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Review Article

Recent trends in microencapsulation: A review

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ABSTRACT

Microcapsules are tiny capsules containing materials (such as adhesive or a medicine) that are released when the capsule is broken, melted or dissolved. The process of forming microcapsules is called microencapsulation. By the process of microencapsulation an active ingredient of interest can be isolated and kept unmodified for extended periods of time and be released(or not) upon a change of the surrounding environmental conditions to target specific needs. Various techniques of microencapsulation have been developed which have wide applications in various fields like pharmaceutics, biotechnology, agrochemical, food industries, cosmetics etc. This article is a review of microencapsulation, materials used in it, morphology of microcapsules, reasons for microencapsulation, new advanced techniques used in microencapsulation (their advantages and disadvantages), drugs incorporated in microcapsules and applications of microcapsules.

Keywords: Core material, Coating material, Microcapsules, Microencapsulation, Micromeritic wall, Polymers, Sustained release.

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INTRODUCTION

Microencapsulation is a rapidly expanding technology, it is a process of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions, which isolate and protects them from the external environment as well as control the drug profile (33). Microcapsules have a number of benefits such as converting liquids to solids (of altering colloidal and surface properties), separating reactive compounds, providing environmental protection, improved material handling properties (Banker GS and Rhodes CT, 2002). Microcapsules usually have a particle size range in between 1-2000µm. The uniqueness of microencapsulation is the smallness of the coated particles and their subsequent use and adaptation to a wide variety of dosage forms and product applications. Because of the smallness of the particles, drug moieties can be widely distributed throughout the gastrointestinal tract, thus potentially improving drug sorption. The word "Capsules" implies a core and shell structure and the term "microcapsules" states the membrane enclosed particles or droplets dispersed in solid matrix.

Microcapsules have diameters between 3-800 µm and contain 10-90 wt. % core. (Benita Simon *et al*., 2014) A wide range of core materials have been encapsulated including: Agrochemicals, Active enzymes, Flavours, Fragrances, Pharmaceuticals, Adhesives, Live cells etc. Most capsule shell materials are organic polymers, but fat and waxes are also used. Microcapsules can have a variety of structures. Some have a spherical geometry with a continuous core region surrounded by a continuous shell. Others have an irregular geometry and contain a number of small droplets or particles of core material.

The first research leading to the development of microencapsulation procedures for pharmaceuticals was published by Bungenburg de jong and kaas in 1931 (Deasy Patrick B., 2007) which dealt with the preparation of gelatin spheres and the use of a gelatin coacervation process for coating. Processes and materials used for coating developed by the pharmaceutical industry to aid in formulation of various dosage forms such as tablets, capsules, injectable, powders and topical.

The recent research results of pharmaceutical research reveal that the absorption rate of a drug can be controlled by controlling its rate of release from the dosage form and this can be achieved by developing the new drug entities, discovering the new polymeric materials that are suitable for prolonging the drug release and improvement in therapeutic efficacy. Microencapsulation can be used to enclose solids, liquids or gases inside a micromeritic wall made of hard or soft soluble film, in order to reduce dosing frequency and prevent the degradation of pharmaceuticals. 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. (Fig. 1)

The technique used for microencapsulation depends on the physical and chemical properties of the material to be encapsulated.

Core Material: The material to be coated

- Liquid or solid
- Liquid core can be dispersed or dissolved material.
- Solid core can be a mixture of active constituents, stabilizers, diluents, excipients' etc.

Coating Material: Inert substance which coats on core with desired thickness

- Chemically compatible with the core material
- Stabilization of core material.
- Inert toward active ingredients.
- Controlled release under specific conditions.
- The coating can be flexible, brittle, impermeable, hard, thin etc.
- Provide desired coating properties such as cohesiveness, permeability, sorption, solubility, clarity, stability etc.
- Abundantly and cheaply available

Composition of coating

- Inert polymer
- Plasticizer
- Colouring agent

E.g. Coating materials

- **Gums:** Gum arabic, sodium alginate, carrageenan
- **Carbohydrates:** Starch, dextran, sucrose
- **Celluloses:** Carboxymethylcellulose, methylcellulose, ethylcellulose.
- **Lipids:** Bees wax, stearic acid, phospholipids.
- **Proteins:** Gelatin, albumin.

MORPHOLOGY OF MICROCAPSULES

The morphology of microcapsules depends mainly on the core material and the deposition process of the shell. (Fig:2).

Mononuclear (core-shell) microcapsules contain the shell around the core.
Polynuclear capsules have many cores enclosed within the shell.
Matrix encapsulation in which the core material is distributed homogeneously into the shell material.

Microcapsules can also be mononuclear with multiple shells, or they may form clusters of microcapsules.

REASONS FOR MICROENCAPSULATION

The reasons for microencapsulation is for sustained or prolonged release of the drug are:

1) Masking the organoleptic properties like taste and odor of many drugs and thus improves patient compliance.
2) Liquid drugs can be converted in a free flowing powder.
3) Protect drugs sensitive to moisture, light and oxygen.
4) The drugs which are volatile in nature may vapourize at room temperature, they can be prevented by microencapsulation.
5) Reduction in toxicity and gastrointestinal irritation can be achieved by microencapsulation.
6) It change the site of absorption which is useful for those drugs which have toxicity at lower pH.

Mechanism of drug release

Major mechanism of drug release from microcapsules include diffusion, dissolution, osmosis and erosion.

1) Diffusion- In this diffusion fluid penetrates the shell, dissolves the core and leak out through the interstitial channels.

2) Dissolution- Dissolution rate of polymer coat determines the release rate of drug from the microcapsule when the coat is soluble in the dissolution fluid.

3) Osmosis- The polymer coat of microcapsule act as semipermeable membrane and allows the creation of an osmotic pressure difference between the inside and the outside of the microcapsule and drives drug solution out of the microcapsule through small pore in the coat.

4) Erosion- Erosion of coat due to pH/or enzymatic hydrolysis causes drug release with certain coat materials.

ADVANTAGES

- Enhanced bioavailability of entrapped bioactive compounds.
- Improve patient's compliance
- Controlled/or targeted release of incorporated drug.
- Reduce the reactivity of the core in relation to the outside environment.
- Decrease evaporation rate of the core material.
- Convert liquid to solid form and to mask the core taste.
- Improved stability of pharmaceuticals.
- Better control over release kinetics of encapsulated compounds.

SHORTCOMINGS

- Difficult to get continuous and uniform film on each and every particle.
- A lot of study and research needs to be carried out to select the right coating material and the appropriate technique of manufacture so that microparticles of appropriate properties and dimensions can be achieved.
- Costly process not economical.

MICROENCAPSULATION FORMULATIONS

The microencapsulated drug or ingredient can be used to form different types of formulation-

- Tablets
- Capsules
- Lotion
- Dry powder
- Parenteral
- Suspensions
- Emulsions

TECHNIQUES OF MICROENCAPSULATION

Air-suspension: The air suspension coating process was invented by Professor Dale E .Wurster [31] at the Department of Pharmacy, University of Wisconsin. Air suspension apparatus consists of different sections such as control panel, coating chamber, air distribution plate, nozzle for applying film coatings. Within the coating chamber of air suspension apparatus, particles are suspended on a upward moving air stream. In the coating zone, coating materials is applied by spraying to the moving core particles. The core material receives an increment of coating material, usually a polymer solution during each pass through the coating zone. The cyclic process is repeated until desired coating thickness is achieved.

Coacervation-phase separation: This process consists of three steps (Fig 3) carried out under continuous agitation [17]:

1) *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.

2) *Deposition of coating*: core material is dispersed in the coating polymer solution. Coating polymer material coated around core. Deposition of liquid polymer coating around core by polymer adsorbed at the interface formed between core material and vehicle phase.

3) *Rigidization of coating*: coating material is immiscible in vehicle phase and is made rigid by thermal, Cross-linking or dissolution techniques.

Multiorifice-centrifugal process: It is a mechanical process for producing microcapsules that utilizes centrifugal forces to hurl, a core material particle through an enveloping microencapsulation membrane [27]. The device has a rotating cylinder which has three circumferential grooves. Processing variables include the rotational speed of cylinder, the flow rate of core and coating materials, the concentration and viscosity of the coating material and the viscosity and surface tension of the core material (Fig 4).

Pan coating: The pan coating process, widely used in the pharmaceutical industries, is among the oldest industrial procedure for forming small, coated particles or tablets [34]. The particles are tumbled in a pan or other device while the coating material is applied slowly to the desired core material in the coating pan. Solid particles greater than 600 microns in size are considered essential for effective coating and the process has been extensively employed for the preparation of controlled-release beads [21].

Solvent evaporation: Solvent evaporation process is carried out in liquid manufacturing vehicle. Polymers are dissolved in volatile organic solvent with low water miscibility like acetone, dichloromethane (DCM) or chloroform. The drugs are then dissolved or dispersed in the polymer solution .With continuous agitation this mixture is then emulsified in a large volume of an aqueous phase containing tensioactive molecules such as magnesium stearate, span 80 to obtain tiny capsules with desired size dispersed in water phase-oil in water (o/w) emulsion. The emulsion is next subjected to solvent removal by evaporation in order to generate microcapsules. These particles are washed, collected by filtration and finally dried or lyophilized to provide free-flowing injectable microcapsules (Fig:6) Solvent evaporation is most widely employed and investigated technique in pharmaceutical industries and research area for microencapsulation process. [28].

Spray drying and Spray congealing: The main difference between the two methods is by is the method of solidification of coating.

In the case of spray drying, the coating solidification is effected by rapid evaporation of solvent in which the coating material is dissolved.

The equipment components of a standard spray dryer include:

1. Air heater
2. Atomizer
3. Spray chamber
4. Blower or Fan
5. Cyclone and
6. Product collector

In spray congealing method, the solidification of coating is by thermally or by solidifying the dissolved coating by introducing the core material mixture into a non-solvent. Removal of the non-solvent from the coated product is then accomplished by sorption, evaporation or extraction techniques.

Polymerization: It is a new method of microencapsulation to form protective microcapsule coatings in situ. Microencapsulation by polymerization involves reaction between a core material and continuous phase in which the core material is dispersed. In polymerization, a liquid or gaseous phase is used as continuous phase or core material and as a result the polymerization reaction occurs at a liquid-liquid, solid-liquid, liquid-gas or solid-gas interface [22].

Single and double emulsification techniques: Single emulsion technique- The single emulsion technique using o/w emulsion solvent evaporation method is the oldest and the most commonly used technique for microencapsulation. In this method, the drug is either dispersed or dissolved in the polymer/solvent system. Then it is added to the aqueous phase by continuous agitation. Agitation of the system is continued until the solvent partitions into the aqueous phase and is removed by evaporation [32].

Double emulsion technique W/O/W is one of the most commonly used technique for the encapsulation of the hydrophilic drugs. The process begins with the use of volatile organic solvent to dissolve the polymer.

The drug aqueous solution is dispersed in the polymer solution to form a w/o emulsion. Finally, a w/o/w double emulsion is produced by dispersing the w/o emulsion in water through mechanical mixing. Removal of the organic solvent by evaporation results in the formation of microcapsules [31].

Polymer-polymer interaction: The interaction of oppositely charged polyelectrolytes in dilute solution region can result in the formation of a complex having such reduced solubility that phase separation occurs (Leon L *et al*, 2013).

Sol-gel encapsulation: Sol-gel encapsulation (R. Ciriminna et *al*, 2011) allows trapping lipophilic components inside the spherical shell of amorphous silicon dioxide. The process can be run, for example, in the oil-in-water (O/W) emulsion with an active material solubilized in the silicon phases such as tetraethoxysilane or tetramethoxysilane. Hydrolysis of the silicon droplets and condensation

of hydrolyzed species to silica occurs at the oil-water interface and leads to formation of hard silica shell [35].

Preparation method of microcapsules

Microcapsules are prepared by using different methods. Various techniques which are currently in use along with their advantages and disadvantages are described in table 2.

Principles of drug release from microcapsules

Based on various studies of the release characteristics, the following generalizations can be made:

1) Drug release rate from microcapsules conforming to reservoir type is of zero order.

2) Microcapsules of monolithic type and containing dissolved drug have release rates that are t ½ dependent for the first half life of the total drug release and thereafter decline exponentially.

3) For a monolithic microcapsule containing large excess of dissolved drug, the release rate is exponentially dependent throughout the entire drug release.

Applications of microencapsulation

The applications of microencapsulation are

- Adhesives
- Anti-corrosive coatings
- Essential oils, flavours and other volatile bioactives for food or in feed additives
- Pesticides and herbicides
- Biotechnology
- Pharmaceuticals, small molecules and recently also peptides and small proteins for oral or sublingual delivery
- Phase change materials
- Powder perfume
- Medicine
- Household and personal care
- Agriculture
- Food
- Chemical industry
- Textiles
- Veterinary
- DNA protection from degradation for product tracing and data storage
- Protection of bioactive compounds that are easily degraded under normal environmental conditions

CONCLUSION

Since the concept of controlled drug delivery was introduced in 1970s, great progress has been made in microencapsulation (Jain NK, 1997). Microencapsulation techniques offer various opportunities such as protection and taste masking, reduced dissolution rate, facilitation of handling and spatial targeting of the core material. A single microencapsulation method cannot be universally applied for a variety of drug materials. In developing a new microparticle system for a given drug, it is important to understand the physicochemical properties of the drug and polymers that best match the properties and find an encapsulation method. The technology of microcapsules is rapidly developing due to its wide application in various fields. Another observation is that till date, the drugs chosen for microencapsulation are mostly belonging to BCS class I and BCS class II. Class II comprise of drugs that have low solubility and high permeability. These drugs get easily be eliminated from the site of absorption as the dissolution rate is slow. This may result in the reduced bioavailability. Thus, to enhance the bioavailability of these drugs, they can be microencapsulated. It may be concluded that a continuous effort is required, in order to make desired drug delivery systems along with minimization of problems associated with physicochemical properties of materials and techniques used in microencapsulation, for further refinement and research.

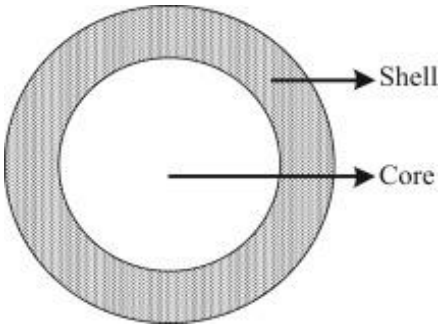

Fig.1: Microcapsule with core and coat

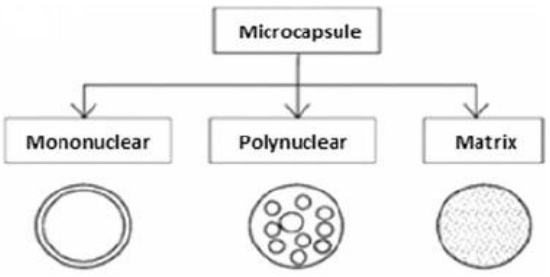

Fig. 2: Morphology of microcapsules

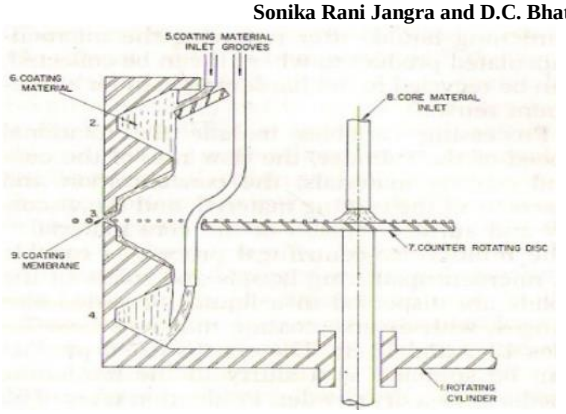

Fig 3 : Multiorifice-Centrifugal Microencapsulation Apparatus

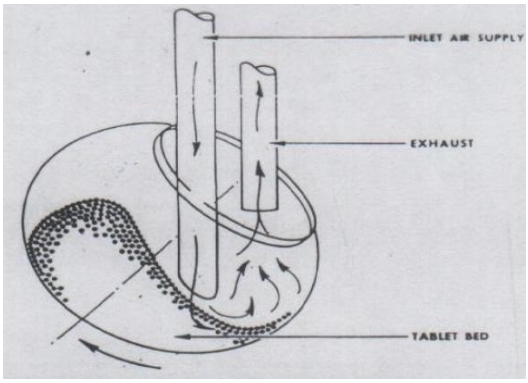

Fig 4: Standard Coating Pan

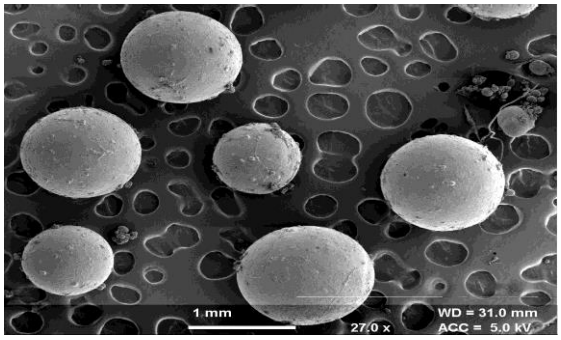

Fig 5: Scanning electron microscopy images of microcapsules prepared by solvent evaporation method

Table 1: Properties of some microencapsulated core materials

Core material	Characteristic property	Purpose of encapsulation	Final product form
Aspirin [20]	Slightly water-soluble solid	Taste-masking; sustained release; reduced gastric irritation	Tablet or capsule
Acetaminophen [19]	Slightly water-soluble solid	Taste masking	Tablet
Activated charcoal [5]	Adsorbent	Selective sorption	Dry powder
Potassium chloride [37]	Highly water-soluble solid	Reduced gastric irritation	Capsule
Progesterone [16]	Slightly water-soluble solid	Sustained release	Varied
Urease [36]	Water-soluble enzyme	Permselectivity of enzyme, substrate, and reaction products	Dispersion
Isosorbide Dinitrate[11]	Water-soluble solid	Sustained release	Capsule
Islet of Langerhans [9]	Viable cells	Sustained normalization of diabetic condition	Injectable
Menthol/methyl salicylate camphor mixture [24]	Volatile solution	Reduction of volatility; sustained release	Lotion
Vitamin A palmitate [2]	Non-volatile liquid	Stabilization to oxidation	Dry powder

Table 2: Advantages and drawbacks of Microcapsule formulation Techniques

S.No.	Techniques	Advantages	Disadvantages
1.	**Pan coating**	Applicable to wide range of coat and coat materials and process flexibility.	Not applicable to very fine particles (less than 500µm), needs great amount of coating material. High material loss and time consuming.
2.	**Air suspension coating**	Applicable to solid cores irrespective of size, shape and wide range of coating materials. It require no skilled labour or expertise.	Not suitable for thermosensitive cores.
3.	**Coacervation - phase separation**	Protect active principles from being altered by exposure to heat or from their partitioning out into dispersing phase.	Difficulties in scaling-up and use of large amount of organic solvent. Complex coacervates are highly unstable.
4.	**Solvent Evaporation**	Prevent eventually hydrolysis of the drug or polymer.	Low yield
5.	**Emulsification polymerization**	High strength and flexible capsule shell walls. Not easy to break and large scale synthesis. Microcapsules with narrow size distribution can be obtained.	Difficult to encapsulate aqueous cores.
6.	**Spray drying and spray congealing**	Can be use without organic solvents. High yield. Ability to handle labile materials.	Core loading is 20-30%, low boiling point compounds volatilize from microcapsules, Agglomeration of microparticles.
7.	**Multiorifice – Centrifugal**	Slower release properties of the microcapsules and high through put rate.	Drops are form by the breakup of a liquid jet, the process is only suitable for liquids or slurries.
8.	**Fluidized-bed Coating**	Total control over temperature and obtain desirable thickness of coating.	Longer duration, too high inlet air temperature lead to unhomogeneous looking films.
9.	**Lyophilization**	Minimizes the changes associated with high temperature.	High cost and long process time.
10.	**Liposome entrapment**	Either aqueous or lipid soluble material can be encapsulated; suitable to high water activity applications; efficient controlled delivery	Mainly used on a laboratory scale.
10.	**Sol-gel Encapsulation**	Low-temperature processing, ease of fabrication and precise microstructural and chemical control.	High cost of precursors.

Table 3: **Parameters for Characterization of Microcapsules**

S.No.	Parameters	Characterization Methods
1.	Particle size Distribution	Optical Microscope, Scanning Electron Microscopy, Atomic Force Microscopy, Mercury Porositometer, Laser Diffractometer
2.	Morphology	Optical Microscope, Scanning Electron Microscopy
3.	Charge Determination	Zeta Potentiometer
4.	Carrier Drug Interaction	Differential Scanning Calorimetry, FT-IR (Fourier Transformation Infrared Analysis)
5.	Crystallinity	X-Ray Diffraction studies
6.	Melting point	DSC (Differential Scanning Calorimetry), Using Melting Point Apparatus
7.	Flow Properties	Angle of repose, Carr's index, Hausner's ratio
8.	Release Profile	*In vitro* release characteristic under physiological and sink conditions
9.	Drug Stability	Bioassay of drug extract from Microcapsules, Chemical analysis of drug, HPLC (High Performance Liquid Chromatography)

Table 4: Drugs incorporated in Microcapsules

PHARMACOLOGICAL ACTIVTY/DISEASE	DRUG	REFERENCE
Anticancer	Mitomycin C Doxorubicin	Hisashi Mori *et al*., 2013 Max Donbrow, 2008
Antimicrobial	Tetracycline Minocycline Doxycycline Chlorhexidine	Asteria Luzardo Alvarez *et al*., 2011
NSAID	Indomethacin Ibuprofen Naproxen Nimesulide	Shiva Kumar *et al*., 2015
Antidiabetic	Insulin	Jia-Qiang He *et al*., 2017
Cardiovascular Disease	Simvastatin	Didier Letourneur *et al*., 2016
Tuberculosis	Rifampicin	Debra C**.** Quenelle *et al*., 2001
Antifungal	Amphotericin B Itraconazole	Frances M.D *et al*., 2001
Antiretroviral	Saquinavir Lamivudine	Benita Simon, 2014 Saleem Basha *et al*., 2016
Antipsycotic	Risperidone	Imen Kahouli *et al*., 2013
Antihyperlipidemic	Probucol	Watts GF *et al*., 2014

REFERENCES

1. Asteria Luzardo Alvarez, Francisco Otero Espinar, Jose Blanco Mendez. The Application of Microencapsulation Techniques in the Treatment of Endodontic and Peridontal Diseases, 2011;3: 538-571
2. Avinash B., Gangurde and Purnima D. Amin. Microencapsulation by spray drying of Vitamin A palmitate from oil to powder and its application in topical delivery system. Scientific research publishing, 2017:11-39.
3. Banker GS, Rhodes CT. Modern pharmaceutics. New York: Marcel Dekker: in pharma publication, 2002:501-527.
4. Benita Simon. Microencapsulation methods and applications. Published by CRC press, 2014: 7(76); 1-9, 43-50, 155-159,451.
5. Chandy T and Sharma CP. Activated charcoal microcapsules and their applications. J Biomater Appl., 1998; 13(2): 128-57.
6. Deasy Patrick B. Microencapsulation and related processes. Marcel Dekker, 2007: 1-11,21-27,289-302.
7. Debra C. Quenelle, Jay k. Stass, Garry A. Winchester, Esther L., W. Barrow. Efficacy of Microencapsulated Rifampicin in Mycobacterium tuberculosis infected Mice. Antimicrobial agent and Chemotherapy, 2001:1144-1151.
8. Didier Letourneur, Maya Juenet, Rachida Aid Launais. Development of polymer Microcapsules Functionalized with Fucoidan to target P-Selectin in cardiovascular diseases. Advanced Healthcare Materials, 2016; 4(6):1-11.
9. Emmanuel C. Opara, John P. McQuilling, and Alan C. Farney. Microencapsulation of Pancreatic Islets for use in a bioartificial pancreas Methods. Mol Biol., 2013 (1001): 261-266.
10. Frances M.D. Gulland, Leslie Dierauf. Marine mammal medicine. Published by CRC Press. Second edition, 2001; 349.
11. Guo-Ming Yang, Jen-Feng Kuo and Eamor M. Woo. Preparation and control-release kinetics of isosorbide dinitrate microspheres. Journal of Microencapsulation, 2006; 6(23), 622-631.
12. Hisashi Mori, Tetsuro Kato, Ryosuke Nemoto, Masaoki Harada, Katsuo Unno. Magnetic Microcapsules for targeted delivery of anticancer drugs, 2013; 3(10): 199-211.
13. Imen Kahouli, Meenakshi Malhotra, Satya Prakash and Shyamali Saha. Microencapsulation for the therapeutic delivery of drugs. Journal of Pharmaceutics, 2013; 236-248.
14. Jain NK. Controlled and novel drug delivery. CBS publisher, 1997:236-237.
15. Jia-Qiang He, Catherine Barrone. Alginate based microcapsules generated with the coaxial electrospray method and its clinical application. Journal of Biomaterial Science, 2017:23-53.
16. Leon L, Herbert AL, Joseph LK. The theory and practice of industrial pharmacy. Varghese publishing house, 2013:412-428.

17. M. N.Singh, K.S.Y. Hemant, M. Ram and H.G. Shivakumar. Microencapsulation: A promising technique for controlled drug delivery. Res. Pharm. Sci., 2010; 5(2):65-67.
18. Max Donbrow. Microcapsules and Nanoparticles in medicine and pharmacy. Published by CRC Press, 2008:258.
19. N. Pearnchob; J. Siepmann; and R. Boddmeier, R. Pharmaceutical applications of shellac: moisture protective and taste-masking coatings and extended release matrix tablets. Drug Dev. Ind. Pharm., 2003; 29, 925-938.
20. N. Shet and I. Vaidya. Taste masking: a pathfinder for bitter drugs. Int. J. Pharm. Sci.Rev. Res. 2013; 18:1-12.
21. Prateek K Jain, Deepak K Mishra and Ashish K Jain. Techniques of Microencapsulation. Int.J. of Pharm. and Chem. Res., 2013; 2(2): 962-977.
22. P.Venkatesan, R. Manavalan and K. Valliappan. Microencapsulation: A vital technique in novel drug delivery system. J. of Pharm. Sci. and Res., 2009; 1(4):26-35.
23. R. Ciriminna, M. Sciortino, G. Alonzo, A.de Schrijver, M. Pagliaro. "From Molecules to Systems: Sol-gel microencapsulation in silica based materials". Chem. Rev., 2011.
24. Roongkan Nuisin and Jaruwan Krongsin. Microencapsulation of menthol by crosslinked chitosan via porous glass membrane emulsification technique and their controlled release properties, 2013; 30(5); 498-509.
25. Saleem Basha N, S.Princely, Nandha kumar S and Dhanaraju Md. Controlled delivery of antiretroviral drug-loaded cross-linked microspheres ionic gelation method. Asian Journal of Pharmaceutical and Clinical Research, 2016; 5(9): 264-271.
26. Shiva Kumar B, Parmod Kumar TM, Manjanna KM. Microencapsulation: an acclaimed novel drug delivery system for NSAIDs in arthritis, 2015; 27(6):509-545.
27. Swagata Dutta Roy, Subhangkar Nandy and Santanu Banerjee. Microencapsulation: Convenient mode of drug delivery in novel drug delivery system. Int. J. of Pharm. and Life Sci., 2012; 3(3): 1555-1562.
28. V Suganya and V Anuradha. Microencapsulation and Nanoencapsulation. Int. J. of Pharmaceutical and clinical research, 2017; 9(3); 233-239.
29. Watts GF, Mooranian A, Negrulj R,Chen-Tan N, Fang Z, Mukkur TK, Mikov M, Golocorbin-Kon S and Fakhoury M. Microencapsulation as a novel delivery method for the potential antidiabetic drug; Probucol, 2014: 1221-1230.
30. Wong PC, Heng PW and Chan LW. Spray congealing as a microencapsulation technique to develop modified-release ibuprofen solid lipid microparticles. J. Microencapsul, 2015;32(8): 725-36.
31. Wurster, D.E.. Air-suspension technique of coating drug particles. J.Pharm.Sci., 1959 (48), 451-454.
32. Yoon Yeo, Namjin Baek and Kinam Park. Microencapsulation methods for delivery of protein drugs. Biotechnol. Bioprocess Eng., 2001, 6: 213-230.
33. http://en.wikipedia.org/wiki/Micro-encapsulation
34. http://www.scribd.com/doc/28977603/Methods-of-Encapsulation
35. http://neoadventtec.com/web/index.php/technologies/drug-delivery/sol-gel-encapsulation
36. https://doi.org/10.1271/bbb1961.43.1133
37. https://www.accessdata.fda.gov>label