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Review On Respirable Spray Dried Microparticles

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Abstract: Microparticles are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 μm . The range of Techniques for the preparation of microspheres offers a Variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs also known as microparticles.

The microparticles are one of the novel drug delivery system which can be given as an effective therapeutic alternative to conventional or immediate release single-unit dosage forms. Microparticles are spherical free flowing powder having particle size less than 200 μm , consisting of synthetic polymers and proteins which are biodegradable in nature. Microparticles improves bioavailability, reduces the side effects, improves stability, decreases dose frequency and targets the drug to specific site at predetermined rate. The different types of microspheres are bioadhesive, floating, radioactive, polymeric and biodegradable microspheres. In future microspheres will track down the focal spot in novel drug delivery conveyance, especially in diagnostics, genetic materials, targeted and effective drug delivery.

I. INTRODUCTION

Microparticles are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microparticles are sometimes referred to as micro particles. Microparticles are defined as “monolithic spheres or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles” or can be defined as structure made up of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. It has a particle size less than 200 μm . Materials used Microparticles used usually are polymers. Microparticles had been explored significantly for their use in the subject of drug transport and various polymers had been utilized for the formulation of the microspheres, which in turn have been assessed for distinctive purposes. Eventually the whole dose and few adverse reactions can be decreased due to the fact that a steady plasma concentration is maintained.

In recent years there is great interest in developing sustained drug delivery systems by using biopolymers to provide many advantages such as reduced side effects, improved drug utilization and decreased dosing frequency when compared with conventional dosage forms. Microparticulate drug delivery system has been widely produced using the spray drying technique and has gained significant importance among the techniques used in the pharmaceutical industries. Pulmonary route is commonly used and has been well accepted as a portal for non-invasive drug delivery for many lung diseases and it is explored for decades as an alternative for systemic as well as local drug delivery.

Pulmonary route is widely being employed to deliver drug molecules into the airways for the treatment of local disorders such as asthma, bronchitis, chronic obstructive pulmonary disorders (COPD) and respiratory infections. There have also been many attempts and increasing interest for systemic delivery of macromolecules through pulmonary delivery 1-4. To achieve the desired therapeutic effect, drug particles have to travel, deposit and penetrate into the appropriate part of the lungs depending on their particle size, size distribution of carriers containing drug, inhaler device and formulation techniques. Spray drying, is one of the

most suitable techniques once the specialized particle type is required and becomes feasible alternative to conventional methods which are already used. Moreover, being a continuous production method.

CHARACTERISTICS OF MICROPARTICLES :-

MICROPARTICLES PROPERTY :-

Sr. No.	Property	Consideration
1	Size Diameter	Uniformity/distribution
2	Composition	Density, Refractive Index, Hydrophobicity/ Hydrophilicity, Nonspecific binding, Auto fluorescence
3	Surface Chemistry	Reactive groups, Level of functionalization, Charge
4	Special Properties	Visible dye/fluorophore, Super paramagnetic

Table 1: Microparticles property

CRITERIA FOR MICROPARTICLES PREPARATION :-

- ❖ The ability to incorporate reasonably high concentrations of the drug.
- ❖ Stability of the preparation after synthesis with clinically acceptable shelf life.
- ❖ Controlled particle size and dispersability in aqueous vehicles for injection.
- ❖ Release of active reagent with a good control over a wide time scale.
- ❖ Biocompatibility with a controllable biodegradability
- ❖ Susceptibility to chemical modification.

DRUG RELEASE MECHANISMS FROM MICROPARTICLES :-

1. Diffusion-controlled Release
2. Erosion-Controlled Discharge
3. Controlled Swelling Release

APPLICATIONS OF MICROPARTICLES :-

- Microparticles in Vaccine Delivery.
- Ophthalmic Drug Delivery
- Gene delivery
- Nasal drug delivery
- Oral drug delivery
- Intratumoral and local drug delivery
- Peroral drug delivery
- Colonic drug delivery
- Multiparticulate delivery system
- Targeting using Microparticulate Carrier.
- Monoclonal Antibodies Mediated Microspheres Targeting.
- Chemoembolisation.

RECENT ADVANCEMENT IN MICROPARTICLES :-

- Important utilizations of chitosan polymer Cholesterol-lowering effects.
- Prolonged release and targeting of anticancer drugs to tumors.
- Increase Stability of Drug.
- Orthopaedic Patients.
- Cosmetics industry.
- Dental Medicine.
- Chitosan as Permeation Enhancer.
- Effect of chitosan: citric acid ratio on drug Release.
- Chitosan as Permeation Enhancer.
- Enhanced Bone Formation by transforming growth factor.

ADVANTAGES OF MICROPARTICLES :-

- Microparticles provide constant and prolonged therapeutic effect.
- Reduces the dosing frequency and thereby improve the patient compliance.
- They could be injected into the body due to the spherical shape and smaller size.
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.

LIMITATION :-

Some of the disadvantages were found to be as follows:

- The modified release from the formulations.
- Differences in the release rate from one dose to another.
- Dosage forms of this kind should not be crushed or chewed.

METHODS OF PREPARATION OF MICROPARTICLES :-

1. Spray Drying
2. Solvent Evaporation
3. Single emulsion technique
4. Double emulsion technique
5. Phase separation coacervation technique
6. Spray drying and spray congealing
7. Solvent extraction

SPRAY DRYING:

Concept of spray drying technique (Fig.1) depending upon the removal of solvent or the cooling of solution the two processes are spray drying & spray is congealing.

Spray drying is the most widely used industrial process involving particle formation and drying. Therefore, spray drying is an ideal process where the end product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density, and particle shape.

PRINCIPLE: Three steps involved in spray drying.

1. **ATOMIZATION:** of a liquid feed change into fine droplets.
2. **MIXING:** it involves the passing of hot gas stream through spray droplets which result in evaporation of liquids and leaving behind dried particles.
3. **DRY:** Dried powder is separated from the gas stream and collected. In this technique polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization spray congealing. Very rapid solvent evaporation, however leads to the formation of porous micro particles.

4. Spray drying process mainly involves five steps :

- I. Concentration: Feedstock is normally concentrated prior to introduction into the spray dryer.
- II. Atomization: The atomization stage creates the optimum condition for evaporation to a dried product having the desired characteristics.
- III. Droplet-air contact: In the chamber, atomized liquid is brought into contact with hot gas, resulting in the evaporation of 95%+ of the water contained in the droplets in a matter of a few seconds.
- IV. Droplet drying: Moisture evaporation takes place in two stages.
- V. Separation: Cyclones, bag filters, and electrostatic precipitators may be used for the final separation stage. Wet Scrubbers are often used to purify and cool the air so that it can be released to atmosphere.

During the first stage, there is sufficient moisture in the drop to replace the liquid evaporated at the surface and evaporation takes place at a relatively constant rate, and The second stage begins when there is no longer enough moisture to maintain saturated conditions at the droplet surface, causing a dried shell to form at the surface. Evaporation then depends on the diffusion of moisture through the shell, which is increasing in thickness.

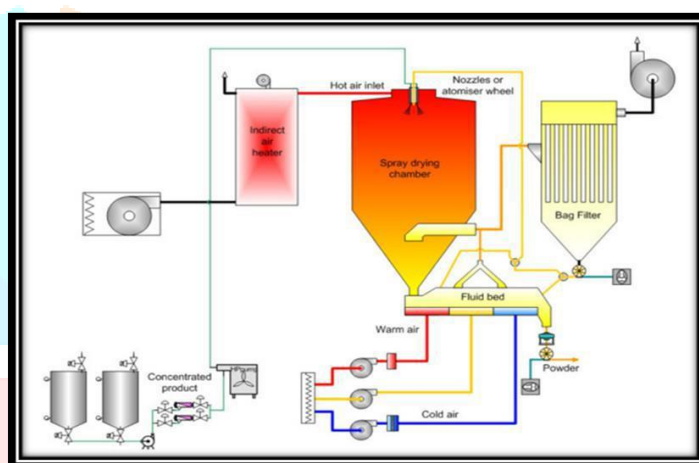


Fig. 1 Spray drying method for preparation of Microparticles.

WORKING :-

1. These processes are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent this processes are named spray drying.
2. In spray drying, the polymer is dissolved in a volatile organic solvent such as dichloromethane, acetone etc. The drug in solid form is dispersed in the polymer solution with high speed homogenization.
3. This dispersion is then subjected to atomization in a stream of hot air. The atomization leads to the formation of small droplets or the fine mist from which the solvent evaporates instantaneously leading to the formation of the microspheres in a size range 1-100µm. Microparticles are separated from the hot air with the help of cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of this process is feasibility of operation under aseptic conditions.

APPLICATIONS OF SPRAY DRYING METHOD :-

Spray drying method is very popular among users in pharmaceutical and food industries since spray drying machine can meet the GMP requirements of the two fields and has superior performance. It is especially suitable for the drying and granulation of Chinese and Western medicines and foods. Granules prepared have strong disintegration, good fluidity, and instant solubility, and can be directly used for tableting, capsule filling, granules, and solid drinks.

Spray drying method is also widely used in dye drying. It can dry dye fine powder, super- fine powder, dust-free powder, and hollow granules. This method can be divided into three categories.

Airflow atomization: which uses compressed air or water vapor to atomize the material liquid.

2. **Pressure atomization:** a high-pressure pump is applied to press out the material liquid from the nozzle at high speed and thus forming a mist.

3. **Rotary atomization:** the material liquid is added to the high-speed rotating disc (7000 ~ 28000r / min) in the atomizer, and then the material liquid is quickly thrown out and atomized. The third category — rotary atomization has a good effect, short time, and high labor productivity, which is favored by the dyestuff industry.

ADVANTAGES OF SPRAY DRYING METHOD:-

1. Rapid drying process.
2. Materials can be directly dried into powder.
3. It is easy to change the drying conditions and adjust product quality standards.
4. There is a certain negative pressure in the drying room, which guarantees the hygienic conditions in the production, avoids the dust flying in the workshop, and improves the purity of the product.
5. High production efficiency and fewer operators.
6. Large production capacity and high product quality.
7. The spray volume can reach several hundred tons per hour.

LIMITATION OF SPRAY DRYING METHOD:-

1. The equipment is complex, covers a large area, and requires a large investment.
2. The price of a spray dryer and powder recovery device is relatively high.
3. The thermal efficiency is not high and the heat consumption is large.

EMULSION SOLVENT EVAPORATION TECHNIQUE :-

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2 % sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with 11emineralized water and desiccated at room temperature for 24 hrs. microspheres were prepared by this technique.

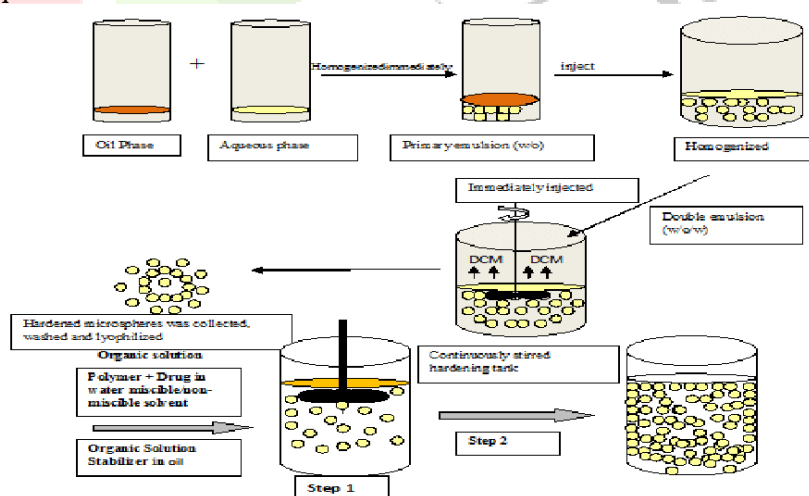


Fig. 2 Emulsion solvent evaporation technique

The emulsion solvent evaporation technique for microsphere creation, while offering advantages like controlled drug release and improved bioavailability, also presents challenges such as potential for burst release and the need for specialized equipment.

ADVANTAGES:

Controlled Drug Release, Improved Bioavailability, Protection of Drugs:

DISADVANTAGES: Potential for Burst Release, High Costs.

SINGLE EMULSION TECHNIQUE :-

Single emulsion technique In this method, microsphere is prepared by emulsification technique; coating polymer is dissolved in an organic volatile solvent which leads to the formation of a polymeric solution. The resultant polymeric solution added into an aqueous phase containing emulsifying agent leads to the formation of o/w emulsion. This emulsion is then stirred for a few hours under constant environmental condition, then filtered, and dried into desiccator



FIG. 3 SINGLE EMULSION TECHNIQUE

ADVANTAGES:-

- High Yield and Reproducibility
- Ease of Scaling Up
- Controlled Particle Size and Morphology
- Versatile for Encapsulation
- Reduced Energy Requirement
- Improved Stability

DISADVANTAGES:-

- Emulsifier Contamination
- Poor Transparency
- Final Stage Requires Coagulation and Aqueous Phase Removal
- Potential for Aggregation
- Challenges in scaling up

DOUBLE EMULSION TECHNIQUE :-

This technique involves the preparation of double emulsion either w/o/w or o/w/o type. The Aqueous solution contains the drug which is dispersed in the organic phase. The organic phase containing coating polymer encapsulates the drug present in the dispersed aqueous phase and leads to the formation of primary emulsion. Then, this primary emulsion undergoes homogenizing or sonicating before adding into an aqueous solution of PVA to form a secondary emulsion, and then prepared microspheres filtered and dried in desiccator.

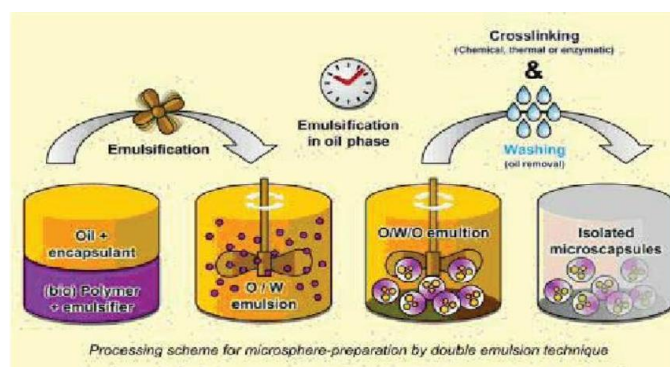


Fig. 4 Double emulsion technique

ADVANTAGES:-

Efficient Encapsulation, Versatile Polymer Choice, Controlled Release.

DISADVANTAGES: Complex Formulation, Potential Instability, Difficulty in Controlling Size Distribution, Higher Costs.

PHASE SEPARATION COACERVATION TECHNIQUE :-

This technique is based on the principle of decreasing the solubility of the polymer organic phase to affect the formation of polymer rich phase called coacervates. In this process, the drug particles are dispersed in a polymer solution and an incompatible polymer is added which makes the first polymer to phase separate and engulf the drug particles. In order to avoid agglomeration stirring should be done.

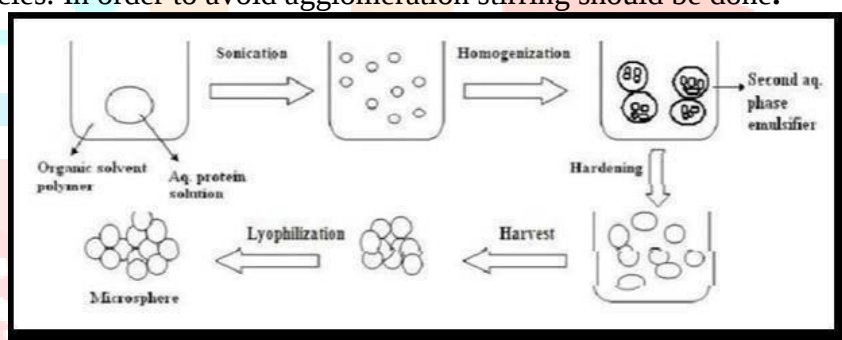


Fig. 5 Phase separation coacervation technique

ADVANTAGES:-

High Encapsulation Efficiency, Reduced Toxicity, Improved Handling and Bioavailability, Simplicity and Scalability Protection of Active Ingredients.

DISADVANTAGES:-

Potential Toxicity, Instability of Core Particles, Poor Drug Stability and Loading Efficiency.

CONCLUSION:

This review mainly emphasis on the microparticles . It is observed that as compared to other novel drug delivery system. The concept of microparticles drug delivery systems offers certain advantages over the conventional drug delivery systems such as controlled and sustained delivery. Apart from that microspheres also allow drug targeting to various systems such as ocular, intranasal, oral and IV route. Microparticles have better choice for drug delivery particularly in pulmonary disease such as TB, COPD, Asthma. Therefore in future microparticles will have an important role to play in the advancement of medicinal field. Micropartilces provide a number of advantages over existing technology. Micropartilces formulation shows more potency and is having more effectiveness in *in-vivo* drug delivery system and also, they are found to be effective carriers for the novel drug delivery system.

REFERENCES

1. Athira K, K Vineetha, Krishnananda Kamath K, A. R. Shabaraya. Microspheres As A Novel Drug Delivery System. *Int. J. Pharm. Sci. Rev. Res.*, 75(1), July - August 2022; Article No. 27, Pages: 160-166
2. B. Sree Giri Prasad, V. R. M Gupta² N. Devanna³ K. Jayasurya A review microspheres as drug delivery system.
3. Xu Y, Liu H, Song L. Novel drug delivery systems targeting oxidative stress in chronic obstructive pulmonary disease: a review. *Nanobiotechnol* 2020;18:145.
4. Microspheres as pulmonary delivery systems- A review. *Journal of Chinese Pharmaceutical Sciences*. 2021;30(7):545555. doi:10.5246/jcps.2021.07.043
5. Anurag Sharma, Dilip Agrawal, M.P.khinchi, Natasha Sharma, M.K.Gupta . formulation and evaluation of rifampicin microspheres for lung targeting. *Asian Journal of Pharmaceutical Research and Development* Vol.1 (2) March– April 2013: 133-142.
6. Kakar S, Jain A. Magnetic microspheres: An Overview. *Asian Pac J Health Sci* 2019;6:81-9.
7. Sharma M, Dev SK, Kumar M, Shukla AK. Microspheres as a suitable drug carrier in sustained release drug delivery: An overview. *Asian J Pharm Pharmacol* 2018;4:102-8.
8. Nidhi P, Anamika C, Twinkle S, Mehul S, Hitesh J, Umesh U. Controlled drug delivery system: A review. *Indo Am J Pharm Sci* 2016;3:227-33.
9. Prasad BS, Gupta VR, Devanna N, Jayasurya K. Microspheres as drug delivery system-a review. *J Glob Trends Pharm Sci* 2014;5:1961-72.
10. Lengyel M, Kállai-Szabó N, Antal V, Laki AJ, Antal I. Microparticles, microspheres, and microcapsules for advanced drug delivery. *Sci Pharm* 2019;87:20
11. Farraj NF, Johansen BR, Davis SS, Illum L. Nasal administration of insulin using bioadhesive microspheres as a delivery system. *J Control Release* 1990;13:253-61.
12. Genta I, Conti B, Perugini P, Pavanetto F, Spadaro A, Puglisi G. Bioadhesive microspheres for ophthalmic administration of acyclovir. *J Pharm Pharmacol* 1997;49:737-42.
13. Chandna A, Batra D, Kakar S, Singh R. A review on target drug delivery: Magnetic microspheres. *J Acute Dis* 2013;2:189-95.
14. Zhang J, Zhang S, Wang Y, Zeng J. Composite magnetic microspheres: Preparation and characterization. *J Magn Magn Mater* 2007;309:197-201.
15. Sangale SB, Barhate SD, Jain BV, Potdar M. Formulation and evaluation of floating felodipine microsphere. *Int J Pharm Res Dev* 2011;3:163-70.
16. Srivastava AK, Ridhurkar DN, Wadhwa S. Floating microspheres of cimetidine: Formulation, characterization and *in vitro* evaluation. *Acta Pharm* 2005;55:277-85.
17. De Cuyper M, Bulte JW, editors. Urs HÄfeli. In: *Radioactive Microspheres for Medical Applications. Physics and Chemistry Basis of Biotechnology*. Vol. 7. Springer: Dordrecht; 2001. p. 213-48.
18. El-Helw AM, Al-Hazimi AM, Youssef RM. Preparation of sustained release phenobarbitone microspheres using natural and synthetic polymers. *Med Sci* 2008;15:39-51.
19. Michael JK. Spray drying and spray congealing of pharmaceuticals. In: *Encyclopedia of pharmaceutical technology*. Marcel Dekker INC, NY. 1993;14:207-221.
20. Ronald CD. Spray drying innovative use of an old process. *Design Elements*. 1997;7:97–113.
21. Roser B. Sterile spray drying for stable liquid 21st century pharmaceuticals. In: *Innovations in pharmaceutical technology*. 2005:50-54.
22. Seville PC, Li Hy and Learoyd TP. Spray dried powders for pulmonary drug delivery. *Crit Rev Ther Drug Carrier Syst*. 2007;24(4):307-360.
23. Shoyele SA and Cawthorne S. Particle engineering techniques for inhaled biopharmaceuticals. *Adv Drug Delivery Rev*. 2006;58:1009–1029.
24. Alipour S, Montaseri H, Tafaghodi M. Preparation and characterization of biodegradable paclitaxel loaded alginate microparticles for pulmonary delivery. *Colloids and Surfaces B: Biointerfaces*. 2010;81(2):521-529. doi:10.1016/j.colsurfb.2010.07.050.
25. Aliasgar kundawala , Vishnu patel , Harshapatel , Dhaglaram choudhary. Preparation, In Vitro Characterization, and In Vivo Pharmacokinetic Evaluation of Respirable Porous Microparticles Containing Rifampicin. *Sci Pharm*. 2014; 82: 665–681.