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A REVIEW ON INNOVATIVE AND NOVEL STRATEGY-FLOATING MICROSPONGES

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Abstract:

Gastroretentive drug delivery system is a novel method for making the control release drug delivery system. Floating or Gastroretentive drug delivery system holds the advantage of both oral delivery and controlled delivery. Many control release formulations are developed with this method. Most useable and efficient technique is floating microsponges. The Microsponges Delivery System is an original polymeric system consisting of porous microspheres. They are tiny sponge like spherical particles. Microsponges having a countless of interconnected size ranging voids of particle from 5-150 µm. This Microsponges floats on the aqueous fluid of stomach and Releases the medicament for prolonged period of time. For those drugs whose half life is too short. Thus, beneficial for increasing their half life and also increase their bioavailability. These microsponges have more surface area so remain float on an aqueous media. Microsponges are prepared by several methods utilizing quasi emulsion system diffusion or by liquid– liquid suspension polymerization system. Thus this is a useful method.

Key Words: *FDDS, Microsponges, Quasi-emulsion solvent diffusion method, Liquid- liquid suspension polymerization , Gastrointestinal system.*

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INTRODUCTION:

Various studies published in the journalism suggests that in vitro pharmaceutical formulations show strong prolonged gastric residence and in vivo is shown by floating behaviour.[1] Floating systems, first described by Davis in 1968, contain a bulk density less than that of gastric fluid and thus remain buoyant in the stomach for an extended period of time. FDDS is suitable for medicines with a stomach or upper small intestine absorption window, and used for medicines that are weakly soluble in the intestinal fluid.

This system helps in the continuous release of drug until it reachs the absorption window. [2, 3,4] The development of FDDS based on the buoyancy mechanism, in which two distinct technologies has been used that is non- effervescent and effervescent systems. Several buoyant systems based on granules and powder, [5]The density of the device should be less than that of the stomach fluid to provide a good floating behaviour in the stomach.

It should be noted, that satisfactory In vitro floating behavior does not involve effective In vivo gastric retention. [6] Since FDDS has a lower bulk density than gastric fluid, it can float in the stomach for an extended period of time without affecting the gastric emptying rate. The non-effervescent and effervescent devices used in the construction of FDDS are based on the buoyancy mechanism. Several buoyant systems were designed on the basis of granules, powder, [7] Laminated films, capsules, tablets, and hollow microspheres. [8]

The development of oral floating dosage formulations with gastric retention capability has lead with these considerations. Where a drug has a small "absorption window," sustained release preparation models combine the continuation of dosage forms during the gastrointestinal transit cycle with controlled drug release.

Gastrointestinal Tract Physiology

The stomach is divided anatomically into three region: [19, 10, 11]

- Fundus
- Body
- Antrum (pylorus).

The stomach Anatomy is divided into three parts. The proximal portion consists of an undigested fundus and stuff is contained within the body such the body is a reservoir and also the antrum (pylorus) is the responsible place for Motion combining and dealing as a pump, cause gastric emptying.[12]

Gastric emptying occurs during fasting as well as fed states. This can be remarked because the inter digestive myoelectric cycle or migrating myoelectric cycle (MMC), which lasts 4 to 6 minutes for Phase III (burst phase). For brief times, it entails strong and intermittent contraction. They are further divided into 4 phases:

1. phase I (basal phase), with rare contractions, last from 30 to 60 minutes.
2. Phase II clinical trial (pre burst phase) last for 20 to 40 minutes, With intermittent nerve impulse and contractions.
3. Phase III clinical trial is for 10 to 20 minutes. For short, it involves strong and periodic contractions.
4. Phase IV lasts zero to five minutes and happen in 2 consecutive intervals between phases III and that I, sweeping from the stomach right down to the small intestine.

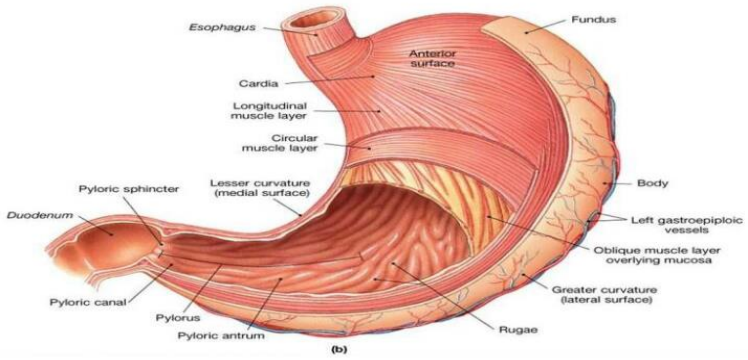

Fig.1: Anatomy of gastrointestinal tract

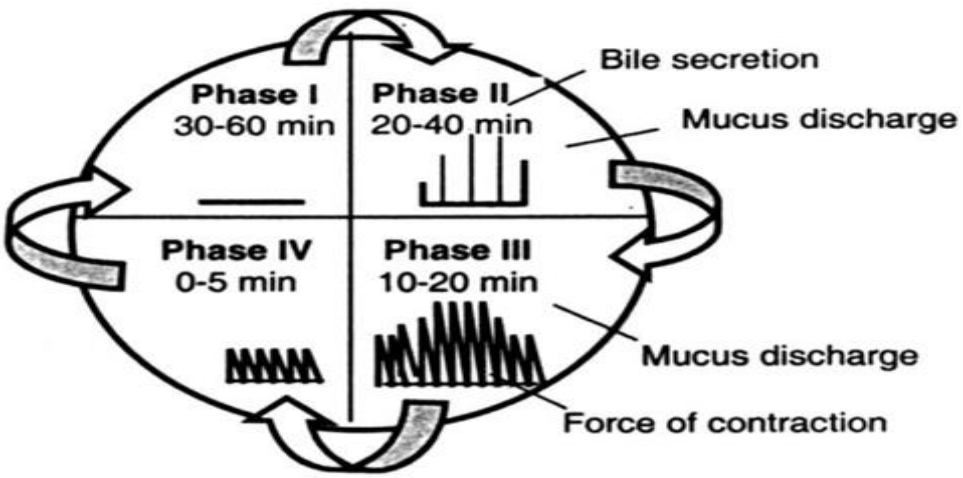

Fig.2: Four connective phases of activity in migrating myloelectric complex

Possible drug candidates for Gastrorententive drug delivery systems

- Drugs that are involved in the stomach locally, such as antacids.[13]
- Drugs that have a thin gastrointestinal tract (GIT) absorption window, such as l-dopa, furosemide, PABA etc .[14]
- Drugs that are degraded in the intestinal pH or offer local effects, such as ranitidine HCl, captopril, metronidazole. [15,16]
- Drugs that interact with natural colonic microbes, e.g., antibiotics and antibacterial agents used to treat peptic ulcers associated with Helicobacter pylori .[17]
- Less soluble drugs at high pH example captopril.[18]

Approaches to Gastroretention [19, 20]

There is fallowing approaches to get gastroretention:

High density system: High density polymers were used to create this type of gastroretentive formulation and those with a density of less than 3g/ml are stored in the stomach and can survive peristaltic movements.

Swelling and expanding systems: It is also known as plug systems because they appear to stay logged in the pyloric sphincters. Drugs may be released in a regulated and maintained manner. This can be accomplished by choosing a polymer that has the right amount of swelling. The polymer absorbs water and expands as it came in contact to gastric fluid. This capacity of polymers cause gastroretention and regulated drug release.

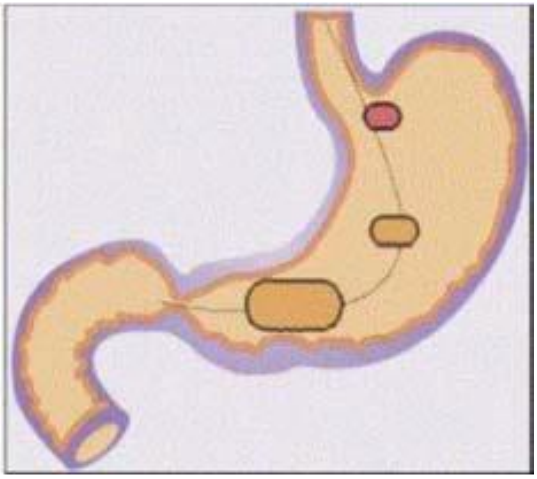

Fig 3: *High density systems*

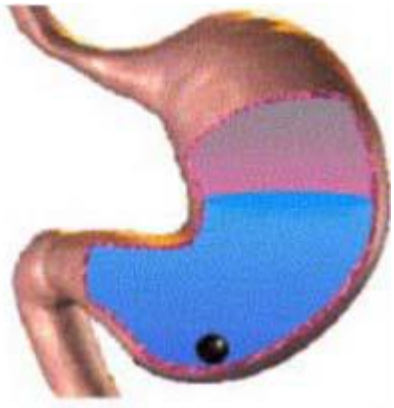

Fig .4: *Swellable tablet in stomach* [21]

Incorporating delaying excipients: It is another effective strategy for preventing gastroretention. It entails using delay excipients in a delivery system, such as trietanolamine myristate, as well as feeding digestible polymers or fatty acid salts that change the motility pattern and increase gastric retention.

Modified systems: This system is made up of non-dissolving geometric shapes molded out of silastic elastomers. The form, scale, and flexural modules of the delivery system all influence GRT.

Mucoadhesive and bioadhesive systems: Bioadhesive polymers that can adhere to the stomach's epithelial surface are used in a mucoadhesive solution. Mucoadhesive polymers include carbohydrates, lectins, chitosan, and CMC. This method is used in the stomach for localized intervention.

Floating systems: Since the thickness of floating drug delivery systems is lower than that of gastric fluid, they can stay in the stomach for longer periods of time without impacting the rate of gastric emptying. The drug has been published from the machine, slowly and at the desired pace Following the publication of the stomach was drained of the drug's residual system. [21]

Drug Delivery of Floating Microsponges

New oral and topical drug delivery technology for microsponges, which is also to suggest that transdermal drug delivery mechanisms are not anticipated for the delivery of active ingredients whose final destination location is the skin.[22,23] A highly porous micro sized, cross-linked, polymeric microsphere and microsponge release method with a unique ability to catch a broad variety of active pharmaceutical ingredients with unreliable pharmacological activities administer at various doses that can be delivered to the intended site target absorption site and then released in response to stimuli on the skin.[24] A microsponge with a standard size range of 25 µm may have a pore length of up to 3000 mm/g with a hole amount of around 1 ml/g. In the tinny nooks of the crannies of the skin, the microsponge absorbs and releases the drug slowly, as the skin needs it. [25] The delivery mechanism of microsponge has benefits over other methods such as liposomes and microencapsulation. [26]

Advantages of FDDS

Significant technical drug delivery systems with gastric retentive actions are developed by floating dosage systems and provide many benefits in drug delivery. Such benefits include:

1. Regulated drug distribution.
2. The distribution of medications in the stomach for local intervention.
3. Minimizing drug-induced mucosal inflammation by slowly releasing drugs at a prohibited rate.
4. Management of stomach conditions such as reflux from the gastro-esophagus.
5. Administration is made easier, and patients are more likely to comply.[27]

Microsponge

Microsponge is a neoteric technology that allows for the sustained release of active pharmaceutical ingredients [28, 29] and is primarily used for topical administration. The biggest problem for the pharmaceutical industry now is to monitor the rate of delivery to a prearranged position of the active pharmaceutical ingredient.

Won invented the microsponge technology in 1987, and Advanced Polymer System, Inc.[30] granted the first patents. Microsponge with a variety of interconnected particle voids ranging in size from 5-150 m.[31]

Properties of Microsponges

1.These formulations are pH stable from 1 to 11.[32]
2. It can withstand temperatures of up to 130°C without losing its properties. [33]
3.They deal with a wide variety of vehicles and excipients.
4.They contain a high trap rate up to 50-60%.
5.They are cost-effective and free-flowing.
6. It has a 12-hour extended-release time. [34]

Methods of Preparation of Microsponges

Solubility characteristics of the polymer and drug are what dictate which encapsulation method is used. The diffusion solvent method is a common method for encapsulating water-insoluble drugs inside water-insoluble polymers.

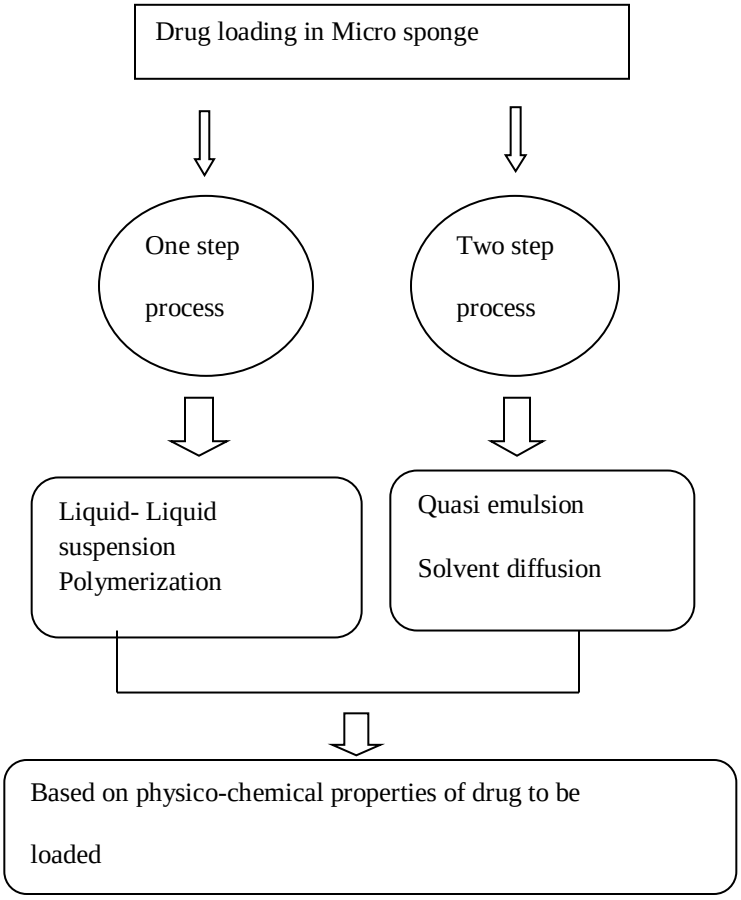

Fig.5: preparation of microsponges

1. Free Radical Suspension Polymerization: (Bottom up approach)

Polymerization mixtures are commonly composed of two-phase particles. The immiscible liquid form comprising the dispensed (or dissolved) monomer is referred to as the "polymerization medium whereas "monomer phase" or "dispersed phase" refers to the monomers. [35]

Starting with the monomer, polymerization is accomplished from the bottom up. To form a pore network, another liquid can be attached to the monomer in addition to the monomers and polymerization media. This substance is referred to as a "monomer diluent" or "porogen," and it is a nonpolar organic solvent that is inert. It produces open, porous structures that resemble sponges when combined with the polymerization reaction, hence the name "microsponges." Microsponge is made from monomers such as Styrene, PHEMA, Crosslinking Agents, Porogen, Toluene, and Divinyl Benzene.[36]

The following is a description of the different steps:

- Mixture of monomer with combination of monomers.
- Arrangement of chain monomers as polymerization starts.
- Ruining of the monomer stepladder to form sphere shaped particle.
- Agglomeration of microspheres leads to the invention of bunches of microspheres.
- Binding of bunch yield microsponges.[37]

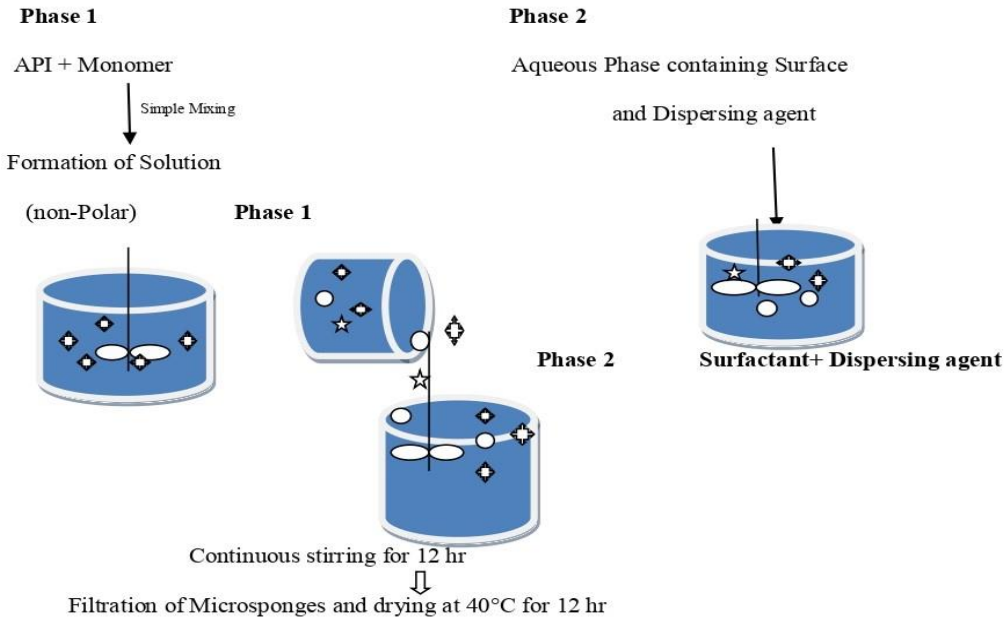

Fig. 6 : Liquid–Liquid Suspension Polymerization

2. Quasi-emulsion solvent diffusion method: (Top down approach)

Similar to emulsions, this process requires the creation of two distinct phases: an inner phase and an external phase. [38]With intense stirring, the inner phase of the drug-polymer mixture formed in an exceedingly volatile solvent like ethanol, acetone, or dichloromethane is applied to the outer phase of the aqueous polyvinyl alcohol (PVA) solution. Stirring causes distinct emulsion globules to form. Solvent is then extract from these globules, resulting in insoluble, rigid microparticles, also known as microsponges. [39] The mixture is then filtered to separate the microsponges and dried out after adequate stirring. Weigh the dried microsponges after 10 to12 hours at 40°C in an air-heated oven. [40].

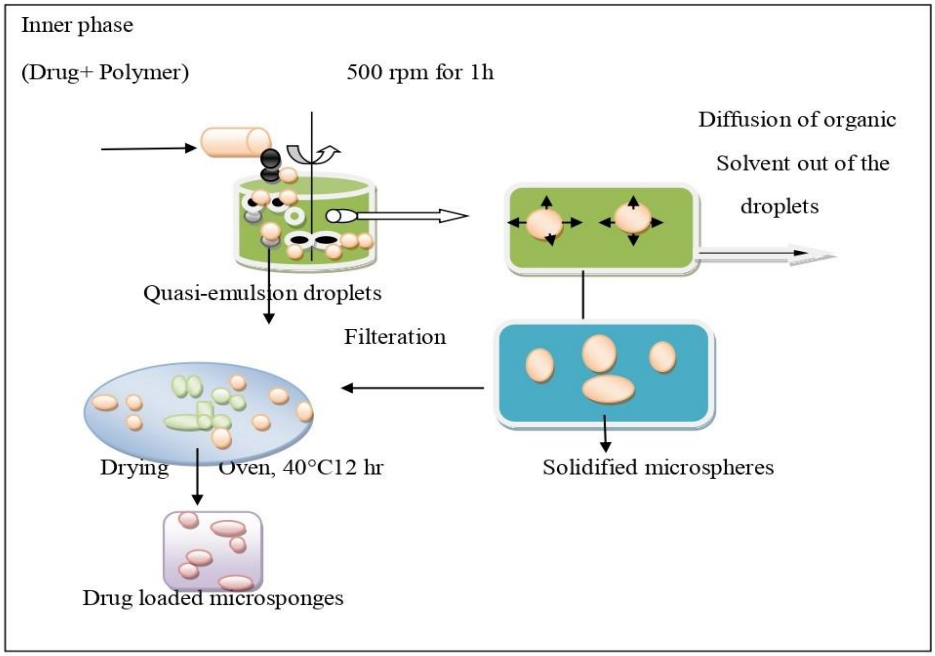

Fig. 7: Quasi- emulsion solvent diffusion method.

Mechanism of Action

- The active substance is entrapped and injected to the vehicle.
  - The active is free to move in and out from particles and into the vehicle as they have an open structure and the vehicle becomes saturated at equilibrium state.
  - Now product is applied to the skin, the active will be absorbed into the skin, depleting the vehicles, which become unsaturated, thus, disturbing the equilibrium.
  - This will inaugurate a flow of microsponge particle to vehicle and from the vehicle to the skin, until the cornium will persist to release the active to the skin and providing delayed release over time.
  - The vehicle is either absorbed or dried. After that the microsponge particles absorbed on the stratum.

Mechanism of drug release

Pressure triggered systems

The active ingredients in microsponges can be released onto the skin by rubbing or applying pressure. [41]

Temperature triggered systems

Some active ingredients can be too viscous at room temperature to run involuntarily from microsponges on the skin. [42] So it is likely to adjust the discharge of substance from the microsponge by altering the temperature. For example, thick sunscreens display a superior release from microsponges when exposed to superior temperatures; thus, a sunscreen would be released from a microsponge only in the presences of heat from the sun.[43]

pH – activated devices

Modify the coating on the microsponge to achieve pH- based active release.[44]

Solubility Activated system

In the presence of water, microsponges contain water-soluble ingredients such as antiperspirants and antiseptics can discharge the ingredient. The presence of an aqueous medium, such as perspiration, can cause active ingredients to release at a faster rate. [45]

EVLUATION METHODOLOGY OF MICROSPONGES

- Particle size evaluation
- Morphology and surface topography
- Loading efficiency
- Production yield
- True density
- Compatibility study
- Release evaluation
- Flexibility
- Stability study

Particle size evaluation: Optical or electron microscopes are used to examine the particle size distribution. Laser light diffractometry or other appropriate methods may also be used to establish the particle size of Microsponges. [46]

Morphology and surface topography: Various techniques are utilized in the morphological analysis of microsponges topography, like photon correlation spectroscopy (PCs) transmission electron spectroscopy (TEM), and scanning electron microscopy (SEM) which are often utilized in the microsponge coated with gold-palladium under an argon atmosphere at room temperature and also the surface morphology of the microsponge. [47]

Loading efficiency: Loading efficiency of the microsponges can be determined by follows equation :-

$$\text{Loading Efficiency (\%)} = \frac{\text{Actual Drug Content in Microsponges}}{\text{Theoretical drug content}} \times 100$$

Production yield: The standard mass of the raw materials and the average mass of the microsponges produced can also be used to calculate the microparticles' output yield.

$$\text{Production Yield} = \frac{\text{Practical Mass of Microsponges}}{\text{Theoretical Yield (Drug +Polymer)}} \times 100$$

True density: The true density of the microsponge is determined from a mean of recurring determinations to use an ultra-pycnometer and helium gas.

Compatibility study: Compatibility of drug can be study by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). [48]

Release evaluation: Diffusion may be used to monitor the release of microsponges or further trigger method such as moisture, pH, temperature, resistance. This method of release use to improve manufactured goods aesthetics. [49]

Resiliency: The microsponges' viscoelastic properties may be changed to make softer bead lets, depending

on the last formulation's requirements. The time of release slows down as cross-linking increases. [50]

Stability study: The durability of the gel formulation is checked in accordance with ICH guidelines. Different replicates were held at 402°C and 755 percent relative humidity in clean, lacquered, collapsible aluminum tubes. At 30, 60, and 90 days, the gel was examined for improvements in outer shell, pH, and in vitro release profile. [51]

Table 1: List of Marketed based on Microsponges Products [52, 53]

S.No.	Product Name	Pharmaceutical uses	Manufacturer
1.	Retin A Micro	Acne vulgaris	Ortho-McNeil Pharmaceutical, Inc Avon
2.	Retinol cream	Helps maintain healthy skin	Biomedic
3.	Ultra Gaurd	Protects baby's skin	Scott Paper Company
4.	Lactrex™12%	Moisturizing cream	SDR Pharmaceuticals, Inc
5.	Retinol 15 Night cream	Anti-Wrinkles	Sothys

APPLICATIONS

- Microsponge for Topical delivery system
- Microsponge for Oral drug delivery system
- Microsponge for Bone and Tissue manufacturing
- Microsponge from Seaweed use in Diagnose the Diseases

Microsponge for Topical Delivery System:
Skin irritation is a common side effect of benzoyl peroxide (BPO), which is commonly used in topical formulations to treat skin diseases. If BPO is applied to the skin in a safe way, the side effect may be minimized.[54] Microsponge distribution of Benzoyl peroxide was achieved using an emulsion solvent diffusion technique by incorporating an organic internal phase comprising benzoyl peroxide, ethyl cellulose, and dichloromethane into a stirred aqueous phase containing polyvinyl alcohol and suspension polymerization of styrene and divinyl benzene.[55] The microsponges were spread in a gel basis, and the antibacterial and skin irritancy behaviors of the microsponge gels were assessed.[56] The drug is released at a slower rate in the entrapped system. A topical delivery method with reduced irritancy has been developed productively. [57]

Microsponge for Oral drug delivery system:
The Eudragit RS 100 quasi-emulsion solvent diffusion method, followed by the direct compression technique to manufacture microsponges tablets, was used to achieve controlled oral delivery of Ketoprofen. [58] Compressibility in the physical mixture of the medication and polymer was considerably increased due to the plastic deformation of the sponge-like microsponge structure, resulting in mechanically stable tablets. A commercial Microsponge 5640 platform was used to monitor colon-specific, guided flurbiprofen distribution. [59, 60]

Microsponge for Bone and Tissue Manufacturing:
Pre-polymerized polymethylmethacrylate powders and liquid methylmethacrylate monomer were combined with two aqueous dispersions of tricalcium phosphate grains and calcium deficient hydroxyl apatite powders to produce bone replacement compounds. The final composites were porous and functioned as microsponges. Based on the biodegradation of the sponge matrix, simple fibroblast growth factor (bFGF) embedded in a collagen sponge layer was sustained released in the mouse sub-cutis and demonstrated dose-dependent local angiogenic behavior. Injection of collagen microsponges containing bFGF resulted in a significant increase in blood flow in the ischemic hind limb of mice, which bolus bFGF injection could not achieve. These findings highlight the significance of type I collagen as a bFGF reservoir and its therapeutic potential. [61]

Microsponge derived from seaweed is used to diagnose diseases:
Microsponges made from seaweed can aid in the diagnosis of heart disease, cancer, HIV, and other diseases in a more convenient and cost-effective manner than conventional clinical approaches.[62] The biomarkers are isolated in tiny sponges placed into an array of inverted pyramid-shaped funnels in the microprocessor heart of the credit card-sized PBNC.[63] As a fluid sample is injected into the

disposable device, micro fluidic channels guide it to sponges inoculated with antibodies that recognize and confine various biomarkers. If caught, they can be analyzed in minutes using a complicated microscope and device built into a compact, toaster-sized reader. [64]

Recent advance techniques in microsponge drug delivery system:

The methods for making nanosponges, nanoferrosponges, and porous microbeads were updated. in a variety of advanced technologies. In compare to polymeric micro or nanosponges, -CD nanosponges have been established that can be use for both hydrophilic and hydrophobic drugs. These nanosponges were generated by re-acting the -CD molecule with diphenyl carbonate and cross-linking it. Nanosponges have also been found by some researchers to be a strong carrier for the distribution of gases. Nanoferrosponge is a novel approach that consists of self-performing carriers that have greater diffusion to the targeted site due to an external magnetic trigger that causes the carriers' ability to reach deeper tissue and then removes the attractive material from the particle, resulting in a spongy device. Porous microspheres have better properties, so a method was created to make porous micro beads.

CONCLUSION:

The microsponge delivery system is a novel technology for controlled release of drug. Floating or Gastroretentive drug delivery system control the advantage of both oral delivery and controlled delivery. Many control release formulations are developed with this method. Most useable and efficient technique is floating microsponges. The Microsponges Delivery System is an original polymeric system consisting of porous microspheres. They are tiny sponge like spherical particles. Microsponges having a countless of interconnected size ranging voids of particle from 5-150 µm. This Microsponges floats on the aqueous fluid of stomach and Releases the medicament for prolonged period of time.

For those drugs whose half life is too short. Thus, beneficial for increasing their half life and also increase their bioavailability and microsponge system are non-allergic, non-toxic, non-irritating, and non-mutagenic. These microsponges have more surface area so remain float on an aqueous media. Microsponges are prepared by several methods utilizing quasi emulsion system diffusion or by liquid– liquid suspension polymerization system. Thus this is a constructive method and it also promote the development of novel product forms. This kind of drug delivery technology may lead to a better apprehension of the relieve of several diseases.

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