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Microballons

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ABSTACT

The purpose of writing this review on micro balloons is to accumulate the recent literature with a special focus on novel technological advancements in floating drug delivery system to achieve gastric retention. Microballoons promises to be a potential approach for gastric retention. Microballoons drug-delivery systems are based on no effervescent system containing empty particles of spherical shape without core ideally having a size less than 200 micrometer. Microballoons drug delivery systems have shown to be of Micro balloons becomes novel technology in pharmaceutical Microballoons are spherical empty vesicles without core and that can remain buoyant in gastric region for prolong period of time without irritation in gastrointestinal tract. Particles having a low-density system that can efficiently prolong the gastric retention time of the drugs, thus enhanced bioavailability and thus improve the dosing frequency. These are less soluble at higher pH environment. As microballoons delivery systems provide longer retention in gastric pH and enhance the solubility of drugs that are less soluble in high Ph environment.

I. INTRODUCTION

Conventional oral dosage forms such as tablets, capsules provide a specific drug concentration in systemic circulation which do not release at the constant rate for prolonged period of time. Microballoons are the gastro retentive drug delivery system and it is based on the no effervescent approach. Generally, microballoons are in spherical shape without core. These microballoons are free flowing powder which consists of protein and synthetic polymers and these microballoons size ranges from 200µm.

Gastro Retentive Drug Delivery System

The gastro-retentive drug delivery system (GRDDS) has recently gained tremendous popularity in the oral drug delivery field. It is a commonly used solution to retaining the dosage type in the stomach for a prolonged period of time and slowly releasing the medication that can tackle many problems associated with traditional oral delivery, including poor bioavailability.

MICROBALLOON

Microballoons are gastro retentive drug-delivery systems with non-effervescent approach. Microballoons (Hollow microsphere) are in strict sense, empty particles of spherical shape without core. These microspheres are characteristically free flowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Microballoons are considered as one of the most favourable buoyant systems with the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere.

MECHANISM OF MICROBALLOONS

Microballoons are low-density systems that have sufficient buoyancy to float over gastric fluid and remain instomach for prolonged period of time. As the system floats over gastric fluid, the drug is released slowly atdesiredMicroballoons. rate resulting in increased gastric retention with reduced fluctuations in plasma drugconcentration. When microballoons come in contact with gastric fluid, the gel forms and polymers hydrate toform a colloidal gel barrier that controls the rate of fluid.

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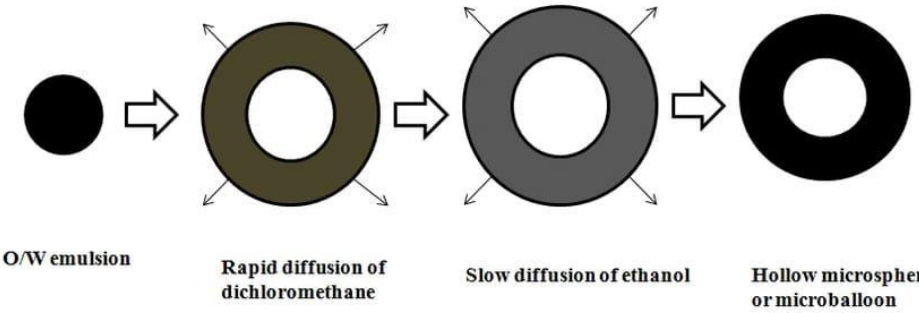

Materials For Preparation OfMicroballoons

1. Drugs
2. Polymer
3. Solvent
4. Processing medium
5. Surfactant
6. Crosslinking agents
7. Hardening agents

1. Drugs: Drugs with narrow therapeutic window in GI tract, mainly absorbed from stomach and upper part of GIT, locally act in the stomach, degrade in the colon, supplements, Chlordiazepoxide, Cinnarizine, Riboflavin, Levodopa, Antacids, Misoprostol, Ranitidine HCl, Metronidazole and Amoxicillin trihydrate.The drugs incorporated in the solidified shell of the polymer were found to be partially or completely amorphous.

2. Polymer: Cellulose acetate, chitosan, eudragit, acrycoat, Methocel, polyacrylates, polyvinyl acetate, Carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene.The use of polymers for synthesizing microspheres enables the production of uniformly shaped and well-defined spheres in a wide range of sizes. Polymeric microspheres can be synthesized using a variety of different methods

3. Solvent:Microballoons were prepared by the solvent evaporation technique as employed by Struebeletal. Metformin, HPMC K4M, and EC were dissolved in a mixture of ethanol and dichloromethane at room temperature Solvents It should have good volatile properties, so that it should easily come out from the emulsion leaving hollow microspheres e.g., ethanol, dichloromethane (DCM), acetonitrile, acetone, isopropyl alcohol (IPA)

4. Processing medium: It Is used to harden the drug polymer emulsified droplets when the drug polymer solution is poured into it, should not interact with the former; mainly used processing medium are liquid paraffin, polyvinyl alcohol and water.

5. Surfactant: They are stabilizers or emulsifiers, play the role of hardening the microspheres as well. E.g., tween 80, span 80 and SLS

6. Cross linking agent: Chemical cross-linking of microspheres can be achieve cross linking agents such as formaldehyde, glutaraldehyde or by using chlorides such as Teri phthaloyl chloride. The method is limited to drugs that do not have any chemical interaction with the cross-linking agent.

7. Hardening agent: This helps to harden the microspheres formed in the processing medium e.g., n-hexane, petroleum ether.

METHOD OF PREPARATION

1. Solvent evaporation method
2. Emulsion solvent diffusion method
3. Solvent diffusion evaporation technique
4. Spray drying

1. solvent evaporation method:

The polymers for development of such systems include Eudragit, HPMC KM4 and ethyl cellulose etc. Polymers are mixed with drug and further this mixture is dissolved in the solution of ethanol, acetone or dichloromethane either alone or in combination to get homogenous polymer solution. The resulting solution is poured into 100 mL of liquid paraffin rotating at 1500 rpm. The emulsion is formed and heated at 35oC temperature for 3hr. After the formation of a stable emulsion, the acetone or dichloromethane is completely evaporated and resulting solidified microspheres is filtered using Whatman filter paper. This hollow microsphere imparts the floating and sustained properties.

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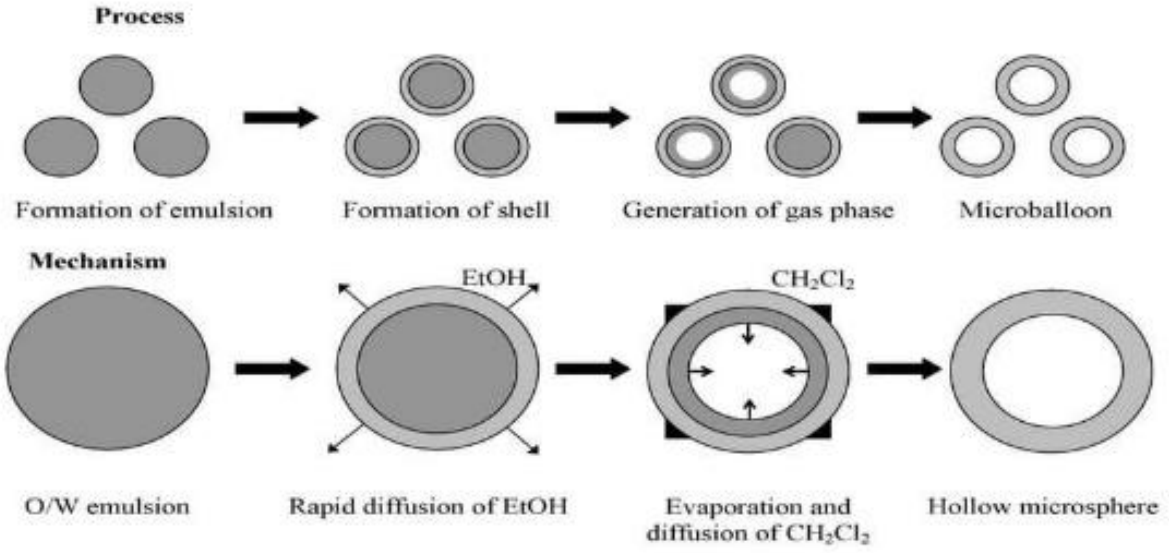

Fig. Solvent evaporation method

2. Emulsion solvent diffusion method:

The mixture of drug polymer is dissolved in the solution of ethanol: dichloromethane and this mixture is adding dropwise to polyvinyl alcohol solution. This solution is stirred at 1500 rpm for 1 hour and at different temperature ranges. In the emulsion solvent diffusion method, the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible. The organic solvent diffuses gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse into the droplets

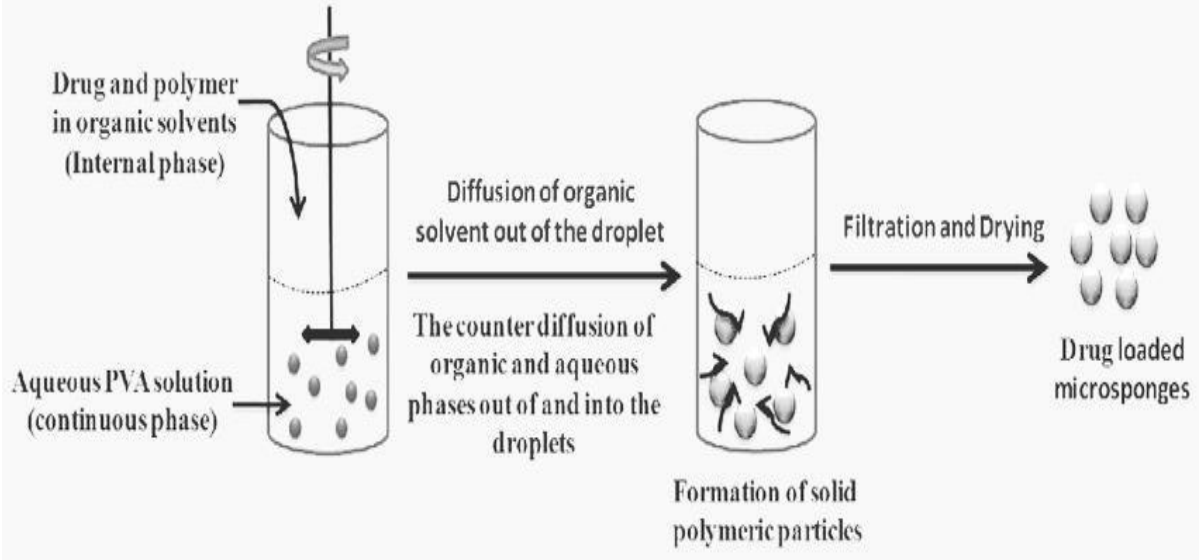

Fig.Emulsion solvent diffusion method

3. Solvent diffusion-evaporation technique:

This technique is with slight modification of both emulsion solvent evaporation method and emulsion solvent diffusion method. Drug, polymers and 0.1% of surfactant such as PEG are mixed in the solution of ethanol: dichloromethane(1:1) at

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room temperature. This solution isslowly introduced into 80 ml of 0.46% w/wof polyvinyl alcohol as emulsifier. This isstirred using propeller agitator usingpropeller agitator for 1 hourforevaporation of organic solution and thenfilteredit. The best formulation is selectedon the basis of optimized result of variousprocess variables such as polymer ratio,drug polymer ratio, stirring speed andconcentration of emulsifier. polymer stirringspeed and concentration of emulsifier.

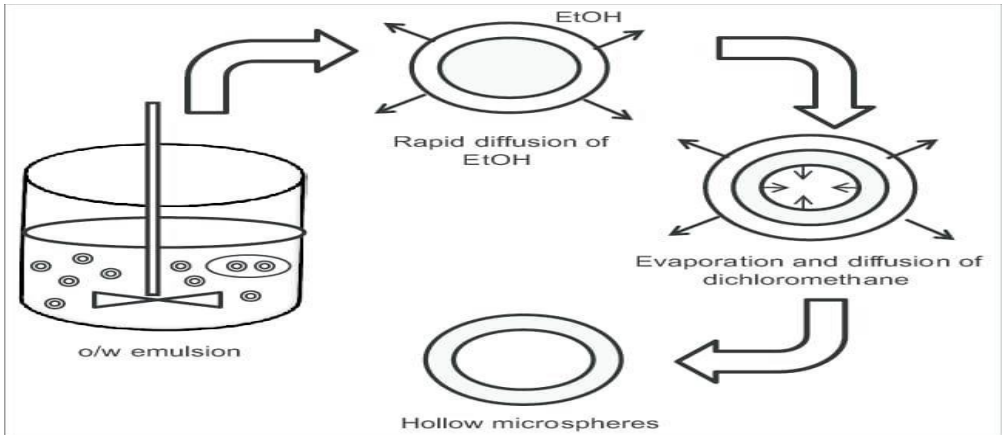

Fig.Solvent diffusion-evaporation technique

4. Spray drying:

Spray drying is the most widely employed industrial process for particle formation and drying. It is an ideal process where the required particle size distribution, bulk density and particle shape can be obtained in a single for 1 hour for evaporation of organic solution and then filtered it. The best formulation is selected on the basis of optimized result of various process variables such as polymer ratio, drug: polymer ratio, stirring speed and concentration of emulsifier. Spray drying is the most widely employed industrial process for particle formation and drying. It is an ideal process where the required particle size distribution, bulk density and particle shape can be obtained in a single step. First of all, polymer is dissolved in a suitable volatile organic solvent such as dichloromethane, acetone etc. to form a slurry. The slurry is then sprayed into the drying chamber, concentration gradient of the solute forms inside the small droplet with the highest concentration being at the droplet surface. This is because the time of the solute diffusion is longer than that of the solvent in the droplets evaporating during the drying process. Subsequently, a solid shell appears leading toward formation of microspheres. Separation of the solid products from the gases is usually accomplished by means of a cyclone separator while the traces of solvent are removed by vacuum drying and the products are used for later use.

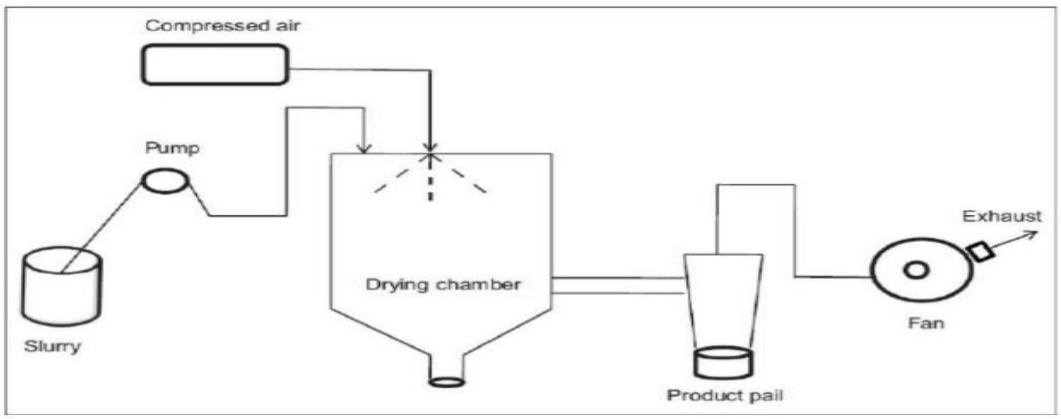

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Fig.Spray drying

FACTORS AFFECTING PHYSIOCHEMICAL PROPERTIES OF MICROBALLOON

1. **Stirring rate**: The size of the microspheres is dependent on the stirring rate. With increase in agitation, there is a decrease in size of the microspheres though the increase in not significant statistically. The bulk of the polymers are not breakable into fine droplets within the range of the study.
2. **Temperature of preparation**: At various temperatures like 20, 30, 40 and 50°C, the drug and the polymer solution is poured into aqueous solution of poly vinyl alcohol. The microspheres with greater porosity on the surface are obtained at 20 or 30°C. the size of the particle decreases with the increase in temperature. At the power of mixing input i.e., at higher temperature the viscosity of the emulsion is reduced and it is much easier for the breakdown of the emulsion,
3. **Plasticizers**: The properties of elasticity and flexibility are given to the formulation with the addition of the plasticizers on to the walls of the material. The rupturing under pressure or brittleness is avoided with the addition of the plasticizers. With the increase in the concentration of the plasticizer the drug release increases significantly.
4. **Volume of aqueous phase (continuous phase)**:The buoyancy increases with increase in aqueous phase as the particle size decreases. The time required for stirring is reduced with increase in volume of aqueous phase. For example, the solubility of the dichloromethane is 1% w/v in water. It is preferred to use 400 to 500ml of aqueous phase as the solidification of the particles occurs at a faster rate than 200ml of aqueous phase .
5. **Solvent ratio**: Irregular shaped microspheres were formed with bridging of small volume of the solvent while the usage of large volume of liquid bridging prevents emulsion droplets solidification. A careful control over the volume of dichloromethane is required [18]. The morphology of the microspheres is affected by the ratio of dichloromethane and ethanol. The ratio must be optimized to give spherical shaped microspheres. The ratio of ethanol to dichloromethane is 2:1 gives spherical shaped microspheres.
6. **Amount of polymer and viscosity**: At lower concentration of the polymer, smaller microballoons were formed and it is exposed to larger surface area which willgive faster drug release.
7. **Effect of solvent**: Dichloromethane is opted as the solvent for the preparation of microballoons as it is a good solvent for polymer and drugs. With the use of dichloromethane, the shape of the microspheres is not spherical in shape hence; methanol is used to solve this problem. Though the shape is spherical with the use of methanol, the texture was not smooth and hence methanol is replaced with ethanol to solve this problem.
8. **Concentration of the emulsifier**: As the concentration of the surfactant reduces from 1% to 0.25%, there is an increase in the particle size and size distribution. Emulsifier plays a vital role in decreasing the interfacial tension between the dispersed droplets and continuous phase and also it protects the droplets from collision and coalescence

ADVANTAGES

1. Reduces the dosing frequency and thereby improve the patient compliance.
2. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects, and despite the first-pass pass effect because fluctuation in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
3. Hollow microspheres are used to decrease material density and Gastric retention time is increased because of buoyancy.
4. Enhanced absorption of drugs which solubilize only in stomach.
5. Drug releases in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved.
7. Reduces dosing frequency and thereby improve the patient compliance.
8. Better drug utilization will improve the bioavailability and reduce the incidence or intensity
9. of adverse effects and despite first pass effect because fluctuations in plasma drug
10. Concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.

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DISADVANTAGES

1. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut Differences in the release rate from one dose to another.
2. Controlled-release release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
3. Dosage forms of this kind should not be crushed or chewed.
4. Drugs having irritant effect on gastric mucosa are not suitable candidates for FDDS.eg: NSAIDs, some antibiotics, digoxin, theophylline, corticosteroids, iron (ferrous sulfate), oral contraceptives, and tricyclic antidepressants.
5. Drugs which are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable e.g., nifedipine.
6. They are not suitable candidates for drugs with stability or solubility problem in stomach e.g., ranolazine.

APPLICATIONS OF MICROBALLOONS

1. Microballoons can ameliorate the pharmacotherapy of the stomach through local drug release and it leads to high drug concentrations in the gastric mucosa, thus eliminating Helicobacter pylori from the sub mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis.
2. These empty microspheres allow sustained drug release behaviour and release the drug over a prolonged period of time.
3. Hollow microspheres are fabricated as a floating controlled drug delivery system.
4. It is recently described that drugs is to be entrapped in hollow microspheres and reduces the fluctuations include Prednisolone, Lansoprazole, Celecoxib, Piroxicam, Theophylline, Diltiazem hydrochloride, Verapamil hydrochloride and Riboflavin, Aspirin, Griseofulvin, lbuprofen, Terfenadine.
5. Floating microspheres can gravity enhance the absorption of those drugs which have poor bioavailability and thus they improve absolute bioavailability.
6. Floating microspheres are site specific drug delivery especially for those drugs which are specifically absorbed from stomach or the proximal part of small intestine.
7. Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug prednisolone.
8. Floating microspheres are especially effective in delivery of sparingly soluble and insoluble drugs.
9. It is known that becomes less as the solubility of a drug decreases, the time availablefordrug dissolution adequate and thus the transit time becomes a significant factor affectingdrug absorption.
10. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheresmay avoid chance for solubility to become the rate-limiting step in release by restrictingsuch drugs to the stomach.
11. The positioned gastric release is useful fordrugs efficiently absorbed through stomachsuch as Verapamil hydrochloride.
12. The gastroretentive floating microspheres will alter beneficially the absorption profile ofthe active agent, thus enhancing its bioavailability.
13. These microspheres systems provide sustained drug release behaviour and release the drugover a prolonged period of time.
14. Hollow microspheres of trainset are fabricated as a floating controlled drug deliverysystem.
15. Polymer granules having internal cavities prepared by de acidification when added toacidic and neutral media are found buoyant and provided a controlled release of the drugprednisolone.

II. CONCLUSION

Microballoons are low-density system and have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period without any irritation to gastro intestinal tract. The drug is released in controlled manner at desired rate when it floats over gastric fluid it resulting in the reduced fluctuations in plasma drug concentration. Hollow spheres promises to be a potential approach for the gastric retention. Optimized microballoons are novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery.

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