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MICROBALLONS: A REVIEW

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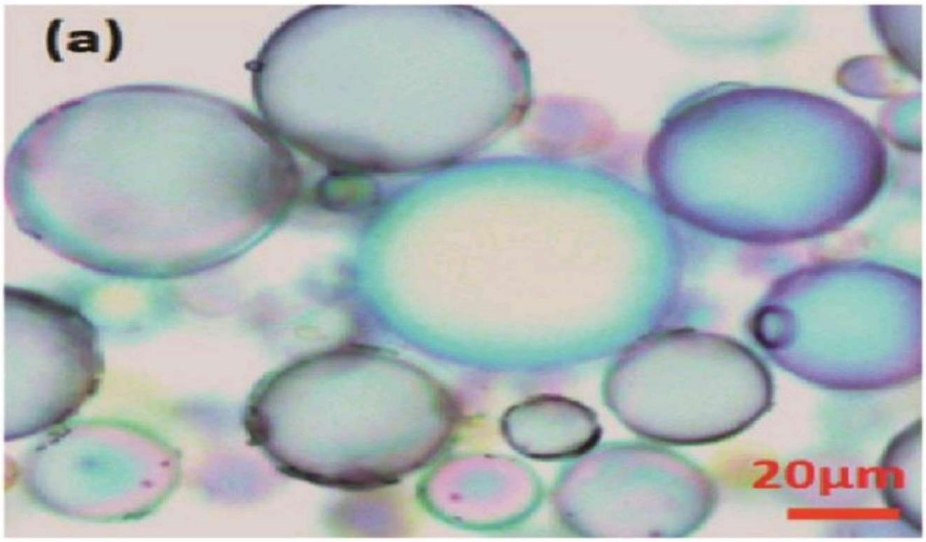
Abstract:

The purpose of writing this review on microballoons is to accumulate the recent literature with a special focus on the novel technological advancements in floating drug delivery system to achieve gastric retention. Microballoons (Hollow microsphere) promises to be a potential approach for gastric retention. Microballoons drug-delivery systems are based on non-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 Better significance in controlling release rate for drugs having site specific absorption. The Floating microballoons showed gastro retentive controlled release delivery with efficient means of enhancing the bioavailability and promises to be apotential approach for gastric retention. Optimized hollow microspheres will find the central place in novel drug delivery, particularly in safe, targeted and effective in vivo delivery promises to be a potential approach for gastric retention. They are gastro retentive drug-delivery systems, which provide controlled release properties. The advantages, limitation, methods of preparation of hollow microsphere, applications, polymers used in hollow microspheres, characterizations of microballoons and formulation aspects with various evaluation techniques and marketed products are covered in Detail.

Keyword: Microballons, Gastro tentative drug delivery system, Hollowsphere, Mucoadhesion, Controlled release, Floating system.

Introduction:

Microballoons are the gastro retentive drug delivery system and it is based on the non-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 200 mm. These microballoons are low density systems which have sufficient buoyancy to float over the Gastric fluid for prolonged period of time without any irritation to gastro intestinal tract. Microballoons are prepared by using different techniques such as simple Solvent evaporation method, double emulsion method, Phase separation coacervation method, polymerization method, spray drying method, spray congealing method and hot melten capsulation method.



Advantages:

- Improves patient compliance by decreasing dosing frequency.
- Gastric retention time is increased. Plasma drug concentration is maintained.
- Controlled release of drug for prolonged period of time.
- Site-specific drug delivery to stomach can be achieved.
- No risk of dose dumping.
- Enhanced absorption of drug which solubilize only in stomach.

Disadvantages:

- The modified release from the formulations.
- 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.
- 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.
- Dosage forms of this kind should not be crushed or chewed.

Application of Microballoons:

- Gastro retentive floating microspheres are very effective in the reduction of major adverse effect of gastric irritation.
- Floating microballoons are very effective approach in delivery of drug that has poor bioavailability because of their limited absorption in the upper GIT.
- The higher dose of drug can reduced due to increase in gastric retention times which lead to low dose frequency.
- These systems remain in stomach for long period of time and hence drug release in controlled manner.
- 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.
- These empty microspheres allow sustained drug release behavior and release the drug over a prolonged period of time. Hollow microspheres are fabricated as a floating controlled drug delivery system.
- 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, Ibuprofen, Terfenadine.
- 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. Floating hollow microcapsules of melatonin showed gastro retentive controlled-release delivery system. Release of the drug from these microcapsules is greatly retarded with release lasting for 1.75 to 6.7 hours in simulated gastric fluid. Most of the mucoadhesive microcapsules are retained within the stomach for more than 10 hours. e.g., Metoclopramide and glipizide loaded chitosan microspheres.

Mechanism of drug release:

When microballoons comes in the contact with the gastric Fluid the gel formers, polysaccharides and the polymers will Hydrate to form colloidal gel barriers that controls the rate Of fluid penetration in the device and the drug will release in Controlled manner. The surface of the drug dissolves the gel Layer is maintained by the hydration. The air trapped by swollen polymers which lowers the density and confers. Buoyancy to the microballons.

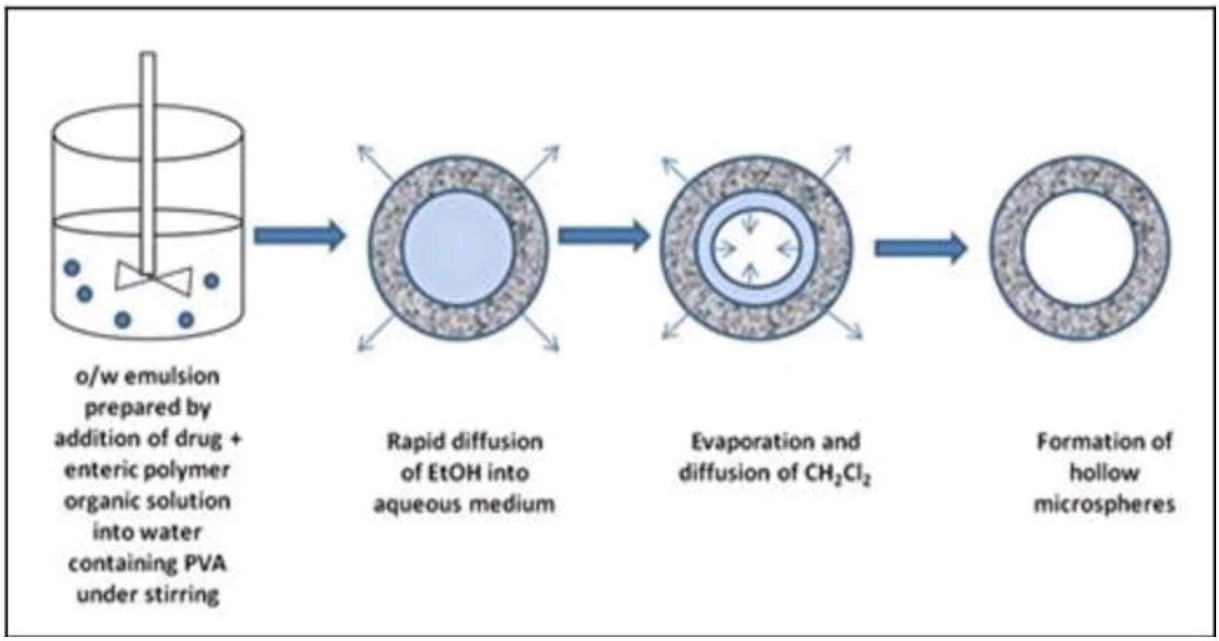


Fig: Microballons

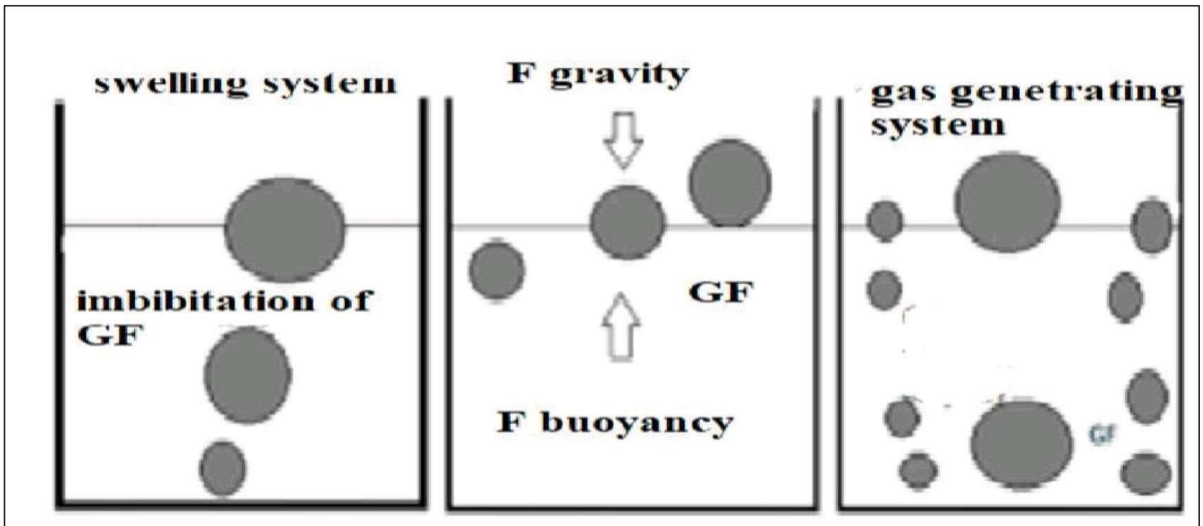
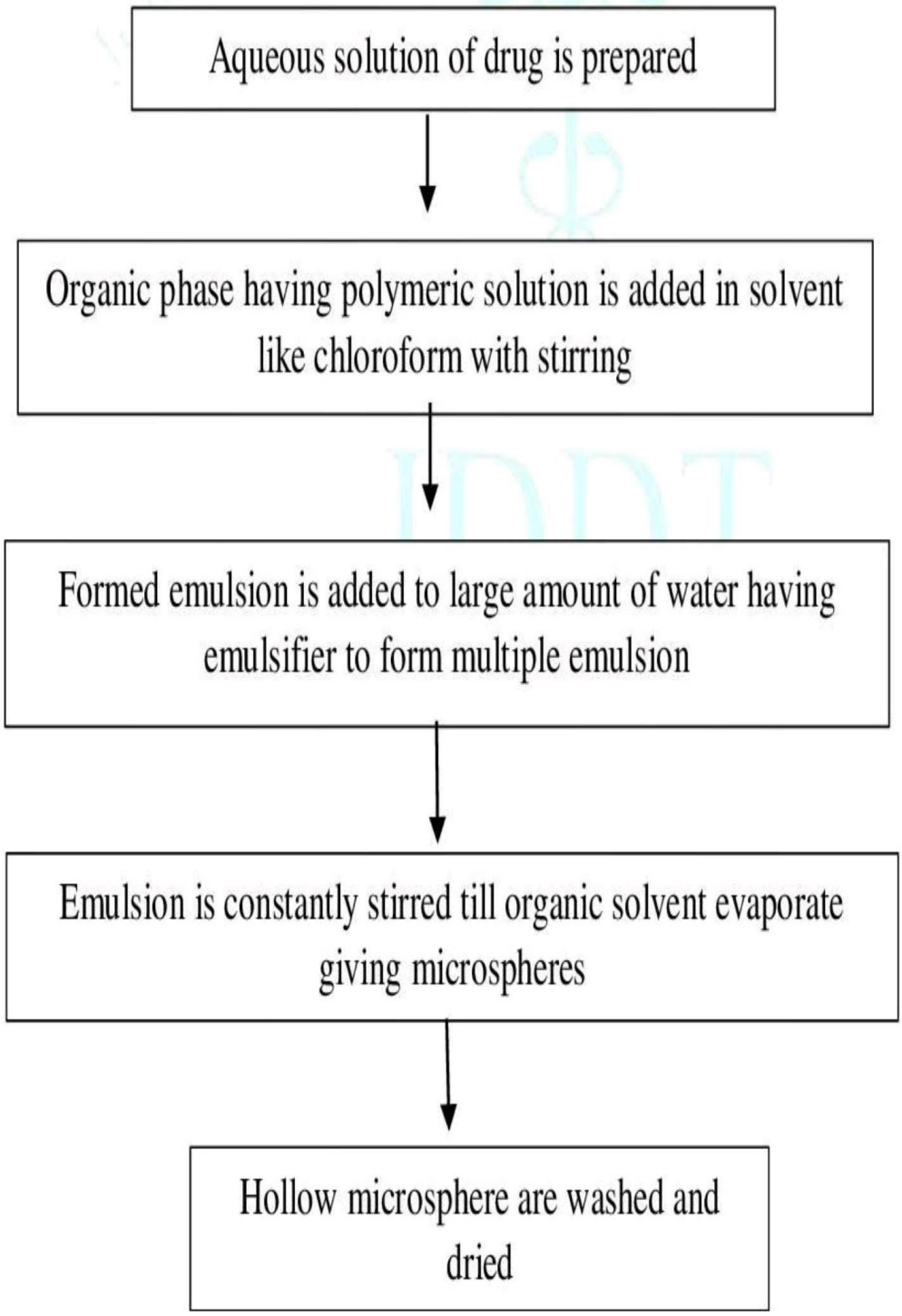


Fig: Mechanism of drug release

Formulation Method:

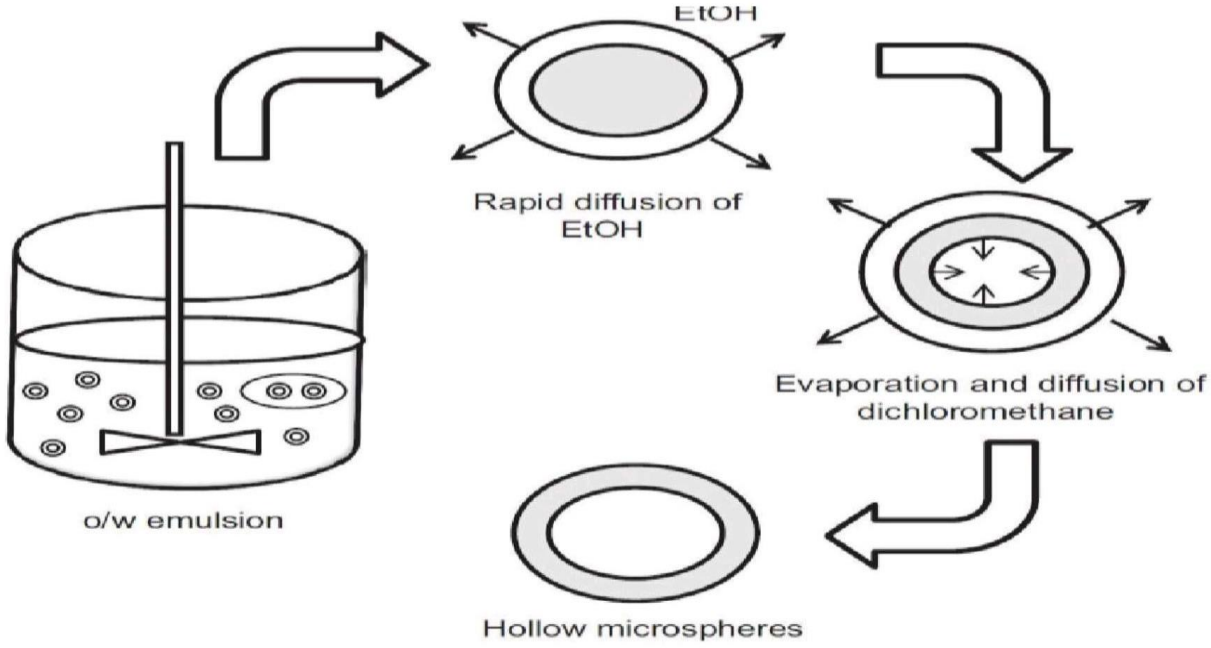
1. Emulsion Solvent Evaporation Method -



2. Emulsion Solvent Diffusion Method -

In this method solution of polymer and drug in ethanol methylene chloride is poured in to an agitated aqueous solution of poly vinyl alcohol the ethanol rapidly partition into the external aqueous phase and the polymer precipitate around methylene chlorine droplets.

The evaporation of entrapped methylene chloride leads to the formation internal cavities within the micro particles.



3. Single Emulsion Technique -

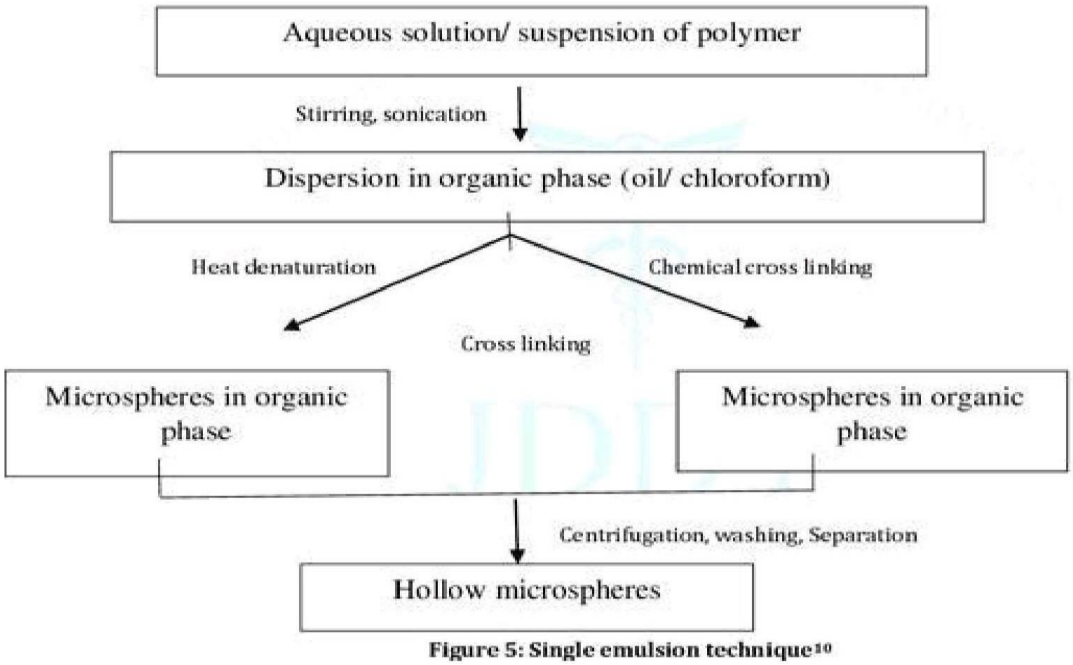
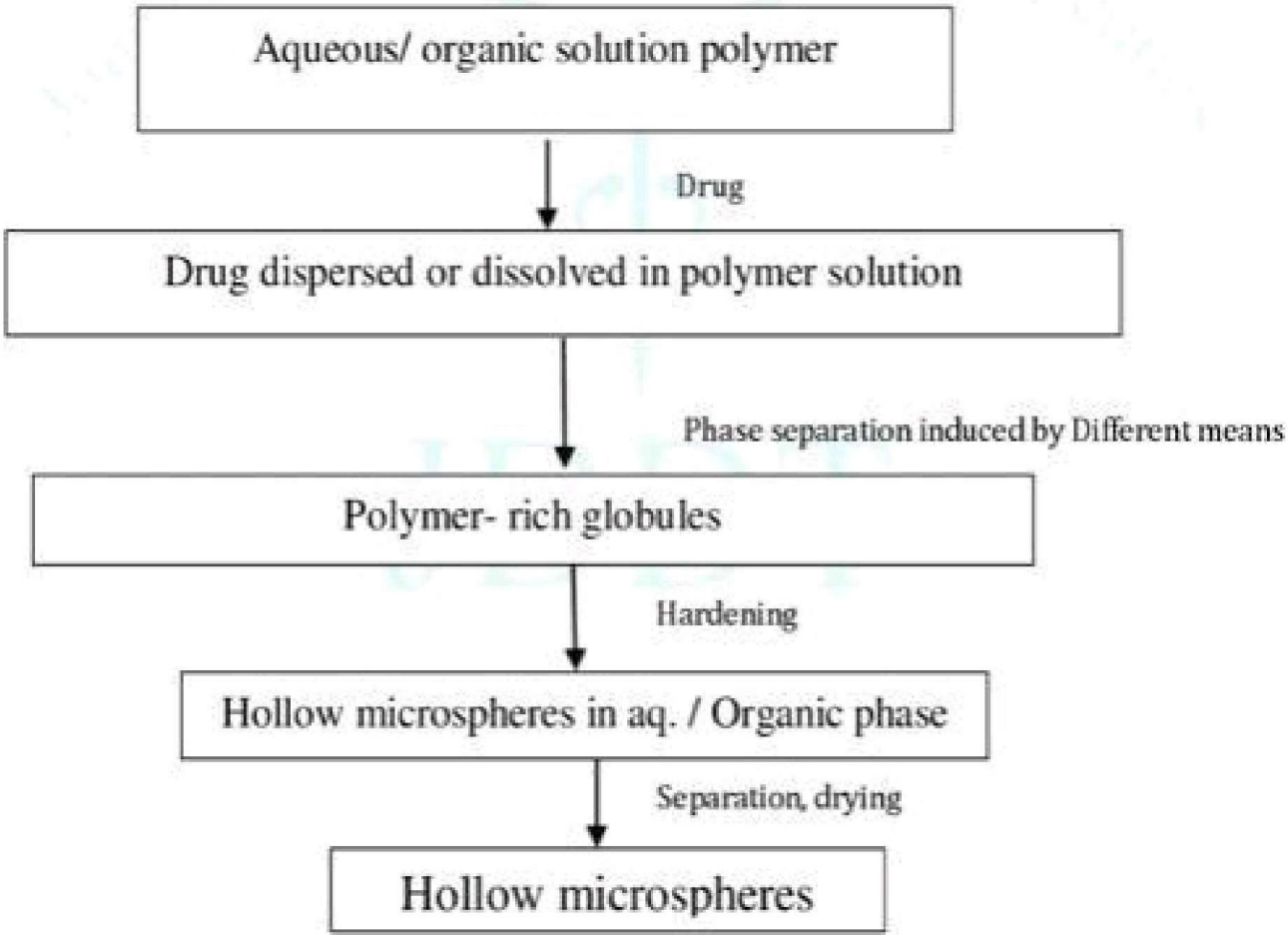


Figure 5: Single emulsion technique[10]

4. Coacervation Phase Separation Technique -



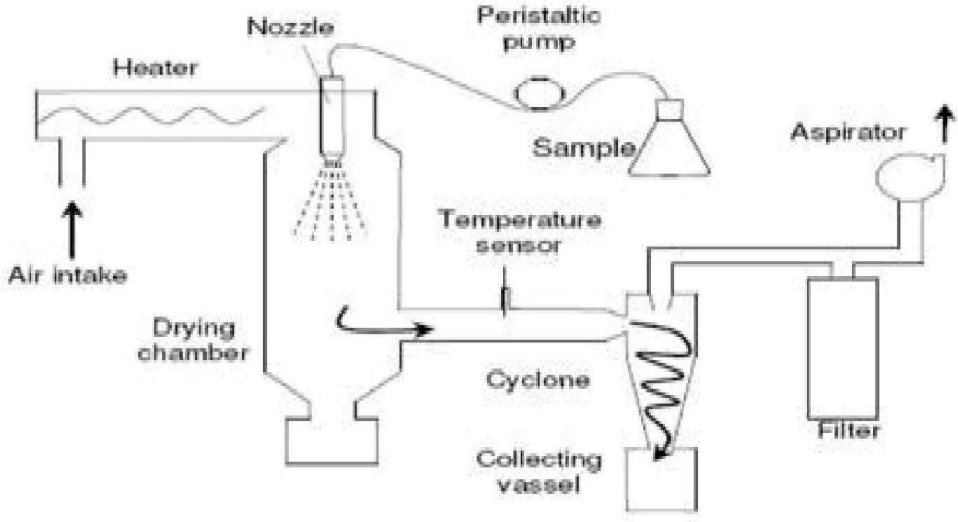
5. Spray Drying and Spray Congealing -

Spray drying: -

The coating solidification can be done by rapid evaporating of solvent in which coating material is dissolved.

Spray congealing: -

The coating solidification can be done by thermally congealing a molten coating material. The Removal of solvent is done by sorption, extraction or Evaporation.



Spray drying/ spray congealing

List of polymers used in hollow microballoons:

1. Cellulose acetate
2. Chitosan
3. Eudragit
4. Acry coat
5. Methoul
6. Polyacrylates
7. Polyvinyl acetate
8. Carbopol
9. Agar
10. polyethylene oxide
11. polycarbonates
12. Acrylic resins.

FACTORS AFFECTING PHYSICO CHEMICAL PROPERTIES OF MICROBALLOONS

a) Stirring rate: The size of the microspheres is proportional to the rate at which they are stirred. Increased agitation results in a reduction in microsphere size, but the difference are statistically insignificant. Within the study set, the majority of the polymers are incapable of being broken down into fine droplets.

b) Preparation temperature: The drug and polymer solution are poured at different temperatures such as 20, 30, 40, and 50 degrees
Celsius. At 20 or 30 degrees Celsius, the surface porosity of the microspheres increases. The size of the particle shrinks as the temperature rises. The emulsion viscosity is decreased at higher temperatures as the mixing input power is increased, making it much easier to break down the emulsion.

c) Plasticizers: Plasticizers are added to the material's walls to give it elasticity and flexibility. The addition of plasticizers prevents bursting under pressure or brittleness. The amount of drug released increases significantly as the plasticizer concentration rises.

d) Solvent ratio: Irregularly shaped microspheres were created by bridging a small volume of solvent, while bridging a large volume of liquid prevents emulsion droplets from solidifying. The amount of solvent must be carefully regulated. The morphology of the microspheres is influenced by the ratio of two solvents. The ratio must be optimized to produce spherical microspheres.

e) Polymer concentration and viscosity: Smaller microballoons were produced at lower polymer concentrations, exposing the drug to a greater surface region, resulting in faster drug release.

f) Emulsifier concentration: As the surfactant concentration decreases from 1% to 0.25 percent, the particle size and distribution increase. Emulsifiers are important because they reduce interfacial tension between dispersed droplets and the continuous phase, as well as prevent droplets from colliding and coalescence.

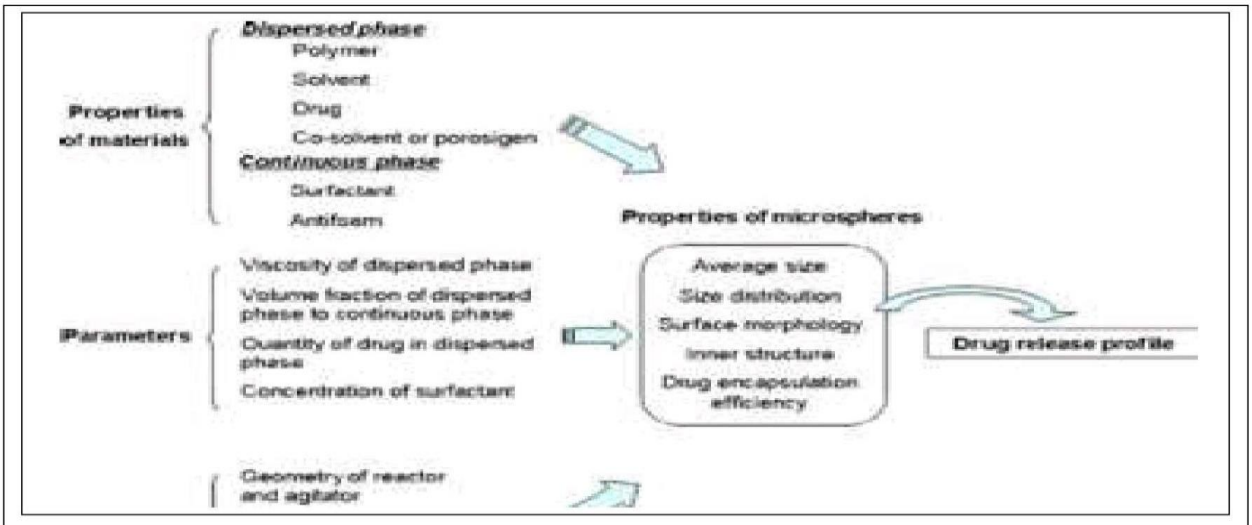


Fig7. Schema of the factors influencing the properties of microspheres.

TECHNIQUES USED IN THE PREPARATIONS OF MICROBALLOONS :

The different methods are used in various microballoons preparation depends on duration of drug release, route of administration & particle size. The various methods of preparations are,

1. Emulsion solvent evaporation technique

2. Oil in water solvent evaporation technique

3. Water-in-oil emulsification. solvent

evaporation technique

4. Emulsion-solvent diffusion technique

5. Ion gelatin technique

6. Coacervation phase separation technique

7. Polymerization technique

8. Spray drying and spray congealing

1. Emulsion-Solvent Evaporation Technique.

The drug is dissolved in chloroform and then dissolved in polymer and resulting solution in added to aqueous phase containing 0.2% sodium of PVP as emulsifier, this mixture was stirred at 500 rpm then the drug and polymer (eudragit) was transformed in to fine droplet which solidified in to rigid microballoons by solvent evaporation and then collected by filtration and washed with demineralized water and desiccated at room temperature for 24 hrs. For these techniques, there are basically two system which include oil-in-water and water-in-oil type.

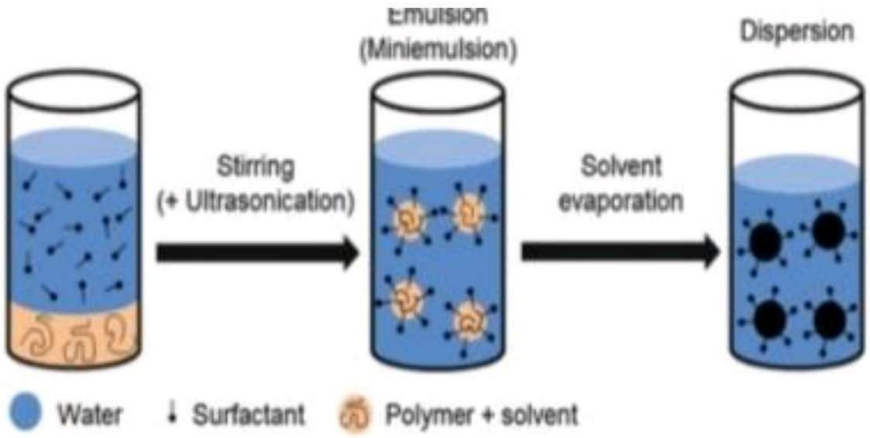


Figure 1: Emulsion solvent evaporation method

2. Oil-in-Water Evaporation Techniques

2. Oil-in-Water Evaporation Techniques

In this technique, both the drug and the polymer should be insoluble in water while a water immiscible solvent is required for the polymer. The polymer is dissolved in an organic solvent such as dichloromethane, methanol and chloroform, the drug is either dissolved or dispersed in to polymer solution and this solution is emulsified in to an aqueous phase to make an oil-in-water emulsion by emulsifying agent. After that the organic solvent is decanted and the microparticle is separated by filtration.

3. Water-in-Oil Emulsification solvent evaporation technique

This water-in-oil emulsification process is also known as
non-aqueous emulsification solvent evaporation. Drug and polymer dispersion. This mixture is poured in to the dispersion medium consisting of light/heavy liquid paraffin in the presence of oil soluble surfactants such as spam. The mixture is then stirred for 2-3 hours at 500 rpm with a propeller agitator to ensure complete evaporation of the solvent. The liquid layer is decanted and micro particle are separated by filtration through a Whitman filter paper, washed with n-hexane and dried for 24 h and subsequent.

4. Emulsion-Solvent Diffusion Technique

The drug polymer mixture was dissolved in a 1:1 mixture of ethanol and dichloromethane, and then added to a sodium lauryl sulphate solution drop by drop. The solution. was stirred with propeller type agitator at room temperature at 150 rpm for 1 hour and formed floating

microballoons were washed and dried in a desiccator at room temperature.

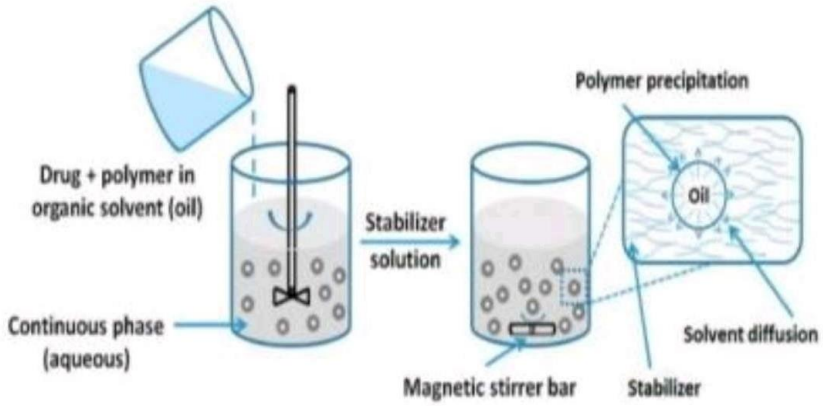


Figure 2: Emulsion Solvent Diffusion Technique

5. Ionic Gelation Technique

The drug was added to 1.2% (w/v) aqueous solution of sodium alginate and continue stirring is preferred for complete solubility. After that was added drop wise to a solution containing ca2+/A13+ and chitosan solution in acetic acid microballoons were kept original solution for 24 hr for internal geilification followed by filtration for separation. The maximum release of the drug was obtained at pH 6.4-7.2 alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique.

6. Coacervation phase Separation Technique

It is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase known as co-acervation. The drug was. dispensed in a solution of the polymer is added to the system which makes first polymer to phase separate and engulf the drug particles..

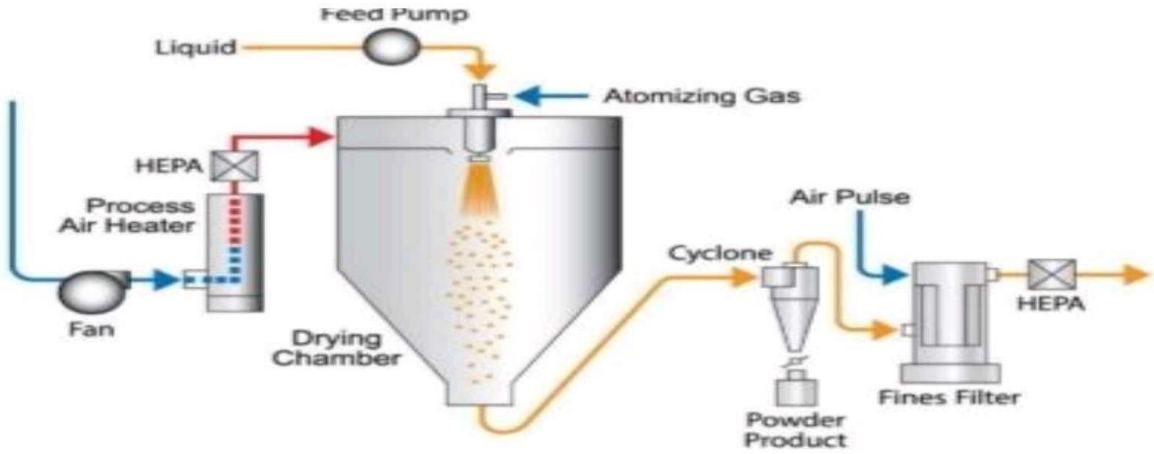
7. Polymerization technique

The polymerization technique conventionally is mainly classified
a. Natural polymerization: It is carried out using cifferent techniques of polymerization like bulk, suspension, precipitation, and emulsion and micellar polymerization process.

b. Interfacial polymerization this technique involves the reaction of monomers at the interface between the two immiscible liquid phases to film of polymer that essentially envelops the dispersed.

8. Spray drying and Spray congealing

These techniques depend on the drying of a polymer and drug mist in the air. The polymer is developed in a suitable volatile organic solvent such as dichioromethane, acetone. and methanol etc. Under high-speed homogenization, the drug in salid form is dispersed in the polymer solution. The mixture is then atomized in a stream of hot air. The atomization prompts the formation of the small croplets or the mist from which the solvent evaporates instantaneously leading the formation of the microballoons in a size. Depending upon the removal of the solvent or cooling of the solution are named spray drying and spray congealing respectively.



EVALUATION OF FLOATING MICROBALLOONS

Micromeritics

Micromeritics are characterized for their micromeritics properties such as particle size, angle of repose, compressibility index, and Hausner's ratio. Prior to filling microballoons into capsules, the micromeritic properties of the microspheres must be considered in order to analyze their flow properties.

Particle Size

The particle size of the microballoons is measure using an optical, microscopic method, and then mean microballoons size is calculated by measuring 100 particles with the help of a calibrated ocular micrometer. Particle size is influenced by process parameters and formulation parameters such as solvent composition, amount of polymer, emulsifier concentration, temperature and stirring rate.

Bulk Density

10g of microballoons is to be placed in to 25 ml graduated measuring cylinder. The volume occupied by the microballoons is observed without disturbing the cylinder, and the bulk density is calculated using the equation,

Bulk density = weight of sample/volume of sample

Tapped Density

About 10 g of microballoons is placed in 25 ml measuring cylinder. The cylinder is dropped at 2 s intervals on to a hard-wooden surface 100 times, from a height of one inch. The final volume is recorded, and the tapped density is calculated by the following equation (the value expressed in gm/cm3),

Tapped density = weight of sample/tapped volume

Carr's Index

It is frequently used as an indication of the flow ability of a powder. Flow property of blend depends on compressibility index. The Carr's index is an indication of the compressibility of a powder. The propensity to shape bridges between particles is indicated by a high Carr's index. Smaller the Carr's index better will be the flow properties. It is calculated by the formula,

Carr's index (%) = tapped density-bulk density/tapped density X 100

Angle of Repose (Ɵ)

The angle of repose shows the substance's flow ability. A funnel is fixed to a burette stand in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample is allowed to flow from the funnel, until the height of the pile just touches the tip of the funnel. The radius of the pile is determined by drawing a boundary along the circumference of the pile and taking the average of the radius of the circumference from three trails. The angle of repose can be calculated by,

Angle of repose (ɵ) = tan-1h/r

Scanning Electronic Microscopy (SEM)

SEM techniques are used for determining the surface morphology of the microballoons. The SEM sample is prepared by sprinkling the powder on the tape stuck attached to an aluminum stub. The stub is coated using the mixture of gold and palladium at a thickness of 250-450 Å under an argon atmosphere in a high vacuum evaporator at a voltage of 20 KV, Current 10 ma, and low pressure. Photomicrographs are taken on the random screening coated samples using SEM.

Percentage Yield

Percentage yield of floating microballoons is calculated by dividing the actual weight of the product to the total amount of all non-volatile components that are used in the preparation of floating microballoons and is represented by formula,

Percentage yield = Actual weight of product / Total weight of drug excipient

Marketed formulations:

Table1: List of marketed formulations of microballoons

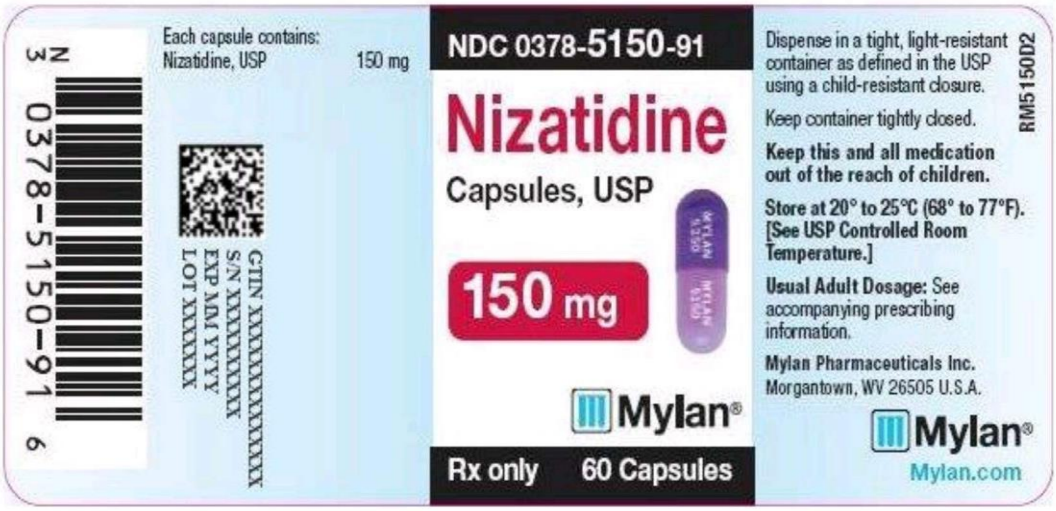
Drug	Brand name	Manufacturer name
Nizatidine	Tazac	Dr. Reddy Laboratories LTD.
Propranolol Hydrochloride	Inderal	Pellets Pharma Limited
Domperidone	Motilium	Nishchem International Pvt. Ltd
Theophylline	Uniphyl	Kores India Limited

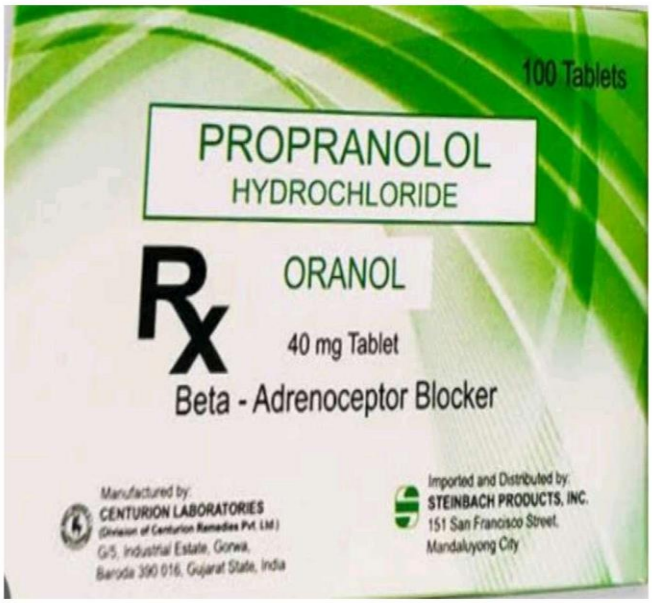
Conclusions

In recent review, we concluded that the floating hollow microspheres showed gastro retentive controlled release delivery system, promises to be a potential approach for gastric retention.

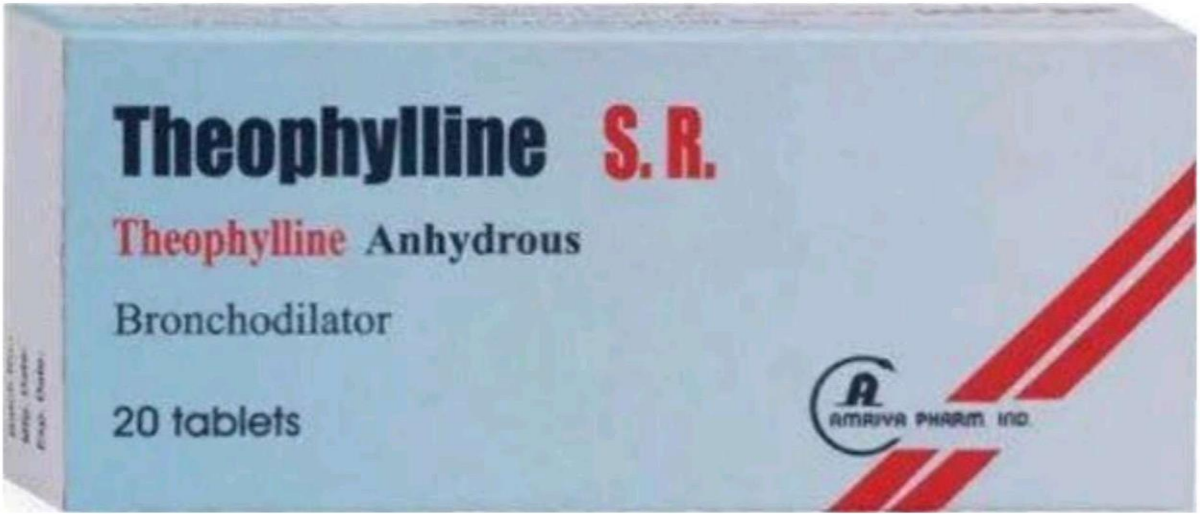
Microballoons are low-density, sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate when it floats over gastric contents resulting reduced fluctuations in plasma drug concentration.

It is efficient means of enhancing the bioavailability. Optimized microballoons will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery.


Each capsule contains:
Nizatidine, USP 150 mg
NDC 0378-5150-91
Nizatidine
Capsules, USP
150 mg
Mylan
Rx only 60 Capsules
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Usual Adult Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.
Mylan
Mylan.com
RM5150D2


100 Tablets
PROPRANOLOL
HYDROCHLORIDE
Rx
ORANOL
40 mg Tablet
Beta - Adrenoceptor Blocker
Manufactured by
CENTURION LABORATORIES
Imported and Distributed by
STEINBACH PRODUCTS, INC.
151 San Francisco Street,
Mandaluyong City


Domperidone
Tablets
10mg
Each tablet contains 10mg of domperidone (as maleate).
Also contains lactose.
30 Tablets
Crescent


Theophylline S.R.
Theophylline Anhydrous
Bronchodilator
20 tablets
AMRIYA PHARM IND.

Reference

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