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## A brief review on microsponges use in chronopharmacology

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### Abstract

The microsp sponge are used to deliver drug to chronopharmacology for improve the drug bioavailability and the potency of active drug. Chronopharmacology is the investigative science that elucidates the biological rhythm dependencies of medication. It is useful to solve problems of drug optimization (to enhance the desired efficiencies or to reduce its undesired effects). The effectiveness and toxicity of many drugs vary depending on dosing time associated with 24 hours rhythm of biochemical, physiological and behavioural process under the control of circadian clock this chronopharmacological process is partial not only by pharmacokinetics but also pharmacodynamics of treatment.

**Keywords:** Microsp sponge, chrono pharmacotherapy, circadian clock, auto induction, auto inhibition

### Introduction

#### Microsponges

Microsponges delivery system is original polymeric system consist of porous microspheres. Micro sponges were originally developed for modern delivery of drugs. Microsponges were macro porous beads typically 11-26 microns in diameter, laden with active agents. Micro sponges are porous polymeric microsphere that was frequently used for delayed typical administration. Microsponges are porous microsphere have interred connected voids of particle size range 4-300  $\mu\text{m}$ . They are homogeneous, sphere-shaped polymer particles. Microsphere are designed to deliver a pharmaceutical active constituent efficiently at smallest amount dose and also to improve stability reduce bad-effect and transform drug liberate profile.

#### Release mechanism

**Pressure triggered systems:** The system delivers required material under pressure/rubbed; the amount of the loose hinge on individual character of the sponge. By varying the type of material and different process variables, the microsp sponge best suited for a given application may be optimized. When compared with mineral oil containing microcapsules, mineral oil containing.

**Temperature-triggered systems:** Some entrap active ingredients can be more viscous at room temperature to flow impulsively from microsp sponge onto the skin. Increased in skin temperature can result in an increased flow rate and hence release. It is possible to mediate the release of drug from the microsp sponge by changing the temperature. For a e.g, sunscreens were originate to show a higher release rate of microsp sponge when expose in elevated temperatures; thus a sunscreen would be released from a microsp sponge only upon exposure to the heat from the sun.

**pH triggered system:** pH-release of active ingredient from the formulation can be achieved by the modification of the covering of microsp sponge. It is applicable at various sites.

**Solubility triggered systems:** attendance of an aqueous medium such as perspiration can trigger the discharge rate of active ingredient. Ingredients like most of antiseptics, deodorants and antiperspirants may be formulated in such types of systems. Release may be achieved based on the capability of the outside medium to dissolve the active, the concentration gradient or the ability to swell the microsp sponge network.

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### Characteristics

- Monomers and polymer would not work without the rise in viscosity.
- Immiscible in water or slightly soluble
- To avoid cosmetics problems incorporation should not be more than 10-12% w/w microsponges.
- Rate of release is controlled by diffusion or moisture, pH and temperature.
- Weighing without drying
- Release is extended in nature.
- Elegancy of product Improves.

### Important feature of Microsponges

- Stable at pH1-11
- Stable at up to 130 °C temperature
- Compatible with most of vehicles
- Higher loading capacity 50-60%
- Cost effective
- Free flowaig

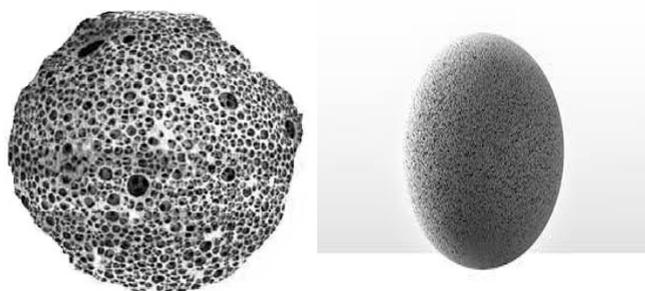


Fig 1: View of Microspong

### Advantages of microsponges

- These formulation are stable over range of pH1-11
- These formulation are stable at room temperature up to 130 °C
- These formulations are compatible with most vehicles' and ingredients.
- These are stabilizing as their average pore size is 0.25  $\mu\text{m}$  where bacteria cannot penetrate.
- These formulations are free flowing and cost effective.
- These are non-irritating, non-mutagenic and non-toxic.

### 1. Microsponge for topical delivery

The Microsponge systems are base on huge, polymer-based microspheres that can sense dangle or deceive wide-reaching variety of material and then be incorporated into a create manufactured goods, such as a gel, cream, liquid or powder. In single Microsponge is as tiny as a constituent part of talcum powder, measuring less than one-thousandth of an inch in diameters. Able to a true sponge, every microsphere comprise of a lots of interconnecting voids inside a non-collapsible structure that can accept a wide variety of substance. The outer surface is characteristically porous, allows the controlled flow of substances into and out of the sponges. As a result, the human body cannot convert them into other substances or break them down. Although they are microscopic in size, these systems are too large to pass

through the stratum corneum when incorporated into topical products. Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne, with skin irritation as a common side. It has been contemplated that regulated release of BPO from a delivery system onto the skin results in reduced secondary response with a reduction of percutaneous absorption.

### 2. Microsponge for oral delivery

The microsponge system has been shown to enhance the rate of resolvable of poorly water-soluble drugs by dissuade such drugs in the microsponge system's pores. As these pores are very small, the drug is in effect reduced to microscopic. Particles and the significant increase in the surface area thus greatly increase the rate of solubilization. The ibuprofen microsponges are achieved by using different excipient lick acrylic, Eudragit RS polymer, by varying their intraparticle impenetrability for oral controlled delivery of drug. Sustained release formulation of chlorpheniramine maleate, using powder-coated microsponges, is prepared by the dry impinge blending method, for oral drug delivery. In case of Controlled oral drug delivery of Ketoprofen microsponge prepared by quasi-emulsion solvent diffusion method with the use different excipient, polymer Eudragit RS 100 and afterwards tablets of microsponges were prepared by the direct compression method. Results indicated that compressibility was much improved in the physical mixture of the drug and polymer; due to the plastic deformation of the sponge-like microsponge structure, producing mechanically strong tablets. Colon-specific, controlled delivery of flurbiprofen was conducted by using a profitable Microsponge 5640 system. *In vitro* studies exhibited that compression-coated colon-specific tablet formulations started to release the drug at the eighth hour, corresponding to the proximal colon arrival time, due to addition of the colon enzyme, following a made to order release pattern, while the drug release from the colon site-specific formulations prepared by pore plugging the microsponges show an increase at the eighth hour, which was the point of time when the enzyme will be active in colon.

### 3. Microsponge for Bone and Tissue Engineering

The combination of pre polymerized powders of polymethyl-methacrylate and liquid methyl methacrylate monomer with two aqueous dissipation of tricalcium phosphate grains and calcium deficient hydroxyl apatite powder use as bone-alternate compounds. The concluding composite appear to be porous and act as microsponges. Basic fibroblast growth factor abandon in a collagen sponge sheet was sustained released in the mouse sub-cutis according to the biodegradation of the sponge matrix, and exhibited local angiogenic activity in a dose-dependent manner. The parental of collagen microsponges incorporate basic fibroblast growth factor (FGFs) induced a significant aggrandizement of the blood flow in the site of action, in the murine ischemic hind limb, which could never have been attained by the bolus injection of basic fibroblast growth factor. These results suggest the significance and therapeutic utility of the type I collagen as a reservoir of basic fibroblast growth factor.

**Table 1:** Application of microspunge system

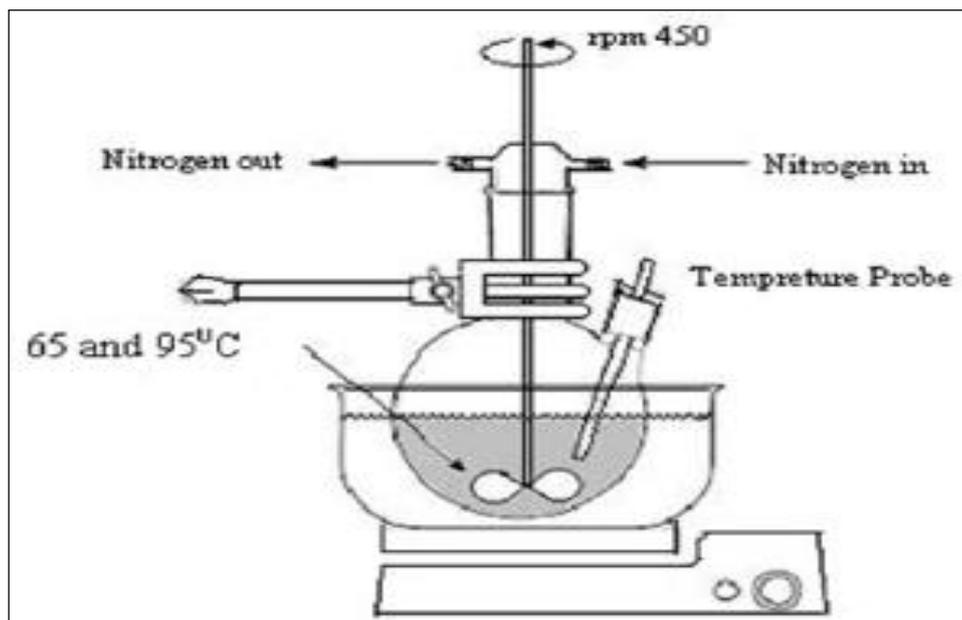
S. No	Active agents	Application
1	Anti-inflammatory e.g. Hydrocortisone	Long lasting activity with lessening of skin allergic response and dermatoses.
2	Anti-dandruffs e.g. zinc pyrithione, selenium sulfide	Reduced unpleasant odor with reduced irritation with extended efficacy and safety.
3	Skin depig-menting agents e.g. hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
4	Anti-Fungal	Sustained release of actives.
5	Anti-acene	Maintained efficacy with reduced skin irritation and sensitization
6	Anti-Pruritics	Extended and improved activity
7	Rubefaciants	Sustained activity with reduced irritancy, greasiness and odor.

**Application of microsponges**

1. Microsponges for topical delivery
2. Microsponge for oral delivery
3. Microsponge for bone and tissue engineering

**Method of Preparation of Microsponge Drug Delivery System****1. Liquid-liquid suspension polymerization**

Immiscible monomers and active ingredient are dissolved in suitable solvent monomers.  
 ↓  
 Dispersed in aqueous phases which consist of additives like surfactant, suspending agent  
 ↓  
 Polymerization is activated by increasing temperature or irradiation or by adding catalyst.  
 ↓  
 Polymerization process is continues the formation of spherical structure.  
 ↓  
 At the end of process the solvent evaporates and forms spherical porous microsponges.

**Fig 2:** liquid-liquid suspension polymerization**2. Quasi-emulsion solvent diffusion method**

Polymer like Eudragit RS 100 was dissolve in Dichloro methane (inner phase).  
 ↓  
 Then the drug is added in solution and dissolved in Ultrasonication at 35 °C.  
 ↓  
 Inner phase was poured into PVA solution in water (outer phase).  
 ↓  
 Continuously stirring 3-4 hour and after that filtered.  
 ↓  
 Dried in oven at 40 °C and microsponge was formed.

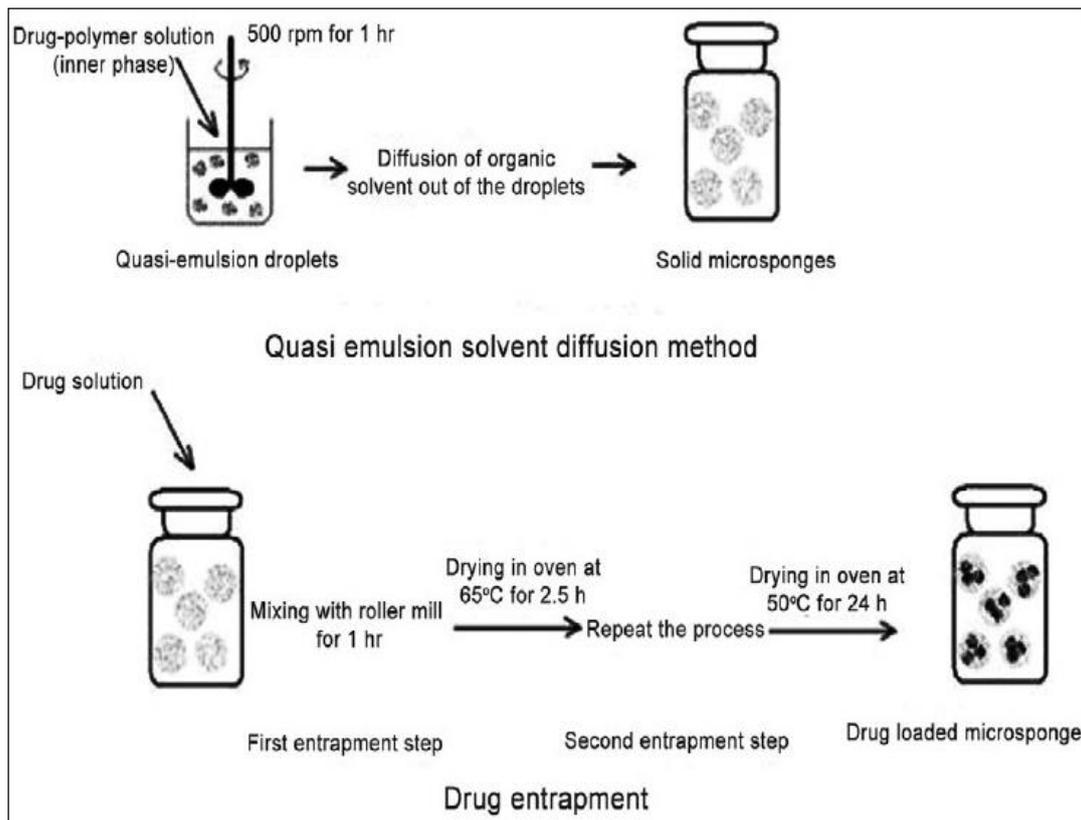


Fig 3: Quasi emulsion solvent diffusion method

**Evaluation Parameters of Microsponges**

**a. Particle Size Determination**

Particle size investigation of stacked and void microsponges can be performed by laser light diffractometry or any other suitable method. The values can be expressed for all formulations as mean particle size range. Cumulative percentage drug release from preparation of different particle size will be plotted standard curve against time to study effect of particle size on drug release pattern. Particles larger than 30µm can impart rough feeling and hence particles of sizes between 10-25µm are preferred to use in final topical formulation.

**b. Morphology and Surface Topography of Microsponges**

The estimation of microsp sponge morphology and exterior topography of microsp sponge was performed by organized microsponges can be covered through gold-palladium under an argon atmosphere at room temperature and then the surface organization of the microsponges can be considered by scanning electron microscopy (SEM). SEM of a fractured microsp sponge particle can also be taken to illustrate its complex structure.

**c. Determination of Production Yield**

The production yield of the micro particles was determined by weighing the accurately initial weight of the raw materials and the last weight of the microsp sponge obtained.  
 Production Yield= Practical Mass of Microsponges

/Theoretical Mass (Polymer + Drug) X 100

**d. Determination of True Density**

The exact density of micro particles was determined with an ultra-pycnometer beneath helium gas & was determined from a mean of repetitive determinations.

**e. Dissolution Studies**

Dissolution profile of microsponges can be studied by use of dissolution apparatus with a modified basket consisted of 5µm stainless steel mesh. Speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by suitable analytical method at various intervals.

**Chronopharmacology**

The branch of pharmacology concerned with interaction of drugs and biorthms.

**Advantages of Chronopharmacology**

1. It prevents an overdosing of any class of drug.
2. It makes the utilization of the drug more appropriate and thus the value of a drug is increased.

It reduces the unnecessary side effects of a drug and helps in carrying out the treatment for a particular or limited period of time.

**Table 1:** Examples of disease states with chronopharmacology application\*

Therapeutic Area	Disease or Condition	Chrono-pharmacology Rationale
Cardiovascular	Angina	Angina (variant) attacks occur 30 times more often between 2:00 am. and 4:00 am. - Larger doses of Nitroglycerin early in the morning.
	Heart Attacks and Strokes	Heart attacks and stroke are most likely between 6:00 am and Noon-> Cardiovascular active drugs before waking.
	Hypercholesterolemia	A circadian rhythm occurs during hepatic cholesterol synthesis, which is generally higher during the night than during daylight. Studies with HMG CoA reductase inhibitors suggest that evening dosing is more effective than morning dosing. ->Simvastatin in evening and during night.
	Hypertension	Automatically and precisely release clonidine or other hypertension drugs in peak amounts to offset the peak symptoms associated with the dangerous morning symptoms.-> Clonidine, Captopril or other medication in the Morning
	Parkinson's Disease	Automated dosing for patient compliance >Selegiline, Bzotropine, Apomorphine
CNS Degenerative Disorder	Alzheimer's Disease	Automated dosing for patient compliance - >Rivastigimine, Mematine
	Diabetes (Type II)	Automated dosing for elderly patient compliance. Oral medication is poorly absorbed. -> Miglitol meals. Sulfonylureas 20-30 min before food,
Diabetes	Epileptic seizure	Epileptic seizures are most likely between 6:00 a.m. And 7:00 a.m. ->Gabapentan or other Epileptic drugs before waking up.
Epilepsy Inflammation	Rheumatoid Arthritis Osteoarthritis	Worst upon a wakening. Cortisol and anti-inflammatory hormones are very low at night ndomethacin or Valdecoxib before waking up
Mental Health	Depression	Selegiline at night can create sleeping disorders (nightmares), but depression symptoms are high immediately upon waking up-> Selegiline before waking up.
	Asthma	Asthma attacks are 100 times more likely between 4:00 am. And 6:00 am. Adrenaline and cortisol are virtually absent at night. ->Albuterol or Tulobuterol in early morning.
Pulmonary	Acute Pain	Neurological pain is worst between 3:00 am. And 8:00 am. -> Fentanyl in the middle of night.
Pain	Acute Pain	Neurological pain is worst between 3:00 am. And 8:00 am. -> Fentanyl in the middle of night.

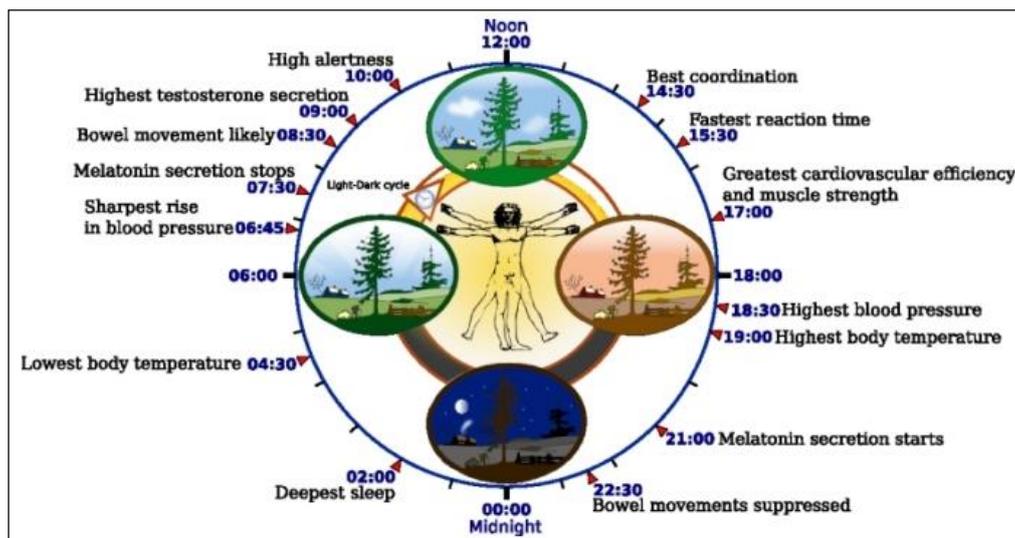
**Reason for Chronopharmacology**

**Auto induction:** A repetitive dose of a drug induces or increases enzymes responsible for its elimination, thereby increasing its clearance. This is called as auto induction. It is dependent on dose and concentration of drug. It has a number of therapeutic consequences. It affects the time to achieve steady state and limits one's ability to use information from a single dose to predict kinetics after repeated dose or continuous administration. Carbamazepine shows time dependence in its disposition. The decrease in its peak concentration on repetitive oral administration that either oral bioavailability decreases or clearance increases with time.

**Auto inhibition:** It may occur during the metabolism of certain drugs. The netabolites formed from drug firstly increase in concentration and further inhibit metabolism of the parent drug. This phenomenon is called as product inhibition or allosteric inhibition or feedback inhibition.

**Need for Chronopharmacology**

It is required to monitor so as to limit the duration of therapy especially in cases where patients are already having compromised renal, cardiac and hepatic or any other function of the body. Any type of accumulation of drugs in these organs causes greater toxicity which may led to diminished function of the organ.



**Human biological circadian clock**

**Biological clocks and circadian rhythm**

A hundred different, measurable parameters in the human body exhibit rhythmic variability within 24 hours. Rhythms affecting our body are ultradian cycles shorter than a day e.g.

msec. for a neuron to fire; Circadian-Circa- about a day, lasting for about 24 hours, e.g. sleep and wake Biological rhythms are innately determined rhythmic biological process or function and self-sustaining cycles; Infradian-cycles longer

than 24 hours e.g. menstrual cycle. Seasonal-like seasonal affective disorder causing depression in people during the short days of winter. While 24-hour clock times and sleep/wake rhythms frequently overlap with the internal clock, they do not always match the circadian rhythm. There are a variety of methods to ascertain the timing of biological clocks. Melatonin provides the most reliable and consistent measure of the circadian pattern and can be measured in the plasma, saliva, or urine. Because secretion of the hormone is acutely suppressed by light exposure, the measurement of the time of onset of the daily melatonin rise during low-light exposure is a more reliable measure of the circadian phase. The dim-light melatonin onset (DLMO) has been used to assess alterations of circadian phase in a variety of diseases. Other markers, such as core body temperature, and cortisol may also serve as biomarkers for circadian rhythms.

**Circadian rhythms:** The cyclical 24-hour period of human biological activity.

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