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A BRIEF REVIEW ON – SUSTAINED RELEASED MICROSPHERES BY SPRAY DRYING METHOD

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Abstract

The most convenient method of sustained delivery of drug is undoubtedly oral, but oral sustained release of the drug for an extended period of time that exhibits more absorption in stomach and upper small intestine, has not been successful with conventional approaches. Microspheres are multiarticulate drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the drug to specific site at a predetermined rate.

Sustained release microspheres are widely used in pharmaceutical formulations to achieve controlled drug delivery and improve patient compliance. In this study, we aimed to develop sustained release microspheres using the spray drying method and evaluate their drug release profiles and physicochemical properties. The present review highlights an introduction to the concept of sustained release drug delivery and the importance of microsphere-based formulations in optimizing therapeutic outcomes. It then delves into the fundamentals of the spray drying technique, including process parameters, equipment, and formulation considerations that influence the properties of microspheres. A critical appraisal of the various polymers commonly used in the preparation of sustained release microspheres via spray drying is provided, highlighting their biocompatibility, biodegradability, and drug release mechanisms. The review discusses the diverse applications of sustained release microspheres prepared by spray drying across different therapeutic areas.

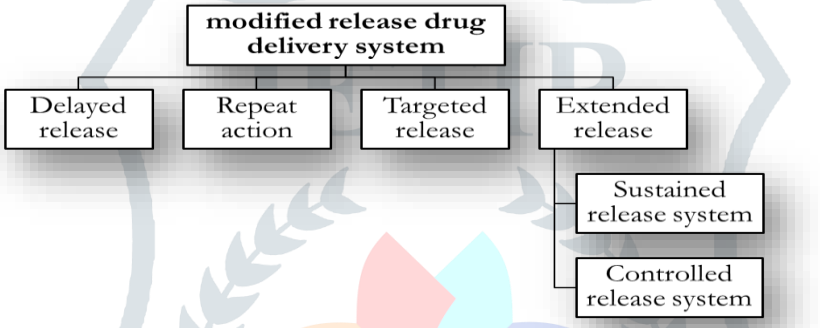
Keywords: Oral drug delivery system, Sustained release drug delivery system, Microspheres, Spray drying technique.

INTODRUCTION

The development of different drug method in the later part of the eighteenth and early part of century. Pills, syrups, capsules, tablets, elixirs, solutions, extracts, emulsion, suspensions, cachets, nebulizers used in this

method and many other conventional delivery mechanisms while many of these delivery systems utilize drugs derived from plant extracts. The modern era of medicine development started from discovery of vaccines in 1885 and in the late nineteenth century technique for purification of drugs from plant sources was discovered.

Substance such as chemical elements, compound, drugs, antibodies, cell or other agents may be administrated by different route as every route have both advantages as well as disadvantages and as, for instance, the absorption, bioavailability and metabolism of substance are factors which should be consider carefully. The orally administered drug delivery is still considered as a standard system in pharmaceuticals field and still considered, safest, convenient and economical method of administration providing best route for patient compliance. Is the most preferred and acceptable option as the oral route gives maximum active surface area amounts all drug delivery system for administration of various drug. [1]



Classification of modified release drug delivery system

SUSTINED RELEASE DRUG DELIVERY SYSTEM

The purpose of designing controlled release dosage forms is to maintain relatively constant concentration of drug in the blood, tissue or target organs. So, it is a dosage from that release one or more drug constantly in predetermined pattern for a fixed period of time. Most of the controlled released drug delivery system involves more than one mechanism and the drug released rate from this delivery system could vary at differed release stages.

Controlled release includes any drug delivery system achieves release of drug over and extend period on time. The first generation from 1952 to 1980 was very productive in developing several oral and transdermal controlled release formulation for clinical application while the second generation from 1980 to 2010 was not as successful in clinical products. The first generation of drug delivery deal with physiochemical problem while second with biological barrier. [3]

Advantages of sustained drug delivery system over the conventional dosage form [4]

- Reduced dosing frequency
- Dose reduction
- Improved patient compliance
- Reduced toxicity due to overdose
- Night time dosing can be avoided

- Concentration of the drug in the blood plasma at a constant level.
- Reduce the fluctuation of peak value constant at rate.

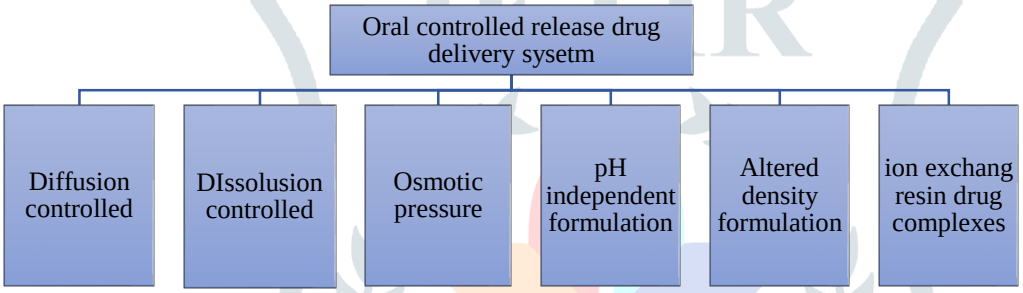
Disadvantages of sustained drug delivery system over the conventional dosage form

- Dose dumping
- Reduce potential for dosage adjustment
- Poor system availability in general
- Unpredictable or poor in vitro and in vivo correlation

Factors affecting sustained drug delivery system [5]

1) Physiochemical factor
   a) Aqueous solubility
   b) Partition coefficient [P(w/0)]
   c) Drug pka and ionization at physiological pH
   d) Drug stability
   e) Molecular size and diffusivity
2) Biological factor
   a) Half life
   b) Therapeutic index
   c) Size of dose
   d) Absorption window
   e) Plasma concentration response relation

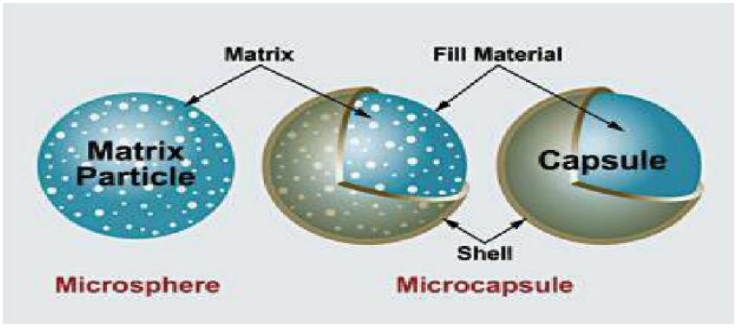
f) Concertation depending on transfer of drug



Types of oral controlled release drug delivery system

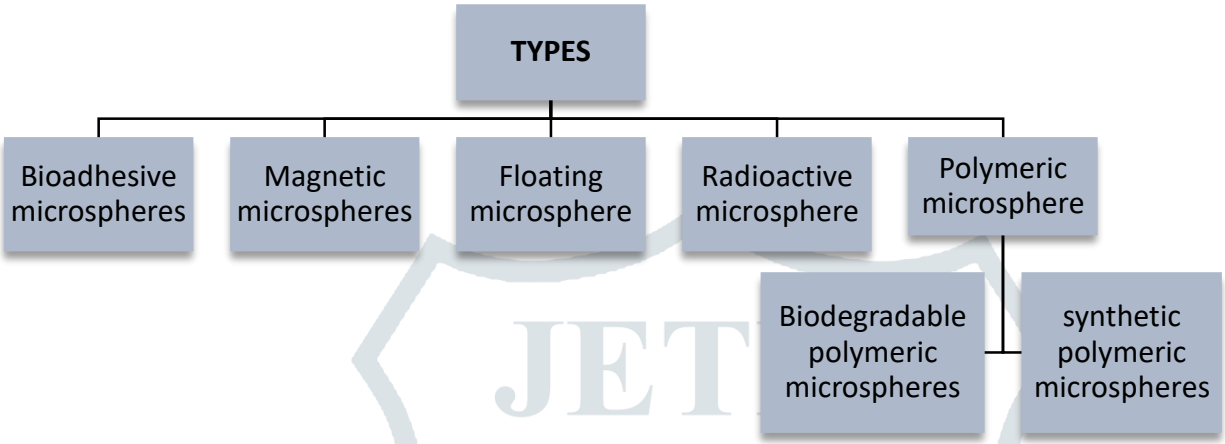
MICROSPHERES

Microspheres are small spherical particles with diameters from 1 to 1000µm (or 50nm to 2mm). In some cases, microspheres are also known as microparticles. Microspheres can be produced from several natural and synthetic polymeric materials or even from inorganic materials for example, microspheres can be produced from commercially available polymers or ceramics. Depending on the method, solid or porous microspheres can be obtained for specific intended application. [6]



The IUPAC defines a microsphere as a *"microparticle of spherical shape without membrane of any distinct outer layer"*, with a note that quality, sphericity, uniformity, particle size, and particle size distribution (PSD) vary wildly. [7]

Types of Microspheres



Types of Microspheres

Method of Preparation of Microsphere [8-18]

1) Solvent removed technique
   A. Emulsion solvent evaporation technique
      a. Oil in water (o/w) emulsion solvent evaporation
      b. Water in oil (w/o) emulsion solvent evaporation
      c. Water in oil in water (w/o/w) emulsion solvent evaporation
   B. Emulsion solvent extract
   C. Emulsion solvent diffusion
2) Coacervation and phase separation technique
   A. By temperature change
   B. By incompatible polymer addition
   C. By non-solvent addition
   D. By salt addition
   E. By polymer- polymer interaction
   F. By solvent evaporation
3) Cross-linking technique

A. Chemical cross linking
B. Thermal cross linking

4) Polymerization technique
   A. Normal polymerization
   B. Vinyl polymerization
   C. Interfacial polymerization
5) Pan coating
6) Precipitation technique
7) Air suspension coating
8) Wax coating and Hot melt method
9) Multi orifice centrifugal process
10) Freeze drying technique
11) Spary drying method

Polymer Used in Preparation of Microspheres [7]

1) **Biodegradable Polymers**:
- Poly (lactic-co-glycolic acid) (PLGA)
- Poly (lactic acid) (PLA)
- Poly(caprolactone) (PCL)

2) **Natural Polymers**:
- Chitosan
- Alginate

3) **Hydrogel-forming Polymers**:
- Hydroxypropyl methylcellulose (HPMC)
- Poly (ethylene glycol) diacrylate (PEGDA)

4) **pH-Responsive Polymers**:
- Eudragit®

5) **Temperature-Sensitive Polymers**:
- Poly(N-isopropylacrylamide) (PNIPAM)

6) **Multiarticulate Systems**:
- Micro sponges

7) **Surface-Modified Polymers**:
- Polyethylene glycol (PEG)

Advantages of Microspheres [7]

- Size reduction leads to increase in surface area which can enhance solubility of the poorly soluble drug.
- Provide constant drug concentration in blood which can increase patent compliance,
- Decrease dose and toxicity.
- Coating of drug with polymers helps the drug from enzymatic cleavage hence found to be best for drug delivery.
- Less dosing frequency leads to better patient compliance.
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- Protects the GIT from irritant effects of the drug.
- Convert liquid to solid form and to mask the bitter taste.
- Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
- Reduce the reactivity of the core in relation to the outside environment.
- Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
- Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Limitation of microspheres [7]

- The costs of the materials and processing of the controlled release preparation are substantially higher than those of standard formulations.
- The fate of polymer matrix and its effect on the environment.
- The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
- Reproducibility is less.

Application of microspheres [7]

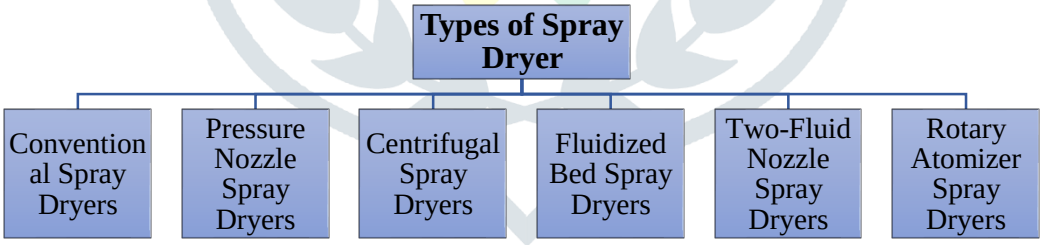
1. **Drug Delivery**: Microspheres are utilized as carriers for drugs, proteins, or genetic materials. Their controlled release properties enable sustained drug delivery, improving therapeutic efficacy and reducing side effects.
2. **Medical Imaging**: In medical diagnostics, microspheres labelled with contrast agents are used for imaging purposes. They enhance the visibility of specific tissues or organs in techniques like MRI, CT scans, and ultrasound.
3. **Cosmetics**: Microspheres are added to cosmetics such as creams, lotions, and makeup for their ability to improve texture, provide smoothness, and control release of active ingredients like vitamins or fragrances.
4. **Biotechnology**: In biotechnology, microspheres serve as platforms for biomolecule immobilization, facilitating processes like enzyme immobilization, protein purification, and DNA hybridization assays.

5. **Environmental Remediation**: Microspheres are employed for environmental applications such as water purification and soil remediation. They can absorb pollutants, heavy metals, and oils, aiding in cleaning contaminated sites.
6. **Coatings and Paints**: Microspheres are used in coatings and paints to control viscosity, improve durability, and create specific textures. They also enhance thermal and sound insulation properties.
7. **Food Industry**: Microspheres find applications in the food industry for encapsulation of flavours, vitamins, and nutrients, enhancing shelf-life, stability, and controlled release in products like beverages, confectionery, and supplements.
8. **Oil and Gas Exploration**: In the oil and gas industry, microspheres are utilized as tracers to analyse fluid flow patterns in reservoirs and wellbores, aiding in reservoir characterization and production optimization.
9. **Tissue Engineering**: Microspheres serve as scaffolds in tissue engineering for cell culture, providing a three-dimensional environment for cell growth, differentiation, and tissue regeneration.

SPRAY DRYER

The spray drying technique was first described in 1860 with the first spray dryer instrument patented by Samuel Percy in 1872. With time, the spray drying method grew in popularity, at first mainly for milk production in the 1920s and during World War II, when there was a need to reduce the weight and volume of food and other materials. In the second half of the 20th century, commercialization of spray dryers increased, as did the number of sprays drying applications. [19,20]

Types of Spray Dryer



Types of Spray Dryer

1. **Conventional Spray Dryers:** Conventional spray dryers are the most widely used type. They operate by atomizing the liquid feed into fine droplets using a nozzle or rotary atomizer. These droplets are then dried by hot air in a drying chamber, resulting in dried powder or granules. Conventional spray dryers are versatile and suitable for a wide range of applications.
2. **Pressure Nozzle Spray Dryers:** Pressure nozzle spray dryers use high-pressure pumps to atomize the liquid feed into small droplets. The advantage of this type is the ability to produce finer droplets, which can lead to better control over particle size and morphology. Pressure nozzle spray dryers are often used for applications requiring precise control over product characteristics.

3. **Centrifugal Spray Dryers:** Centrifugal spray dryers utilize a spinning disk or wheel to atomize the liquid feed. The feed is pumped onto the spinning surface, where centrifugal force generates fine droplets that are then dried in a drying chamber. Centrifugal spray dryers are suitable for processing heat-sensitive materials and can produce uniform particles.
4. **Fluidized Bed Spray Dryers:** In fluidized bed spray dryers, the liquid feed is atomized into droplets that are introduced into a fluidized bed of hot air. The droplets dry as they come into contact with the hot air and are continuously agitated within the fluidized bed, resulting in rapid drying and the formation of porous particles. Fluidized bed spray dryers are commonly used for heat-sensitive materials and products requiring controlled particle morphology.
5. **Rotary Atomizer Spray Dryers:** Rotary atomizer spray dryers use a rotating disk or wheel to atomize the liquid feed into fine droplets. The droplets are then dried in a drying chamber using hot air. Rotary atomizer spray dryers are known for their high throughput and are often used in large-scale industrial applications.
6. **Two-Fluid Nozzle Spray Dryers:** Two-fluid nozzle spray dryers use two streams of gas (usually air) to atomize the liquid feed into droplets. One stream carries the liquid feed, while the other provides the atomization gas. This type of spray dryer offers good control over droplet size and distribution and is suitable for processing heat-sensitive materials.

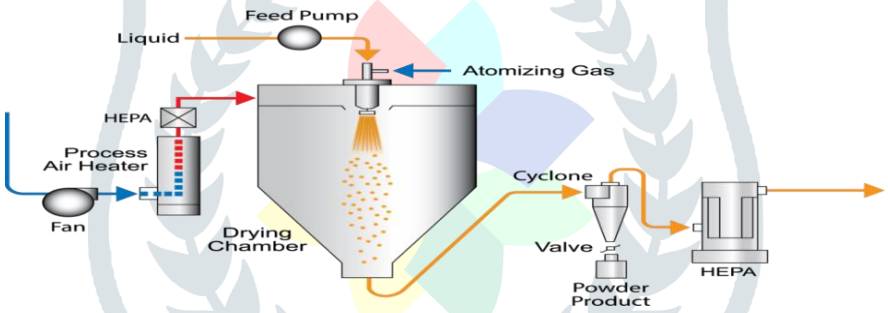


Fig 12. Spray dryer

A Spray Dryer Consist Of [22]

1. **Liquid Feed System**: This system involves the preparation and delivery of the liquid feed material to the spray dryer. It includes components such as pumps, tanks, and piping to transport the feed material to the atomization device.

2. **Atomization Device**: The atomization device is responsible for breaking down the liquid feed material into fine droplets. Common atomization devices include pressure nozzles, rotary atomizers, and two-fluid nozzles.

3. **Drying Chamber**: The drying chamber is where the atomized droplets come into contact with hot air or gas to facilitate evaporation of the moisture. It is usually cylindrical or conical in shape and is constructed from materials such as stainless steel, carbon steel, or specialty alloys to withstand high temperatures and corrosive environments. The size of the drying chamber variations in between 2.5 to 9 m and also elevation is 25 m or even more.

4. **Air Handling System**: The air handling system includes components for heating, filtering, and circulating the drying air or gas. This system ensures that the air entering the drying chamber is at the desired temperature and humidity level for efficient drying.
5. **Particle Collection System**: After drying, the particles are collected from the drying chamber. Various collection methods may be used, including cyclone separators, bag filters, or electrostatic precipitators, to separate the dried particles from the exhaust air.
6. **Exhaust System**: The exhaust system removes the moisture-laden air and any fine particles from the drying chamber. It typically includes a fan or blower to generate airflow and ductwork to vent the exhaust air to the atmosphere or to a filtration system.
7. **Control System**: The control system monitors and regulates various parameters such as inlet air temperature, feed flow rate, and outlet moisture content to maintain optimal conditions for the drying process. It may include sensors, controllers, and human-machine interface (HMI) panels for operator control and monitoring.

Working

- The liquid feed material, which can be a solution, suspension, or emulsion, is prepared and pumped to the top of the spray dryer.
- The liquid feed material is introduced into the drying chamber through a nozzle or atomizer. The atomizer breaks the liquid into small droplets, increasing the surface area for rapid evaporation.
- **i**nside the drying chamber, the atomized droplets come into contact with a stream of hot air or gas. The hot air rapidly evaporates the moisture from the droplets, leaving behind dried particles.
- As the droplets travel through the drying chamber, heat from the hot air causes the moisture within the droplets to evaporate.
- As the moisture evaporates, the dissolved or suspended solids in the liquid feed material become concentrated, forming solid particles.
- Once the particles are formed, they settle to the bottom of the Drums or cyclones. It usually used to collect solids practical. The collected particles can be discharged from the bottom of the cyclones for further processing or packaging.
- The moisture-laden air and any fine particles entrained in the air stream are exhausted from the drying chamber through an exhaust system. The air may be filtered to remove any remaining particles before being released into the atmosphere or recirculated back into the dryer.
- Throughout the drying process, various parameters such as inlet air temperature, feed flow rate, and outlet moisture content are monitored and controlled by a control system.

Advantages

- Fast Drying
- Enhanced Product Stability
- Improved Solubility
- Reduced Risk of Contamination
- Powdered products are often easier to handle, transport, and store compared to liquid or semi-solid forms.
- Reduce the environmental impact associated with traditional drying methods
- Cost-effective in the long run due to its high efficiency and productivity.
- Control over particle size distribution, resulting in uniform product quality.
- Highly efficient for large-scale production. [21]

Disadvantages

- Can be expensive to purchase and maintain, which may pose a barrier to entry for smaller businesses or startups.
- Consumes a significant amount of energy.
- Reducing the overall yield and potentially impacting product quality.
- Cause degradation or loss of volatile components in heat-sensitive materials.
- Limited Application for Certain Materials [21]

Application

1. **Food Industry**:
   - **Powdered Food Products**: Used to produce powdered food products such as milk powder, coffee powder, fruit powders, and flavouring.
   - **Encapsulation**: Used for encapsulating sensitive food ingredients such as vitamins, Flavors, and probiotics to protect them from moisture, oxidation, and degradation during storage and processing.
   - **Dairy Products**: Employed in the production of dairy products such as whey powder, cheese powder, and yogurt powder, enabling the preservation of dairy components and the creation of value-added ingredients.
2. **Pharmaceutical Industry**:
   - **Drug Delivery Systems**: Used to produce drug delivery systems such as inhalable powders, microspheres, and nanoparticles for controlled release and targeted drug delivery applications.

- **Pharmaceutical Ingredients**: Produce pharmaceutical ingredients such as APIs (Active Pharmaceutical Ingredients) and excipients in a powdered form, improving solubility, bioavailability, and processing efficiency.
- **Formulation Development**: Development of formulations for oral, injectable, and topical dosage forms, enabling the creation of stable, uniform, and patient-friendly drug products.

3. **Chemical Industry**:
   - **Catalyst Production**: In the production of catalysts and catalyst supports for chemical reactions, enabling high surface area and uniform particle size distribution for improved reaction kinetics and efficiency.
   - **Detergent Powders**: In the manufacturing of detergent powders for household and industrial applications, providing enhanced cleaning performance and convenience in handling and storage.
   - **Pigments and Dyestuffs**: To produce pigments, dyes, and colorants in a powdered form for applications such as paints, inks, coatings, and textiles.
4. **Ceramics Industry**:
   - **Ceramic Powders**: In the production of ceramic powders for forming processes such as pressing, extrusion, and casting, enabling uniform particle size distribution and improved green strength.
   - **Advanced Materials**: In the synthesis of advanced materials such as nanomaterials, composites, and functional coatings for electronic, automotive, aerospace, and biomedical applications.
5. **Environmental Applications**:
   - **Waste Management**: Processes to convert liquid waste streams into dried solids for easier handling, transportation, and disposal.
   - **Air Pollution Control**: Systems to remove pollutants from gas streams by converting them into dry particulate matter for collection and disposal

Examples of microsphere work dealing with spray drying method

Sr. no.	Drug	Outcome	Reference
1.	Etanidazole	Aim of the study was prepared and evaluated Etanidazole sustained release microspheres by spray drying method using non-halogenated solvents and PLGA polymer. It resulted that, the	**[23]**

		spherical and porous microspheres prepared by DCM, the microspheres prepared by the solvent EA are all nonporous with a doughnut like surface structure due to its comparatively rapid phase transition but slow solvent evaporation rate. It was found that larger percentage of EA in the fabrication of PLGA 65:35 microspheres decrease the initial burst, release rate and prolongs the release duration of Etanidazole.	
2.	Paclitaxel	Aim of the study was prepared and evaluated injectable paclitaxel-loaded poly (D, L-lactide) sustained release microspheres for the inhibition of brain glioma by spray drying method employing ethyl acetate as solvent. It resulted that microspheres possess a narrow size distribution with the average diameter of 4.6 μm. The surface of the microspheres was smooth, and the paclitaxel dispersed in microspheres in amorphous state. Compared with the commercial formulation, the sustained release microsphere showed a stronger inhibition on the tumour cells, suggesting the potential application of long-term delivery of paclitaxel-loaded PLA microspheres in clinic tumour therapy.	**[24]**
3.	Ketoprofen	Aim of the study was prepared and evaluated Ketoprofen Spray-dried Microspheres Based on Eudragit® RS and RL. Polymer type and drug–polymer ratio as well as manufacturing parameters affect the preparation. It resulted that, good yields of production, high drug content, and encapsulation efficiency using appropriate spray-drying technological parameters. All formulations have good morphological and dimensional characteristics spherical shape, smooth surface, and narrow size distribution. RS and RL 100 used as mixture and in the drug-to-polymer ratio of 1:3 are suitable to produce microspheres containing	**[25]**

		ketoprofen, by spray-drying.	
4.	Acetaminophen	Aim of the study was prepared and evaluated microspheres of Chitosan–Tripolyphosphate by spray drying method using Acetaminophen as model drug. it resulted that, the size range of 3.1–10.1 mm. positively charged (zeta potential ranged from +18.4 to +31.8). The encapsulation efficiency of these microspheres was in the range of 48.9–99.5%. The swelling capacity of chitosan–TPP microspheres increased with increases in the molecular weight of chitosan and decreases with increasing volume of 1% wt./vol TPP solution used for the cross-linking reaction.	**[26]**
5.	Levofloxacin	Aim of the study was prepared and evaluated Dual Cross-Linked Chitosan sustained release microspheres with Spray-Drying Technique using Levofloxacin. It resulted that, the microspheres demonstrated high encapsulation efficiency (72.4~98.55%) and were uniformly spherical with wrinkled surface. The mean particle size was between 1020.7±101.9 and 2381.2±101.6 nm. All microspheres were positively charged (zeta potential ranged from 31.1±1.32 to 42.81±1.55 mV). The in vitro release profiles showed a sustained release of the drug and it was remarkably influenced by the cross-linking process.	**[27]**
6.	Aceclofenac	Aim of the study was prepared and evaluated of spray-dried mucoadhesive microspheres using solutions of ACE and three polymers, namely, Carbopol, chitosan, and polycarbophil, for investigated as a means of controlling drug release and minimizing or eliminating local side effects. It resulted that, size was found to be (6.60–8.40 μm), production yield was found (34.10–55.62%), and encapsulation efficiency was found (58.14–90.57%). In vitro release studies were performed	**[28]**

		in phosphate buffer (pH 6.8) up to 10 hours. The spray-drying process of solutions of ACE with polymeric blends can give prolonged drug release.	

Conclusion

This review gives brief information about sustained release microspheres by spray drying method multiunit dosage from which improve safety and efficacy of active ingredients excellent flow property which is fabricated in single dosage from. Sustained release microspheres offer numerous advantages over conventional dosages, including improved efficacy, reduced dosing frequency, enhanced patient compliance, and minimized side effects, making them valuable tools in pharmaceutical drug delivery. Now a day spray drying technique has gained much interested technique in pharmaceutical formulation development, offering opportunities for enhanced drug solubility, stability, bioavailability, and dosage form versatility. Today spray drying method represent efficient pathway for novel drug delivery in the scope for different oral immediate and controlled delivery system.

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