Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Review Article

Microspheres and Microcapsules: A Review of Manufacturing Techniques for Pharmaceutical Industries

PAROMA AREFIN[1]*, MD SHEHAN HABIB[1], NAZIM UDDIN AHMED[2], MD ABDURRAHIM[2], MD IBRAHIM [2], SREEBASH CHANDRA BHATTACHARJEE[1], DIPANKAR CHAKRABORTY[1], SUMON DAS[1], DEBABRATA KARMAKAR[1] , DIP BHOWMIK[1] ,SHIRMIN ISLAM[3], MD SAIDUL AREFIN[4]

[1] Bangladesh Council of Scientific and Industrial Research (BCSIR) Laboratories, Chattogram, Bangladesh;

[2] Bangladesh Council of Scientific and Industrial Research (BCSIR) Laboratories, Rajshahi, Bangladesh;

[3] Genetic Engineering and Biotechnology, Rajshahi University

[4] Institute of Nutrition and Food Science, University of Dhaka, Bangladesh

ARTICLE DETAILS

Article history:
Received on 24 November 2020
Modified on 15 December 2020
Accepted on 23 December 2020

Keywords:
Microsphere,
Microcapsule,
Solvent Evaporation,
Spray Drying,
Coacervation.

ABSTRACT

Microencapsulation is a technique by which a layer of polymer or any other coating material is provided to small particles of solid or liquid substances. Microspheres are used for a number of purposes like in food industries, food preservation, drug formulations, and so on. Depending on purposes of use and production requirements, different methods are used. In case of drug formulations, microencapsules or microspheres facilitate masking bitter or undesirable taste of a substance, long duration of action, site-specific release, separation of incompatible substances, and protection against moisture degradation or oxidation, modifying elements' physical characteristics.Microspheres can be produced in various ways. These methods can be categorized as physical, physicochemical and chemical methods. They can also be categorized as chemical and mechanical processes. Researchers have always explored different ways of microsphere production to discover new applications. In this review paper, we have highlighted different methods used for the microsphere and microcapsule preparation. Spray drying or congealing, coacervation and solvent evaporation techniques are most commonly used for drug formulation preparation. This research can be a guideline to find out the most suitable method of microsphere preparation depending on the desired output.

INTRODUCTION

Microcapsules are coated with filmy coating elements by a method known as microencapsulation, where solid, liquid, or gas active components are packed inside with the coating shield of the size of 1 to 100 microns range [1, 2]. Desired active elements are coated with a shell named microcapsule (Fig. 1). The architecture of microcapsules varies from symmetrical spherical design to any type of the desired form. In the spherical system, a uniform shell acts as a cover of the core active material. The radius parameter of a microcapsule is ranged from 0.5 to 500µm. For mass production, a coating shell radius range from 1.5 to 400µm covers core active material range from10% to 90% of the weight [3, 4].

If the radius is below 0.5µm, it is called nanoparticle, and if it is 500µm, the name will be microcapsule. Alternatively, it is also called microgranules [3-7].

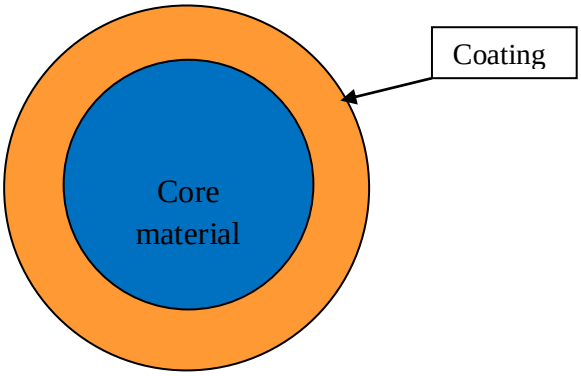

Figure 1: A Typical Microcapsule Structure

Microencapsulation is a process where micron level solid, liquid, or gas material is covered with

Author for Correspondence:
Email: paroma.arefin@gmail.com

a uniform film [8]. A particular type of uniform cover film protects the core active material from any kind of decay or damage from the external environment. The film has no reaction tendency with the core sample [4-6]. The uniform cover film will maintain an optimum decay period and active core release [9]. In agriculture, cosmetic, and textile systems, this encapsulation technology has been developed with immense progress. Now the uniform film coating technology is adapted to preserve the odor and quality of the active core sample, for optimum desired release, for better consistency, bioavailability of active samples. For a particular active molecule supply with maintained molecule flow, a multi-particulate dosage method is much reliable.

A monolithic entity with a spherical shape is the main feature of a microsphere in which the active agent is evenly spread at the molecular level or the particle level**.** These two types of distributions are the broader type of microparticle. The radius range of a microparticle is 0.5µm to 500µm regardless of the internal or the external structure. Among all the microparticle types, the microsphere is an extended category of Microcapsules. In the microparticle, the core is surrounded by active material, where the material type is different from the core [1,10]. A microsphere is the uniform distribution of the active agent and the polymer. Besides, in microcapsules, the polymer film is used as a thin film coat with the random distribution of active drug inside [5, 6]. Different types of microparticle architecture have been shown in Fig. 2. The microcapsule turns into microparticle according to the attenuation of the size of the active drug [11].

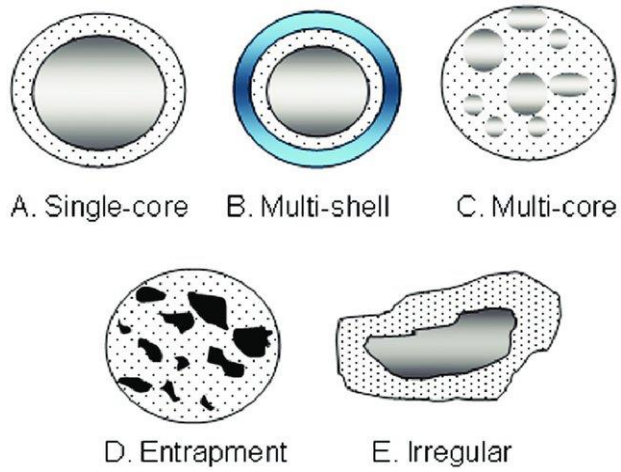

Figure 2: Variations of microparticle formulations [12]

Advantages of Microsphere and Microencapsulation Technology [4, 5, 13, 14]

To lessen the active agent's side effect, the microencapsulation technology is suitable as it more feasibly help the utility of the sample dosage [3]. For a specific application, the release profile of the active elements can be controlled according to the demand. The active material release includes faster release, prolonged release, and release to the target application. The microencapsulation method introduces membrane coating of severe testing agents for chewing drug intake where there is no need to drink water during intake. Hence in medical science, microencapsulation acts as a different type of medium for the desired application of active agents [7]. Despite all the development in the microencapsulation process, there are many resistances yet to be resolved in the way of precise fixation of the active agent, shell element, and product methodology [14].

In most of the drugs taken orally, there is no mechanism of release maintenance or target fixation. That's why the conventional method incorporates a toxic range with the rising active molecule, and the active longevity becomes less than demand up to re-administration [4]. The adequate release of the active agent during the required period in fix target and application results in reduced drug toxicity and harmful after-effect. For desired and optimal active agents and targets, microencapsulation is the best option [3, 5, 15]. If a consistent plasma concentration is maintained, the formulation could decrease the dose-volume and side effects of the drug. The drug efficiency could be improved by a well-built drug system and well maintained active agent supply to the fixed target site. For this, different ways are to be adopted to deliver the drug for an appropriate release maintenance system of the active agent [16]. The microsphere formulation is one of the feasible ways [17].

Microencapsulation Technologies [3-5, 13, 14]

There are various methods of microencapsulation. The methods are divided into three types:

1. Physical methods
2. Physico-chemical methods
3. Chemical methods

1. Physical Methods

- Spray drying and spray congealing
- Fluidized bed technology

- Pan coating
- Centrifugal extrusion
- Spinning disk
- Air suspension coating

2. Physico-Chemical Methods

- Coacervation
- Polymer-polymer incompatibility
- Solvent evaporation
- Polymer encapsulation
- Hydrogel microspheres

3. Chemical Methods

- Interfacial polycondensation
- Interfacial cross-linking
- Interfacial polymerization
- Matrix polymerization

According to Curt Thies, there are two processes of microencapsulation [18]. The process is operated according to the phase [19]. They are as follow:

I. A Type/ Chemical process
II. B Type/ Mechanical process

I. **A Type**: Here, the capsule formation is held entirely in a liquid-filled stirred type tank filled with liquid, or it is a reactor with a tubular system.

II. **B Type:** Here, the capsule formation held by coating elements covers the core element by spraying droplets of the coating element. That is why the encapsulated drug formed.

Table 1: List of Type A and Type B processes

Type A (chemical) processes	Type B (mechanical) processes
Complex coacervation	Spray drying
Polymer-polymer incompatibility	Spray congealing
Interfacial polymerization in liquid media	Fluidized bed coating
In situ polymerization	Electrostatic Deposition
Solvent evaporation or In-liquid drying	Centrifugal extrusion
Thermal and ionic gelation in liquid media	Spinning disk or Rotational suspension separation
Submerged nozzle extrusion	Polymerization at solid-gas or liquid-gas interfaces
	Pressure extrusion or spraying into solvent extraction bath

Stable dispersion and emulsion are very crucial for the two processes as A and B types.

Type A Encapsulation Processes

Complex Coacervation

There are two methodologies to conduct coacervation. One is simple and the another is complex processes. In the simple method, the phase separation is held by adding an agent, which will be desolvation type. Besides, during the complex method, two polymers which are differently charged are being incorporated [20]. First of all-polymer solution is being dispersed with the core element (usually oil) (a cationic aqueous polymer, gelatin). After that, polymer (anionic, water-soluble, gum arabic) solution is then added to the prepared dispersion. The coating material deposits over the core particle when the complex of the two polymers happened. An addition of salt or a change of pH or thermal condition or the medium dilution accelerates the process. In the end, with formaldehyde cross-linking, desolvation or thermal adaptation, the microcapsules become stabilized. Microcapsules are being manufactured from Complex coacervation, which contains fragrant oils, liquid crystals, flavors, dyes, or inks as the core material.

Polymer-Polymer Incompatibility

Incompatibility between polymer and polymer is known as a phase separation process. In this process, two types of polymer have been used, which are soluble in a common solvent but do not mix with each other. Among the two phases of the polymer, one phase becomes the shell of the capsule, and the other phase act as a separator. Besides, the second phase polymer is not a part of the capsule shell. A cross-linking of chemical or nonsolvent material desolves the shell. This way, microcapsules are manufactured. The capsule is prone to attach to each other during the production process [20]. In an aqueous or aqueous free environment, the encapsulation between polymer and polymer incompatibility is conducted. Besides, organic media is essential in the initial stage.

Interfacial Polymerization (IFP) in Liquid Media

Over the outer surface of the active core, a coated shell will be formed by reactive monomer polymerization [20]. The monomer is a multifunctional type. The monomers are used with a single form or combined form. In the liquid core material, the multifunctional

monomer is dissolved, which will result in dispersion in the aqueous phase that holds the dispersing element. An amine type additional reactant will be mixed. After an accelerating polymerization, the coated shell will be formed.

The reaction between isocyanate and amine results in polyuria membrane. Consequently, acid chloride and amine reaction result in polynylon or polyamide—a reaction between isocyanate and hydroxyl results in polyurethane shell. By the Interfacial polymerization process, polyurethane-urea encapsulates diammonium hydrogen phosphate. The elemental analysis makes 62% by weight DAHP, which will act as fill. This fill will produce 22% microcapsules in powder form. 13.35mm is the normal size of DAHP, and 30.1mm is the average size of 95% particle.

In Situ Polymerization

In the encapsulation reactor, the addition of polymerization monomers creates a capsule coated shell as same as IFP. In this process, no reactive elements are mixed with the core element. In the continuous phase of the dispersed core element, polymerization happens. In the beginning, the weight of the polymer that creates the shell will be less. After that, the thickness of the polymer will grow when the time progresses and the polymer will become a capsule shell.A unique feature of *in situ* encapsulation technology is that polymerization occurs in the aqueous state the polymerization occurs. This criterion makes the in situ encapsulation process different from other methods. For this reason, over the dispersed type core element, a condensed material shell is created. In this process, the coated capsule membrane has higher cross-linked vale, water insolubility. The total polymerization process happens in the aqueous area; that's why the reactive material does not dissolve in the core element. This method has become a widely introduced way for the mass production of capsules.

Evaporation of Solvent or Drying of In-Liquid [21]

This method has also been widely adapted for microencapsulation. The introduction of emulsification with active agent and polymer with an extra medium do not dissolve throughout the emulsification process.It is a simple method for microcapsules with different types of compound elementscontain a variety of polymers [22, 23]. To whole evaporation technique can change microsphere properties. The dispersing element, the ratio between the active element and polymer, core material solubility, the rate of stir accelerate the emulsion and production process [23, 24]. The hydrophilic or the hydrophobic behavior of the drug is the deciding factor for effective drug encapsulation. For hydrophobic drug material, oil-in-water process is mostly used. This oil-in-water method is easy to execute, and a different method follows this method. Four significant stages of oil-in-water method as follows:

1. Hydrophobic drug is dissolved in polymer organic solvent.
2. The dispersed phase indicates about emulsification of the organic element. Besides, an aqueous phase indicates continuous phase.
3. A continuous phaseextract the solvent from the dispersed phase where solvent evaporates become solid material from droplets.
4. To get rid of the residual solvent drying and recovery process is useful.

For highly hydrophilic drug material, there is a need for a different method. There is a probability that the organic solvent will not be able to dissolve the highly hydrophilic drug. At the emulsion period, the active agent may reach the continuous phase, which will result in drug loss [17, 25].

The feasible alternative way as follows:

a) Water-oil-water double emulsion method: The emulsion of hydrophilic drag in an aqueous solution happens in the organic phase. Then again, an emulsion process will happen in an aqueous solution for a second emulsion layer.
b) Oil-water co-solvent method: If the drag doesn't dissolve in the organic solvent, then an auxiliary is introduced to make the drag soluble.
c) Method of Oil-water dispersion: With a powder and solid form of the drug is dispersed in a polymer and the organic solvent.
d) Method of oil-oil non-aqueous solvent evaporation: The oil takes the place of the aqueous phase.

At first, the drag should be in an aqueous form. There should also be a viscosity builder and stabilizer element in the arrangement. Some solvents named dichloromethane, chloroform is

essential for the formation of water by a high, stirring process.

With PVA or PVP, an emulsifier is introduced in a high amount of water for the emulsion process in the water-oil-water method. For the evaporation of the organic part in the solvent, the emulsion is then directed to a high, stirring process. Afterward, by a washing and drying process, the final microspheres are prepared.

Type B Encapsulation Processes

Spray Drying

In a polymer solution the core drag materials are dispersed, and a hot chamber is used for spraying. After the evaporation of the applied solvent, the outer membrane material becomes solid. Finally, a polynuclear or matrix kind of microcapsule is formed [26]. The encapsulating method is cost-effective. In this process, the quality of the drag oil, fragrance and flavor remains unchanged.

Spray-Congealing

The coating material is melted, and the core element is dispersed in it. If the spraying process of a solution happens in a cold air stream, then the solid coating shell forms [27].

Fluidized Bed Technology

By this method, Solid and liquid get absorbed inside the porous material.Using jet air, the Solid external material gets away.[27] After that, a liquid coated material is being sprayed over it. An accelerating evaporation process makes an external layer over the material. The process is being continued till the required weight and thickness are achieved [27]. There are various types of units for the fluid-bed coater [28]:

a) Top-spray
b) Bottom-spray
c) Tangential-spray

a) Top-Spray Units

Fat and wax get met in a hot environment. That's why this type of spraying material is being introduced over the solid material bed, which was fluidized before. With this method, the capsules are being made bearing solid shells. In the production of water-soluble type drug or food production, this method is common. In the application of solution spraying to the shell element, the top-spray method has limitations. During the spraying, the solution droplets pass in the opposite direction of the stream of the gas, which will disappear from the fluidized bed. For a superficial coating of shell element deposition and evaporation, this method is very propitious [27].

b) Bottom-Spray Units

Professor D.E. Wurster first improved this unit. So the alternative name of this unit is Wurster's Coater. A chamber is mainly used in this unit for coating purposes, which contains a nozzle with a cylindrical shape and a plate with a perforated bottom. The function of the cylindrical shaped nozzle is to spray the coating elements.[6]The drug is driven through the perforated plate and then went through the nozzle. In this way, the drug is encapsulated with the coating element.Afterward, from an evaporation process of the coating solvent and from a decreasing thermal condition; the coating element adjusts over the drug. Over several repetitions of this process, a required thick and adequate shell is obtained [27, 29].

c) Tangential-Spray Units

The name of this unit itself describes the operation. Here the coating element is applied on the circular bottom of the container from a tangential angle with the circle. A rotating disk makes an evenly distributed uniform coating shell. The rotation speed always remains constant for a uniform coating. A Consider flow bed provides consistent air circulation for fluidization. Besides, the rest of the procedures are the same as the other methods. By this unit, a uniform and adequate coating shell can be produced. The release of the active agent from the drug is essential. In this unit, a controlled release of an active agent drug can be manufactured. To prevent an unfortunate drying, the spray material is driven to a nozzle connected to the production bed.

Centrifugal Extrusion [30]

There are nozzles by which two kinds of solution can pass through it, and at the same time, it can spin. For the core and shell elements, the liquid can be driven by a pump through the nozzle.Here for two-fluid mechanisms, a metal rod or column is used. This metal column divides the solution into droplets, which are mainly spherical in shape when the solution passes through the nozzle. The shell membrane element is the deciding factor for the way of capsules conversion from the droplets [27, 30].

Spinning Disk or Rotational Suspension Separation

Rapid, low-cost, and easy to execute criteria make this method very efficient for production.There is a rotating disk where the solution of the core material is poured.The mechanism of spinning makes the membrane shell over the core element.After the end of the shell building mechanism, the unwanted particles are thrown away by the centrifugal force of the rotation of the disk.Finally, by decreasing thermal condition, the coated element becomes rigid and firm over the surface of the core agent.

Other Processes Widely Used For Microencapsulation

Pan Coating

It is a physical method of microencapsulation. To manufacture small-sized coating particles it is a widely used commercial method.Here the coating element is taken with the dry condition along with the required solid particles.After the rise in the heating energy, the coating element get melts, and the gap between the coating material and the core element eliminates. When the thermal condition decreases, then the shell material turns into a solid form [27].

Air Suspension Coating

Professor Dale E. Wurster from the University of Wilconsin first introduced this method.Here particles of solid drug elements are applied in an auxiliary stream of air. There is a chamber for the coating process where the drug particle is separated with a stream of airflow. The operation condition of the chamber is significant for coating performance. This process is operated up to a hundred times for better coating shell production. The thermal condition of the applied air stream is acceleration the drying process of the product. So here, the airflow and the thermal condition of the air is directly accelerating the drying process of the product [31].

Supercritical Fluids Rapid Expansion for Polymer Encapsulation

Highly compressed gases are considered to be super critical fluids that have a lot of properties along with the liquid and gaseous form.In these criteria, Carbon-di-oxide and Nitrous-oxide are dominant in applied section.Thermal condition and the operating pressure are crucial game changing factor for the density of the fluid [32].

The effective agent material and the coating element are kept in heavy pressure, and the element release is maintained in normal room pressure through a dedicated nozzle. These changes of pressure make the coating material dissolve and arrange over the core element and create the coating membrane [32, 33]. Active elements are being encapsulated by this process—for example, taste, vitamin & mineral, color, pigment & pesticides. For the outer shell membrane paraffin type wax and glycol from polyethylene are mainly applied.There is one condition to be met: The active element and the shell element need to be soluble in the fluids, which is supercritical [32].

Hydrogel Microspheres

Microspheres made of gel-type polymers are the constituent elements of the microsphere, for example, from the polymer dissolved method in aqueous solution. Then, the active element needs to be separated from the mixing total. To make micro-level droplets, the elements need a precise device that makes the element harder step by step through a stirring process. Then fall into a hardening bath that is slowly stirred where a solution of calcium chloride is present [34]. This is an aqueous solution-based method. Here the residual elements are being separated in the microspheres.

The particle size is maintained by:

- Changing extruders measurement.
- Changing flow rate of the polymer.

Polycondensation of Interfaces

A rapid reaction occurs in an interface between two reactants. Here the reaction of Schotten-Baumann occurs for chloride acid and reactive hydrogen-containing compound materials. The most known materials are polyester, polyurethane. But alcohol holding OH group, amine, and polyuria are also applicable [35]. In this method, a thin, flexible membrane is being formed in the interface using this condition. A solution is taken, which will be an aqueous type, and there will be some additional amine and polyfunctional isocyanate. The reaction process is acidic. To make it balanced according to pH value, there is a presence of a base. Over the interface of the droplets of the emulsion, a condensed membrane shell is produced.

Interfacial Cross-Linking

This type of cross-linking is explored from interfacial polycondensation [36]. To reduce the

toxic effect of Diamines, this method is used. In addition to this, in commercial medicine production and the cosmetic industry, this method is also widely used. The polymer from biosource takes the place of a small bifunctional monomer as same as protein. This type of monomer has reactive hydrogen. Over the surface of the emulsion, the reaction mechanism occurs. The reaction between different types of protein functional groups and the acid chloride results in the membrane shell [37].

Matrix Polymerization

At the time of the particle formation, there is an embedded process for the core element in the matrix of the polymer. A spray and drying mechanism accelerates the solvent evaporation in the matrix material. A change in the chemical environment can ameliorate the solid form of the matrix [38].

DISCUSSION

All these methods are being successfully used for microsphere preparation Researchers have always searched for various upgraded approaches of microsphere production for different purposes. In our study, different methods used for the microsphere and microcapsule preparation have been discussed. We found that spray drying or congealing, coacervation and solvent evaporation techniques are most commonly used for drug formulation preparation.

CONCLUSION

The latest analysis paper shows that microspheres are a great approach for the drug delivery. In days ahead, microsphere preparation could be a great way for targeted drug delivery, sustained or immediate action of drug, better bioavailability, low cost from manufacturing point of view and low price for consumers. So, proper method for microsphere formulation is crucial to determine the cost and feasibility. Spray drying or congealing, coacervation and solvent evaporation techniques are most commonly used for drug formulation preparation as the previous studies show. But depending on materials involved, we can opt for different methods. On basis of this research, we would be able to determine the most suitable method for microsphere preparation specific to our purposes. The research describes different microsphere preparation methods, facilities required for using different methods of preparation and concerned convenience. So, it can be a guideline to find out the most suitable method of microsphere preparation based on the budget, available set-up, objectives of preparation and target of the food and pharmaceutical industries.

CONFLICT OF INTEREST

The authors have no conflict of interest.

REFERENCES

[1] Nordstierna L, Abdalla AA, Nordin M, Nydén M. Comparison of release behaviour from microcapsules and microspheres. *Progress in Organic Coatings*. 2010; 69(1): 49-51. doi:10.1016/j.porgcoat.2010.05.003

[2] Tadros T. Microcapsule. In: *Encyclopedia of Colloid and Interface Science*. Springer Berlin Heidelberg; 2013: 687-687. doi:10.1007/978-3-642-20665-8_118

[3] Gupta A, Dey B. Microencapsulation for controlled drug delivery: a comprehensive review. *Sunsari Technical College Journal*. 2013; 1(1): 48-54. doi:10.3126/stcj.v1i1.8660

[4] Khandbahale S V. Microencapsulation-A Novel Approach in Drug Delivery: A Review. *Asian Journal of Research in Pharmaceutical Science*. 2020; 10(1): 39. doi:10.5958/2231-5659.2020.00009.0

[5] M.N. Singh, Hemant KSY, Ram M, Shivakumar HG. Microencapsulation: A promising technique for controlled drug delivery. *Research in Pharmaceutical Science*. 2010; 5(2): 65-77.

[6] DT B, L. B-P. Microparticle drug delivery systems. In: DM B, ed. *Drug Delivery Systems in Cancer Therapy.* ; 2003: 17-136.

[7] Jadupati M, Tanmay D, Souvik G. Microencapsulation: an Indispensable Technology for Drug Delivery System. *International Research Journal of Pharmacy*. 2012; 3(4): 8-13.

[8] Yeo Y, Baek N, Park K. Microencapsulation methods for delivery of protein drugs. *Biotechnology and Bioprocess Engineering*. 2001; 6(4): 213-230. doi:10.1007/BF02931982

[9] Kemala T, Budianto E, Soegiyono B. Preparation and characterization of microspheres based on blend of poly(lactic acid) and poly(ε-caprolactone) with poly(vinyl alcohol) as emulsifier. *Arabian Journal of Chemistry*. 2012; 5(1): 103-108. doi:10.1016/j.arabjc.2010.08.003

[10] Lengyel M, Kállai-Szabó N, Antal V, Laki AJ, Antal I. Microparticles, microspheres, and

microcapsules for advanced drug delivery. *Scientia Pharmaceutica*. 2019; 87(3). doi:10.3390/scipharm87030020

[11] Limpa SI, Islam Z, Reza MS. Comparative Evaluation of Bromhexine HCl Mucoadhesive Microspheres Prepared by Anionic, Cationic and Nonionic Polymers. *Bangladesh Pharmaceutical Journal*. 2020; 23(2): 117-124. doi:10.3329/bpj.v23i2.48331

[12] Whelehan M, Marison IW. Microencapsulation using vibrating technology. *Journal of Microencapsulation*. 2011; 28(8): 669-688. doi:10.3109/02652048.2011.586068

[13] Wong CY, Al-Salami H, Dass CR. Microparticles, microcapsules and microspheres: A review of recent developments and prospects for oral delivery of insulin. *International Journal of Pharmaceutics*. 2018; 537(1-2): 223-244. doi:10.1016/j.ijpharm.2017.12.036

[14] Patel K, Patel M. Preparation and evaluation of chitosan microspheres containing nicorandil. *International Journal of Pharmaceutical Investigation*. 2014;4(1):32. doi:10.4103/2230-973X.127738

[15] Morais AÍS, Vieira EG, Afewerki S, et al. Fabrication of Polymeric Microparticles by Electrospray: The Impact of Experimental Parameters. *Journal of Functional Biomaterials*. 2020; 11(1): 4. doi:10.3390/jfb11010004

[16] Hasan M, Ahamed SK, Billah MM, et al. New Approach for Sustained Release Dosage Form Design: Aceclofenac. *Mahidol University Journal of Pharmaceutical Science* . Published online 2015. doi:10.14456/mujps.2015.12

[17] Arefin P, Hasan I, Islam MS, Reza MS. Formulation and In vitro Evaluation of Eudragit RL 100 Loaded Fexofenadine HCl Microspheres. *Bangladesh Pharmaceutical Journal*. 2016; 19(1): 58-67. doi:10.3329/bpj.v19i1.29240

[18] Thies C. A survey of microencapsulation processes. In: Benita S, ed. *Microencapsulation: Methods and Industrial Applications.* ; 1996: 1-19.

[19] Bansal H, Preet kaur S, Gupta AK. Microsphere: Methods of prepration and applications; A comparative study. *International Journal of Pharmaceutical Sciences Review and Research*. 2011; 10(1): 69-78.

[20] Jyothi NVN, Prasanna PM, Sakarkar SN, Prabha KS, Ramaiah PS, Srawan GY. Microencapsulation techniques, factors influencing encapsulation efficiency. *Journal of Microencapsulation*. 2010; 27(3): 187-197. doi:10.3109/02652040903131301

[21] Deshmukh R, Wagh P, Naik J. Solvent evaporation and spray drying technique for micro- and nanospheres/particles preparation: A review. *Drying Technology*. 2016; 34(15): 1758-1772. doi:10.1080/07373937.2016.1232271

[22] Bolourtchian N, Karimi K, Aboofazeli R. Preparation and characterization of ibuprofen microspheres. *Journal of Microencapsulation*. 2005; 22(5): 529-538. doi:10.1080/02652040500161941

[23] Haznedar S, Dortunç B. Preparation and in vitro evaluation of Eudragit microspheres containing acetazolamide. *International Journal of Pharmaceutics*. 2004; 269(1): 131-140. doi:10.1016/j.ijpharm.2003.09.015

[24] Islam MS, Jalil R. Effects of Release Modifier and Annealing on Polyvinyl Acetate-Polyvinyl Pyrrolidone Microspheres Containing Diclofenac Sodium. *Dhaka University Journal of Pharmaceutical Sciences*. 2013; 12(1): 41-50. doi:10.3329/dujps.v12i1.16299

[25] Arefin P, Hasan I, Reza MS. Design, characterization and in vitro evaluation of HPMC K100 M CR loaded Fexofenadine HCl microspheres. *SpringerPlus*. 2016;5(1). doi:10.1186/s40064-016-2322-2

[26] Oxley JD. Spray cooling and spray chilling for food ingredient and nutraceutical encapsulation. In: *Encapsulation Technologies and Delivery Systems for Food Ingredients and Nutraceuticals*. Elsevier; 2012: 110-130. doi:10.1533/9780857095909.2.110

[27] Garg A, Chhipa K, Kumar L. Microencapsulation Techniques in Pharmaceutical Formulation. *European Journal of Pharmaceutical and Medical Research*. 2018; 5(3): 199-206. www.ejpmr.com

[28] Guignon B, Duquenoy A, Dumoulin ED. FLUID BED ENCAPSULATION OF PARTICLES: PRINCIPLES AND PRACTICE. *Drying Technology*. 2002; 20(2): 419-447. doi:10.1081/DRT-120002550

[29] Meiners JA. Fluid bed microencapsulation and other coating methods for food

ingredient and nutraceutical bioactive compounds. In: *Encapsulation Technologies and Delivery Systems for Food Ingredients and Nutraceuticals*. Elsevier; 2012: 151-176. doi:10.1533/9780857095909.2.151

[30] Manjanna KM, Shivakumar B, Kumar TMP. Microencapsulation: An Acclaimed Novel Drug-Delivery System for NSAIDs in Arthritis. *Critical Reviews™ in Therapeutic Drug Carrier Systems*. 2010; 27(6): 509-545. doi:10.1615/CritRevTherDrugCarrierSyst.v27.i6.20

[31] Wurster DE. Air-Suspension Technique of Coating Drug Particles. *Journal of the American Pharmaceutical Association (Scientific ed)*. 1959; 48(8): 451-454. doi:10.1002/jps.3030480808

[32] Kim J-H, Paxton TE, Tomasko DL. Microencapsulation of Naproxen Using Rapid Expansion of Supercritical Solutions. *Biotechnology Progress*. 1996; 12(5): 650-661. doi:10.1021/bp9600492

[33] Matson DW, Fulton JL, Petersen RC, Smith RD. Rapid expansion of supercritical fluid solutions: solute formation of powders, thin films, and fibers. *Industrial & Engineering Chemistry Research*. 1987; 26(11): 2298-2306. doi: 10.1021/ie00071a021

[34] Suzuki D, Horigome K, Kureha T, Matsui S, Watanabe T. Polymeric hydrogel microspheres: design, synthesis, characterization, assembly and applications. *Polymer Journal*. 2017; 49(10): 695-702. doi:10.1038/pj.2017.39

[35] Arshady R. Preparation of microspheres and microcapsules by interfacial polycondensation techniques. *Journal of Microencapsulation*. 1989; 6(1): 13-28. doi:10.3109/02652048909019898

[36] Atyabi F, Manoochehri S, Moghadam SH, Dinarvand R. Cross-linked starch microspheres: Effect of cross-linking condition on the microsphere characteristics. *Archives of Pharmacal Research*. 2006; 29(12): 1179-1186. doi:10.1007/BF02969311

[37] Zhang H, Dicker KT, Xu X, Jia X, Fox JM. Interfacial bioorthogonal cross-linking. *ACS Macro Letters*. 2014; 3(8): 727-731. doi:10.1021/mz5002993

[38] Pachuau L, Sarkar S, Mazumder B. Formulation and evaluation of matrix microspheres for simultaneous delivery of salbutamol sulphate and theophylline. *Tropical Journal of Pharmaceutical Research*. 2008; 7(2): 995-1002. doi:10.4314/tjpr.v7i2.14684