	Palmitate ester
2	Clindamycin	Palmitate ester
3	Triamcinolone	Diacetate ester

4) **Mass extrusion method (Dispersion coating)**

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste. [23]

5) **Air-suspension coating**

Microencapsulation by air suspension techniques is generally ascribed to the inventions of Professor Dale E. Wurster, basically the Wurster process consists of the dispersing of solid,

particulate core materials in a supporting air stream and the spray coating of the air suspended particles.

6) **Coacervation-Phase separation**

Microencapsulation by coacervation-phase separation process consists of three steps carried out under continuous agitation;

1) Formation of three immiscible chemical phases

2) Deposition of coating

3) Rigidization of coating

Step 1 of the process is the formation of three immiscible chemical phases; a liquid manufacturing vehicle phase, a core material phase and a coating material phase. To form the three phases, the core material is dispersed in a solution of the coating polymer, the solvent for the polymer being the liquid manufacturing vehicle phase.

Step 2 of the process consists of depositing the liquid polymer coating upon the core material. This is accomplished by controlled, physical mixing of the coating material and the core material in the manufacturing vehicle. Deposition of the liquid polymer coating around the core material occurs if the polymer is absorbed at the interface formed between the core material and the liquid vehicle phase, and this adsorption phenomenon is a prerequisite to the effective coating.

Step 3 of the process involves rigidizing the coating, usually by thermal, cross linking, or desolvation techniques to form a self sustaining microcapsule.[24]

7) Solvent Evaporation

This technique has been used to produce the microcapsules. The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated (if necessary) to evaporate the solvent for the polymer. In the case in which the core material is dissolved in the coating polymer solution, a matrix-type microcapsule is formed. Once all the solvent for the polymer is

evaporated, the liquid vehicle temperature is reduced to ambient temperature with continued agitation. At this stage the microcapsules can be used in suspension form, coated on to substrates or isolated as powders.[24]

8) Polymerization

A relatively new microencapsulation method utilizes polymerization technique to form protective microcapsules coating in situ. The method involves the reaction of monomeric units located at the interface existing between a core material substance and a continuous phase in which the core material is dispersed. The continuous or core material supporting phase is usually a liquid or gas and therefore the polymerization reactions occurs at a liquid-liquid, liquid-gas, solid-liquid, or solid gas interphase .

In Interfacial polymerization, the two reactants in a polycondensation meet at an interface and react rapidly. The basis of this method is the classical Schotten-Baumann reaction between an acid chloride and a compound containing an active hydrogen atom, such as an amine or alcohol, polyesters, polyurea, polyurethane. Under the right conditions, thin flexible walls form rapidly at the interface. A solution of the pesticide and a diacid chloride are emulsified in water and an aqueous solution containing an amine and a polyfunctional isocyanate is added. Base is present to neutralize the acid formed during the reaction. Condensed polymer walls form instantaneously at the interface of the emulsion droplets.

9) In-situ polymerization

In a few microencapsulation processes, the direct polymerization of a single monomer is carried out on the particle surface. In one process, e.g. Cellulose fibers are encapsulated in polyethylene while immersed in dry toluene. Usual deposition rates are about 0.5μm/min. Coating thickness ranges 0.2–75 μm (0.0079–2.95 mils). The coating is uniform, even over sharp projections.

Research Envisaged

1. **Wasfy M. Obedat et. al.** has suggested that Several methods and techniques are potentially useful for the preparation of polymeric microparticles in the broad field of microencapsulation. The preparation method determines the type and the size of microparticle and influence the ability of the interaction among the components used in microparticle formulations. This review is devoted to describe and allocate the recently awarded and pending patents regarding the technical and formulation innovations in

microparticles involved in drug delivery that are based mainly on the emulsion solvent removal methods. The term microparticle designates systems larger than one micrometer in diameter and is used usually to describe both microcapsules and microspheres. Microparticles-containing drugs are employed for various purposes including but not restricted to- controlled drug delivery, masking the taste and odor of drugs, protection of the drugs from degradation, and protection of the body from the toxic effects of the drugs. Polymeric carriers being essentially multidisciplinary are commonly utilized in microparticle fabrication and they can be of an erodible or a non-erodible type. [25]

2. Umer Hammad et al suggested that Microencapsulation is a process in which tiny particles or a coating to give small capsules with many useful properties surrounds droplets. 'Small is better' would be an appropriate motto for the many people studying microencapsulation. In its simplest form, a microcapsule is a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. Most microcapsules have diameters between a few micrometers and a few millimeters. The reasons for microencapsulation are countless. Microencapsulation system offers potential advantages over conventional drug delivery systems and also established as unique carrier systems for many pharmaceuticals. Although significant advances have been made in the field of microencapsulation, still many challenges need to be rectified during the appropriate selection of core materials, coating materials and process techniques.[26]

3. Malkaar Jadupati et al. suggested that Microencapsulation is a process in which tiny particles or a coating to give small capsules with many useful properties surrounds droplets. 'Small is better' would be an appropriate motto for the many people studying microencapsulation. In its simplest form, a microcapsule is a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. Most microcapsules have diameters between a few micrometers and a few millimeters. The reasons for microencapsulation are countless. Microencapsulation system offers potential advantages over conventional drug delivery systems and also established as unique carrier systems for many pharmaceuticals. Although significant advances have been made in the field of microencapsulation, still many challenges need to be rectified during the appropriate selection of core materials, coating materials and process techniques.[27]

4. Agnihotri N et. al. suggested that The review of Microencapsulation is a well-

established dedicated to the preparation, properties and uses of individually encapsulated novel small particles, as well as significant improvements to tried-and-tested techniques relevant to micro and nano particles and their use in a wide variety of industrial, engineering, pharmaceutical, biotechnology and research applications. Its scope extends beyond conventional microcapsules to all other small particulate systems such as self-assembling structures that involve preparative manipulation. The review covers encapsulation materials, physics of release through the capsule wall and /or desorption from carrier, techniques of preparation, many uses to which microcapsules are put.[28]

5. Tiwari S et. al. suggested that Micro-encapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules many useful properties. In a relatively simplistic form, a microcapsule is a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. Most microcapsules have diameters between a few micrometers and a few millimeters. The reasons for microencapsulation are countless. In some cases, the core must be isolated from its surroundings, as in isolating vitamins from the deteriorating effects of oxygen, retarding evaporation of a volatile core, improving the handling properties of a sticky material, or isolating a reactive core from chemical attack. In other cases, the objective is not to isolate the core completely but to control the rate at which it leaves the microcapsule, as in the controlled release of drugs or pesticides. The problem may be as simple as masking the taste or odor of the core, or as complex as increasing the selectivity of an adsorption or extraction process.[29]

Application of microcapsules

The application of microencapsulation is numerous. The ones mentioned below are some of the most common ones

- Carbon less papers
- Scratch-n-sniff
- Flavors and essences
- Pesticides and herbicides
- Pharmaceuticals

- Textiles
- Adhesives
- Visual indicators
- Thermochromic dyes
- Phase change materials
- temperature release (controlled release)

Medical application[17]

- Release of proteins, hormones and peptides over extended period of time.
- Gene therapy with DNA plasmids and also delivery of insulin.
- Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra-arterial/ intravenous application.
- Tumour targeting with doxorubicin and also treatments of leishmaniasis.
- Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
- Used in isolation of antibodies, cell separation, and toxin extraction by affinity chromatography.
- Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal. Radioactive microsphere's application[18]
- Can be used for radioembolisation of liver and spleen tumours.
- Used for radiosynvectomy of arthiritis joint, local radiotherapy, interactivity treatement.
- Imaging of liver, spleen, bone marrow, lung etc and even imaging of thrombus in deep vein thrombosis can be done.

Other applications

- Fluorescent microspheres can be used for membrane based technologies for flow cytomettry, cell biology, microbiology, Fluorescent Linked Immuno-Sorbent Assay.
- Yttrium 90 can be used for primary treatment of hepatocellular carcinoma and also used for pre-transplant management of HCC with promising results.

REFERENCES

1. Christian W, Steven PS. Principles of encapsulating hydrophobic drugs in PLA/PLGA microparticles. Int J Pharm 2008; 364: 298- 327.
2. Simon B, Eds. Microencapsulation: Methods and industrial applications, 2nd ed. Drugs Pharmaceut Sci Marcel Dekker, Inc. N.Y. 2006; 158: 1-55.
3. Kondo A. Microcapsule processing and technology. Van Valkenburg JW. Ed. Marcel Dekker, Inc N.Y. 1979; 106-120.
4. Kreitz M, Brannon-Peppas L, Mathiowitz E, Eds. Microencapsulation. Encyclopedia of controlled drug delivery. John Wiley Sons, Inc. 1999; 493-553.
5. KHAN, G. M. Controlled release oral dosage forms: Some recent advances in matrix type drug delivery systems, *The Science*, 2001, 1: 350–354.
6. BAKAN, J. A. Microencapsulation. IN: LIBERMAN, H. A. *et al*. (Eds.). *The Theory and Practice of Industrial Pharmacy*, 3rd edition, pp.1986. 142–429 (Philadelphia, New York: Lee & Febiger).
7. JEGAT, C. & TAVERDET, J. L. Stirring speed influence study on microencapsulation process and the drug release from microcapsules, *Polymer Bulletin, 2000,*44: 345–351.
8. Benita, s. & donbrow, m. Controlled drug delivery through microencap-sulation, *journal of pharmaceutical sciences*, 1983, 71: 205–210.
9. Thies, c. & bissery, m. C. *Biomedical applications of microencapsulation*, pp.1983, 53–74 (florida: crc press inc.).
10. Reis, m. A. A., sinisterra, r. D. & belchior, j. D. an alternative approach based on artificial neural networks to study controlled drug release, *journal of pharmaceutical sciences*, 2004,93: 418–430.
11. Berkland, c., kipper, m. J., narasimhan, b., kim, k. Y. & pack, d. W. microsphere size, Precipitation kinetics and drug distribution control drug release from biodegradable polyanhydride microspheres, *journal of controlled release*, 2004,94: 129–141.
12. Davis, s. S., hardy, j. G., taylor, m. J., whalley, d. R. & wilson, c. G. A comparative study of the gastrointestinal transit of a pallet and tablet formulation, *international journal of pharmaceutics, 1984,* 21: 167–177.
13. Farid, d. J. & nokhodchi, a. dissolution of compacted aspirin microcapsules, *indian journal of pharmaceutical sciences*, 1991: 5: 222–223.
14. James S: Encyclopedia of Pharmaceutical Technology .Third Edition, 1325-1333.

15. Berger HL. Ultrasonic Liquid Atomization. 1St edition Hyde Park, NY: Partridge Hill Publishers; 1998.
16. Blanco MD and Alonso MJ. Development and characterization of protein-loaded poly (lactideco-glycolide) nanospheres. Eur J Pharm Biopharm, 1997, 43:287-294.
17. Brazel SC, Peppas NA. Modeling of drug release from swellable polymers. Eur J Pharm Biopharm, 2000, 49: 47–48.
18. Benita S, Donbrow M. Controlled drug delivery through microencapsulation, J. Pharm Sci, 1982, 71: 205–210
19. Cassidy, JP, Landcert NM, Quardos E. Controlled buccal delivery of buprenorphine. J.control .Rel, 1993, 25: 21-29.
20. Lachman, L.; " Theory and practice of Industrial pharmacy"; Third Edition, 1986
21. Rao, M.Y.and Bader,F., " Masking the Taste of Chloroquine by Multiple Emulsion," The East. Pharm, 1993, 123, (11).
22. Manek, S.P.; Kamat, V.S.; Indian Journal of Pharmaceutical Science; 1981, 43, 209-212.
23. Kasturagi, Y., Sugiura, Y.C., Lee, K., Otsugi, and Kurihara, "Selective Inhibition of Bitter Taste of Various Drugs by Lipoprotein." Pharm. Res., 1995, 12,5, 658-662.
24. Hafeli U, 2002, Physics and Chemistry Basic of Biotechnology. Focus on biotechnology. Review. Radioactive Microspheres for Medical Application, 7:213-248.
25. Wasfy M. Obeidat "recent patents review in microencapsulation og the emulsion solvent removal method" recent patetn on drug delivery and formulation, 2009, 3, 178-182.
26. Hammad Umer, Hemlata Nigam, Asif M Tamboli, M.Sundar Moorthi Nainar, "Microencapsulation: process, Technique and Application " International journal of research in pharmaceutical and biomedical sciences; 2011, 2(2), 474-481.
27. Malkar Jadupati, das tanmay and Ghatak Souvik " Microencapsulation: An Indispensable technology for Drug delivery system" international research journal of pharmacy: 2012: 3 (4) : 8-13.
28. Nikita Agnihotri, Ravinesh Mishra, Chirag Goada "Microencapsulation – A novel approach in drug delivery": indo global journal of pharmaceutical sciences, 2012: 2(1); 1-20.
29. Sunderlal Tiwari, Achrish goel, Keshri Kishore Jha, Akhil Sharma, " Microencapsulation technique and its application" The pharma Research, 2010: 3; 112-116.