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Microsponges as a Game Changer in Cancer Treatment: A Review of its Potential and Progress

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A B S T R A C T

Microsponges are class of porous, polymer-based microspheres that are potential to deliver drug for controlled and targeted therapies. These are characterized with encapsulation of wide range of therapeutic agents, improved stability, sustained release of drug, reducing side effects and enhanced therapeutic efficiency. These microsponges are prepared using various methods like quasi emulsion solvent diffusion method and liquid- liquid suspension polymerization. These microsponges are further formulated into gels, creams, tablets and transdermal patches. Therapeutically, these are used in formulating drugs for various therapeutic activity like antiepileptic drug, osteoarthritis, antifungal activity, anti-inflammatory activity, in cosmetics like sunscreen and cancer. Here, in the following microsponges prepared using different cancer drugs are discussed below regarding their preparation method used and their benefits over the conventional ones in terms of drug release and therapeutic efficiency.

Keywords: Microsponges, liquid-liquid suspension polymerization, quasi emulsion solvent diffusion method, therapaeutic application, polymers utilized, cancer therapy

INTRODUCTION:-

Cancer is a multifactorial disease in which a series of molecular alterations cause uncontrolled growth along with proliferation of cells. Cancer cells grow using oxygen and supplements of healthy cells and can turn their surrounding environment in their favor, resistant against immune system of body and exploiting physiology of other cells. They interfere with apoptosis, drug resistance, DNA damage, DNA replication or immune reactions. With the reports of mustard gas killing lymphatic tissues and bone marrow chemotherapy came into existence. Chemotherapy prevents cancer cells from further growth and divison. The major drawback of chemotherapeutic treatment is their non specificity in targeting leading to side effects or toxic effects.[39] The drug technology have been developing since many years yet there is a need for delivery system that can cause controlled release along with targeted site delivery. For which various nanoparticle and microparticle based formulations were developed but we still face the issue of controlled release (especially in transdermal application and topical delivery), lower entrapment efficiency, preparation difficulty and less stability.[40][41] The discovery of microsponges which are porous polymeric drug systems have reduced these drawbacks.[1]

It was in 1987 when Won initially developed microsponge, which was first patented to advanced polymer system. Microsponge delivery system also known as solid phase porous microsphere.[2] These are multiparticulate systems which consists of highly crosslinked polymeric porous microspheres where the interconnected pores causes controlled release of drug entrapped through diffusion. Microsponges are believed to have self sterilized property since their diameter size ranges between 5 μm to 300 μm with average pore size of 0.25 μm which is very less than average size of various microorganisms.[3]

Polymers used to prepare microsponges can resist wide range of temperatures upto 1300 C and pH ranging between 1-11.[3] Hence, exhibiting greater stability than liposomes. Comparative to liposomes it is found to have entrapment efficiency higher that is greater than 50%.[1] The high degree of polymeric cross linking between microparticles of microsponges provides insolubility and satisfactory strength against high shear.[4]

The microsponges are not limited to transdermal but also extended to oral, parentral and pulmonary drug delivery.[5]

ADVANTAGES:[1][2]

Compared to other marketed topical applications microsponges containing formulation of creams, lotions, gels etc. cause less irritation to patients as it absorbs more than 4 times oil present on skin.

Microsponges required comparatively less API than other conventional topical formulation. Thus, reducing side effects.

Microsponges because of use of specific polymers have thermal, physical and chemical stability.

Microsponge preparation can be done in commercialized level. It is flexible for devoloping novel drug delivery system.

When compared to other microparticulate it has better compressibility efficiency for the preparation of tablets.

Compared to other delivery system it provides higher amount of drug due to high traverse time in small and large intestine.

DISADVANTAGES:[2]

Microsponges cannot protect drug from microbial flora at release site.

The polymers used when degraded into monomers may cause harm to body.

DRUG RELEASE FROM MICROSPONGES:

Microsponges being a polymeric microparticle, drug may be distributed/ dissolved in matrix and released either by diffusion or erosion of matrix. Initial burst release is observed during the release followed by sustained release mainly due to the adsorbed drug onto the large surface area of polymer rather then being incorporating within the particle.[3][36]

Microsponges when given orally or through other routes, there are different external factors that may trigger drug release which include pH dependent, change of temperature, pressure and solubility.[5] Temperature improves drug release proportionally, as with increase in temperature there is an increase in release of sunscreen active ingredient from microsponges. By applying pressure through rubbing release of active ingredient takes place into skin. Modifying coating of microsponges with pH sensitive polymers like eudragit can cause pH triggered release when microsponges are orally administered. Based on the partition coefficient of the ingredient between microsponges and external system that is vehicle solubility of the active ingredient varies leading to altering of drug release.[4][9][10]

Orally administered poorly water soluble drugs can be efficiently administered through microsponges technology. The release of drug can be regulated by pH. Enteric coated property can protect the microsponges from gastric juice (pH: 1-3). The coating dissolves in gut at targeted site of colon due to the enzymes (glycosidases). [6]

When microsponges based formulation is applied on to skin it retains on the surface and cannot pass through it. The rate of release depends on the partition coefficient of active ingredient between the polymer used in formulation and skin, surface area of microsponge and mean diameter of pore of microsponge. Active ingredient in the microsponge diffuses out into the vehicle used in the formulation and reaches finally into skin.[1]

Active ingredient entrapped in vehicle is allowed to move in and out of particles until equilibrium is reached. When the product is applied to skin, active ingredient is absorbed depleting its concentration in vehicle hence disrupting equilibrium which causes flow of active ingredient from microsponge into vehicle and further into skin until it is completely dried or completely absorbed. This tells us about importance of vehicle in the formulation of microsponge. Equally, solubilizing power of the active ingredient must be studied as if highly soluble then active ingredient may not have effective release to the therapeutic site. Minimum solubility of active ingredient is required in the vehicle for microsponge formulation as it provides initial loading dose. Comparative to conventional formulation which solubilizes the active ingredient in vehicles. [7][8]

As discussed above, release of drug is affected by various factors which includes not only include properties of drug but also physical properties of polymers used in microsponge. Other than partition coefficient of drug even its solubility shall be studied because hydrophilic drugs show significant decrease in entrapment of drug. Even preparation methods influence pore size and drug release. If the pore size is too decreased then contact surface may increased due to increase in surface area leading to increase in drug release. In terms of sustained action, initial burst release (with higher release rate before 2 hrs,) followed by decline (with low flux between 2 and 12 hrs) and extended release for 24 hrs is seen in case of reduction of size. This is observed even though microsponges being incorporated in gels, emulsions, tablets and capsules. Porosity can influence apparent diffusion coefficient of drug thus affecting its release.[3]

Amount of polymer also affects drug release as on increasing concentration of PVA aqueous dispersion did not change curcumin release but by changing PVA amount from 30 to 70mg resulted in reduction of 37% of drug release. Time taken for polymer to swell for drug to be released totally depends on stabilizer concentration used, proportionally.[3]

Ratio between drug and polymers and type of organic solvents used for the preparation of microsponges can affect kinetic mechanism. Microsponges prepared using risperidone and celecoxib had same polymers and solvents in their formulation but had different n values i.e., between 0.5 and 0.1 indicating a non-fickian diffusion mechanism.[3]

PREPARATION:

Microsponges of different drugs like benzoyl peroxide, dicyclomine, fluocinolone acetonide. Ketoprofen, retinol tretinon, ibuprofen, flubiprofen, fluconazole, etc. are prepared using polymers like polyhydroxyethyl methacrylate, ethylcellulose, acrylic polymers, eudragit RS100 and polystyrene. Preparation of microsponges involves important step of studying physicochemical properties of active ingredient. Active ingredient shall not be reactive

with monomer and shall be stable. Also, active ingredient shall not be miscible with water rather shall be miscible with monomer used for the preparation of microsponges.[1][6] For the preparation of microsponges there are two methods; 1. Liquid-liquid suspension polymerization and 2. Quasi- emulsion solvent diffusion.

1. Liquid-liquid suspension polymerization:

It is also called free radical suspension polymerization. It is a bottom up approach for the synthesis of microsponges. The particles are formed using monomers through which the process starts and these monomers are called as dispersed phase. The immiscible liquid containing monomer is called as polymerization medium.[1]

In this method, drug and the polymer are dissolved in organic solvent and other additives like surfactants which are water soluble are dissolved in water or the aqueous phase. The solution of drug and polymer is water immiscible. The other liquid that is used which is immiscible with the organic solvent, i.e., polymerization medium but miscible with monomers are referred to as monomer diluent or porogen. It is the reason to form pore network. This method is carried out using three necked round bottom flask where each neck is meant for stirrer, thermometer and and water condenser.[2][4][6][11]

When nonpolar organic solvents are added to the polymerization process polymeric beads with open, porous structure can be obtained which when observed under the SEM represent sponge. Hence, called microsponges. The reaction in the preparation procedure depends upon catalysis, increased temperature or irradiation. Temperature plays major role during reaction as it affects rate of decomposition and polymerization along with initiation into free radicals. As the polymerization process continuous the microspheres interconnect with each other forming interconnecting reservoirs in which porogen is entrapped and the reservoirs formed open to the surface of the spheres through which drug or the active ingredient is released.As the polymerization continous and microsponge are prepared they shall be recovered, washed and thoroughly processed which makes them ready to use following their characterization tests. It is termed to be single step process which involves particle formation and incorporation of the active ingredient. If drug is sensitive, two step process must be used for preparation of microsponge.[7]

Difference between one step process and two step process:[7]

ONE-STEP PROCESS	**TWO-STEP PROCESS**
Polymerization occurs in single step without prepolymer formation.	Polymerization occurs in two steps which includes formation of pre polymer solution and then polymerizing into microspheres.
Monomers, crosslinkers and initiators are directly suspended in aqueous phase.	Pre polymer solution is prepared first and dispersed in continuous aqueous phase.
Due to rapid polymerization low porosity and there less control on the polymerization process therefore wider particle size distribution.	Due to controlled polymerization, higher porosity is observed and uniformity in particle size distribution.
Lower encapsulation of active ingredient.	Higher and efficient encapsulation of active ingredient especially which is sensitive to polymerization process.

2. Quasi- emulsion solvent diffusion method:

This method preparation involves two phases which include internal phase and external phase just like emulsions. The internal phase is made by dissolving drug along with polymer in organic solvent. The organic solvent chosen is volatile in nature. For example: ethanol, acetone, dichloromethane, etc. internal phase is prepared at 600c. The external phase involves aqueous solution of polyvinyl alcohol. Both the internal and external phase are vigorously stirred to form quasi-emulsion globules, at room temparature.[2][4][6][11]

In order to form insoluble and rigid microsponge solvent Is extracted out. To provide plasticity to it triethylcitrate is added. After the removal or extraction of organic solvent, microsponges are filtered out and dried in air heated oven for 12 hours or in vacuum oven for 24hrs at 400C. As the organic solvent is extracted out, there will less traces of solvent left when compared to microsponges prepared through liquid-liquid suspension polymerization. Hence, reduced toxicity due to solvents.[12]

The mechanism involved in the method for the preparation is diffusion of aqueous phase within quasi- emulsion droplets decrease drug and polymer solubility results in co precipitation of both. Also, continuous diffusion of organic phase results in solidification thus producing matrix type porous microspheres.[9]

3. Other methods:

For formulating thermolabile materials like proteins, water soluble or water insoluble drugs water in oil in water emulsion solvent diffusion method can be used where the internal aqueous phase containing emulsifying agents (ex.: span, polyethyleneimine and stearylamine) is dispersed in organic phase containing polymer. It is the novel technique meant for preparing biodegradable porous microspheres. In case of oil in oil emulsion solvent diffusion method volatile organic liquid is used a s internal phase which evaporates slowly on continuous stirring. For example, hydroxyzine HCL loaded eudragit RS 100 microsponges were prepared using acetone as dispersed solvents.[2][12][13]

PROCESS PARAMETERS CONSIDERATIONS:

In order to prepare efficient microsponges various aspects shall be considered. Polymers play a major role in preparing the infrastructure of microsponges forming non collapsible structure with covalent bonds are formed. Polymers shall be compatible with API and shall cause low toxicity and low adverse effects. For the preparation of microsponges polymethacrylate group of polymers are primarily used and they are approved by FDA for its use in preparation of microsponges. Other than polymethacrylate polymers other polymers like eudragit RSPO, eudragit RS100, eudragit S100, polylactic acid, polyvinyl benzene, HPMC, etc are also used. In order to obtain porous and less bulky microsponges polyvinyl benzene can be used. Other excipients like emulsifier (example: polyvinyl alcohol) and plasticizer (example: triethyl citrate) are used.[2]

During optimization of formulation it is important to focus on drug/polymer ratio. As drug/polymer ratio increases particle size decreases. In preparation of benzoyl peroxide microsponge preparation, two drug/polymer ratios were considered and their particle size was compared and found that among the ratios 3:1 and 13:1 microsponge with drug/polymer ratio exhibited smaller size with mean diameter 310+/-34 µm. When the dispersed phase used in the preparation of microsponges has higher viscosity when poured into dispersion medium gives droplets of bigger size, i.e., mean particle size increases. [14]

The stirring rate influences the particle size. Care shall be taken while adjusting stirring rate. For which we can take example from the formulation of ethylcellulose based microsponges loaded with clobetasol. Different stirring rate were taken like 500, 1000 and 1500 rpm and result showed that as stirring rate increases particle size reduces. As the stirring rate is low there will be low shear force leading to aggregation of particle but if stirring rate is high shear force increases leading to greater and rapid dispersion of particles, thus preventing aggregation of particle. There is a chance that due to high stirring rate there are chances of loss of polymer particles as they may get stick to wall of beaker or the polymer may adhere to padd;e due to turbulence created within external phase due to high shear force. Hence, production yield gets affected; decrease in yield is observed. The influence of stirring rate was also studied while studying morphology of eudragit S-100 based microsponges bearing dicyclomine. As the speed of stirring rate increases (Upto 1000rpm), the spherical microsponges formed are with mean particle size 59.54+/-5.24 µm.[15]

Depending on the amount of emulsifying agent production yield gets affected. As the amount of emulsifying agent increases production yield decreases and particle size increases. In the study of morphology of eudragit S-100 based microsponges bearing dicyclomine, as there is an increase in amount of emulsifying agent production yield decreases from 73% to 67% and increase in mean particle size from 59 to 62 µm.[15]

Microsponge based drug delivery systems are also used in formulating cosmetics like creams, gels, lotions, powders, etc. During formulation of cosmetics, in order to avoid cosmetic based problems it is necessary that 10- 12% w/w microsponges must be incorporated into the vehicle of cosmetics.

Along with chemical factors mentioned above there are other physical factors that affect the development of the microsponges. Physical factors include stirring speed, power delivery and mechanical force, which influence and control fluid dynamics of mixed liquid to develop microsponge. These factors inturn affect physical appearance, particle size, yield and entrapment efficiency.[16]

THERAPEUTIC APPLICATION OF MICROSPONGES:

Given below are few different microsponge based formulations for therapeutic purpose:

DRUG	**POLYMER AND METHOD USED**	**REMARKS**
Oxybenzone - broad spectrum of sunscreen agent [22]	• Ethyl cellulose (0.1-0.3%) • Quasi emulsion solvent diffusion method	On testing sun protection factor (SPF) it was found that microsponge gel produces SPF 25, through enhanced topical retention of drug for prolonged period of when compared to marketed preparation (SPF 20).
Mupirocin – topical antibiotic [23]	• Ethyl cellulose • Emulsion solvent diffusion method	On performing ex-vivo study deposition results obtained in micropsonge based emulgel (204.4 µg /cm^2) were higher when compared to emulgel (87.57 µg /cm^2) and ointment (37.03 µg /cm^2). Hence, frequency of administration reduced making it significant in treatment of primary and secondary infections caused by gram positive and gram negative bacteria.
Curcumin [24]	• Ethyl cellulose • Quasi emulsion solvent diffusion method	Curcumin microsponges which were filled in capsule shells exhibited 93.2% release in 8hrs study following zero order release kinetics. Curcumin microsponges loaded in carbopol gel when tested for ex vivo drug release through franz diffusion cell showed 77.5% drug release in 24hrs. upon release amount of drug retained was observed to be 207.61 µg /cm^2 Curcumin based microsponges filled in capsules fitted in zero order drug release kinetics. Hence

DRUG	**POLYMER AND METHOD USED**	**REMARKS**
		useful than conventional in terms of topical and oral drug delivery.
Acyclovir-antiviral against herpes simplex virus [25]	Eudragit RS100 and triethyl citrate Quasi emulsion solvent diffusion method	Acyclovir is believed to have 20-30% of bioavailability. Upon formulating as microsponge using QbD the obtained cumulative drug release % obtained was 87.03. Thus, increase of oral bioavailability of acyclovir.
Fluconazole-triazole antifungal drug [26]	Ethyl cellulose Quasi emulsion solvent diffusion method	Developed microsponge of fluconazole when undergone through in vivo skin deposition study found that microsponge based formulation of gel has deposition amount of 120.45 µg /cm^2 which is 3-4 fold higher than marketed gel formulation. Thus, the developed form of microsponge based gel of fluconazole was proven to be non irritant to skin and showed enhanced retention of drug on skin. So, effective antifungal therapy.
Carbamazepine - anti epileptic drug [27]	Ethyl cellulose Quasi emulsion solvent diffusion method	With increase in the concentration of ethyl cellulose there is increase in entrapment efficiency, particle size and reduction in release rate when compared to immediate release. This was observed by comparing formulation 1 (ethyl cellulose:800mg) and 7 (ethyl cellulose:1200mg) it was observed that significant reduction in carbazepine release. Thus, providing sustained release of drug with increase in bioavailability.
Flurbiprofen [28]	Eudragit RS 100 Quasi emulsion solvent diffusion method	A novel colon specific drug delivery system containing flurbiprofen microsponges were prepared for specifically targeting colon site for drug delivery. Specific site drug delivery was observed due to triggering mechanism through microflora activation and avoiding release of drug in small intestine. Also, microsponges formulation promoted uniform distribution of drug in colon and help drug to be spread out throughout colon surface for efficient absorption.. Thus, providing effective treatment as an NSAID towards inflammation, pain or rheumatoid arthritis with plasma half life 3-6hrs.
Mitiglinide calcium – insulinotropic agent [29]	Ethyl cellulose and eudragit RS 100 Quasi emulsion solvent diffusion method	Mitiglinide calcium was formulated into gastroretentive drug delivery system with highly porous nature due to which it imparted extended buoyancy over 24 hrs along with pattern of sustained release. Through this type of formulation mean residence time is enhanced followed by bioavailability. Hence, frequency of administration was reduced when compared to immediate release.
Diclofenac diethylamine – arthritis therapy [30]	Eudragit RS Quasi emulsion solvent diffusion method	Microsponge based gel formulation prepared in this study is effective in treatment of rheumatoid arthritis, juvenile rheumatoid arthritis , osteoarthritis and ankylosing spondylitis. Formulation prepared with 1:2 drug-polymer ratio was found effective in reducing frequency of administration from the observation of release of drug (75.88% at 8hrs) when compared to conventional formulation (81.11% at 4hrs). thus, the microsponge based preparation found effective than the marketed formulation.
Celecoxib – familial adenomatous polyps [38]	Eudragit S 100 and PVA Quasi emulsion solvent diffusion method	Microsponges of celecoxib prepared were found to be stable and porous microsponges. Drug released from microsponges was observed to be 90% for 12 hours. Hence,

DRUG	POLYMER AND METHOD USED	REMARKS
		providing extended release profile to the drug from the microsponges.
Entacapone	Polymethacrylate polymers [Eudragit L, S and RS 100]	It has low solubility causing increasing frequency of administration 200mg 8times a day. By formulating as microsponges, frequency of administration is reduced and aking it effective to be used for anti parkinsons treatment.

MICROSPONGES IN CANCER THERAPY :-

Cancer is a global serious health issue leading to many deaths. It was in 2018 when about 1.7 million cases of cancer were reported globally with 1670 deaths per day.[17] In order to treat various types of cancer various methods are used for the treatment like radiation, chemotherapy and surgery but they produce adverse effects that badly affect healthy cells of patients. Hence, microsponge based drug delivery along with high entrapment efficiency of drug also plays major role in protecting active ingredient from external GIT environment and also provides controlled drug delivery to lower GIT. Microsponges can be used orally to obtain sustained release with decreased toxicity along with targeted site delivery by modifications in formulation as in the case of targeted delivery of 5-FU for colon cancer therapy and curcumin drug release specifically at the site of stomach as discussed below.[18][19]

There are few chemotherapeutic agents like 5-FU even though being potent can't be used for treatment of various types of cancers especially, colorectal cancer because of the bioavailability issues due to which IV administration of drug becomes necessary for the treatment purpose, but it is found that the drug gets quickly distributed and eliminated. 5-FU is an anti neoplastic (anti-metabolite), which inhibits RNA and DNA synthesis by inhibition of formation of thymidylate from uracil. IV administration of 5-FU causes severe systemic toxic effects like GI disturbances, blood complaints and skin diseases along with other neural and cardiac effects to the healthy human cells. Also, dihydropyrimidine dehydrogenase enzyme is responsible for the catabolism of 5-FU in liver and GI (as the enzyme is in high concentration in GIT epithelium). This lead to development of microsponge based delivery of 5-FU. Microsponge based 5-FU drug delivery increases the ability of macrophages concentrated at tumor site of colon tissue to absorb those microsponges drug delivery systems due to their smaller size of 200 μm. Also, microsponges help in retaining the drug at the tumor site by accumulation. On comparison, 5-FU microsponge was found to be more effective than 5-FU on viable cells. It was found in one of the study conducted by Othman MH et al. that, pure 5-FU was found to be released in 20 min, while microsponge based formulation causes initial immediate burst release (due to drug adsorbed on the surface of microsponge) followed by moderate slow release. Different works were done to develop microsponges formulation of 5-FU. Earlier, it was reported that microsponges were prepared through W/O/W emulsification method but it produced low entrapment efficiency due to solubility property of 5-FU in water (solubility: 12mg/ml). Later, using oil in oil emulsion solvent diffusion method microsponges were prepared in which usage of magnesium stearate of 3% produced spherical, uniform and free flowing microsponges, along with which as there is an increase in drug to polymer ratio leaching of drug during fabrication was reduced due to high entrapment efficiency. Even though oil in oil emulsion solvent diffusion method provides high entrapment efficiency greater than 95%. Caution shall be taken regarding dispersed phase viscosity as increase in viscosity of dispersed phase when compared to dispersion medium led to larger particle sizes. Magnesium stearate is used in formulation as a stabilizer such that it prevents coalescence flocculation of the microsponge particles being formed. [31]

Calcium pectinate beads based drug delivery systems targets drugs to colon which are obtained by pectin gelatinization in presence of calcium salts. Comparatively, it is less water soluble than natural pectins. Pectin is the polysaccharides involved in colon specific delivery. They get selectively biodegradable by pectinolytic enzymes of colonic bacteria microflora and control drug release via pH and time controlled mechanism. Due to the high solubility of pectin, it cannot effectively shield the drug in stomach and intestine, hence it is important that its solubility must be decreased through crosslinking with calcium ions to produce calcium pectinate networks. Research work was performed on enteric coated HPMC capsules constituting of 5-FU loaded microsponges in combination with calcium pectinate beads by Gupta et al. HPMC coat causes slow drug release in acidic media and faster drug release on basic media, providing desired release in small intestine and colon. Under the work, microsponge was prepared by quasi emulsion solvent diffusion technique by using Eudragit RS 100 as polymerIn vitro drug release study was performed based on USP protocol using pH change method. Enteric coated HPMC capsules exhibited 8hrs of drug release with no drug release at pH 1.2 upto 2 hrs indicating the strength and intactness of the enteric coat. Pure eudragit coat exhibited delayed drug release when compared to blend one. Release of drug from the formulation is observed through diffusion along with erosion of eudragit layers. With respect to calcium pectinate beads in the formulation it was found that calcium pectinate plugged ES-100-coated HPMC capsules didn't release cytotoxic 5-FU in stomach and small intestine. Targeted colon release was observed due to microbial degradation of calcium pectinate plug because of the presence of pectinase enzyme.[21]

It was in the year 2018, when about 99,500 new cases of skin cancer were reported along with 13, 640 deaths among which cases of cancer being diagnosed was higher in females with age less than 50 and this rate becomes double and triple in case of males with the age of 65 and 80 years. 5-FU is considered to be a gold standard anti cancer drug used for skin cancer and actinic keratosis. WHO has registered it for various applications like skin non-melanoma and actinic keratosis (AK) lesions. Commercially, 5-FU are present in the form of creams and solutions where the topical formulations are recommended for 2-3 weeks for actinic keratosis and 4-6 weeks for basal cell carcinoma. But, they have drawbacks of local inflammatory reactions, intense itching, high skin irritation potential, long treatment periods, poor retention at tumor site and high frequency of administration. To overcome these drawbacks various microcarriers have been studied for their efficiency in altering dermal kinetics and biopharmaceutics of drug release and microsponges

were choosen among them because of their porous nature along with their high surface area due to which large amounts of drug are absorbed, also they can further be formulated into topical and oral administration based formulation. Subheet Kumar Jain et al through two step quasi emulsion solvent diffusion technique was used to create microsponges using polymers ethylcellulose or eudragit RL 30D. Followed by microsponges preparation, carbopol 934 based gel was prepared. The formulation texture properties were studied and result was reported that hardness value is about 0.0722+/- 0.0004 N, adhesiveness value is 0.767+/-0.0003 N and cohesiveness value is 0.8709+/- 0.0002 N, which are less when compared to commercial products. It is found that with increase in polymer concentration adhesiveness property increases leading to reduction in spreadability and enhancement of retention of formulation on skin. Under the ex vivo study, microsponge formulation was compared with commercial cream (Flonida 1% w/w) on pig ear skin and the result reported was microsponge based formulation had showen better skin permeation and deposition along with cumulative amount of drug released to be 85.98+/-2.60mg which is almost double of commercial formulation along with drug deposition observed to be 2.63 fold higher for optimized microsponge formulation. Comparative increase in skin permeation rate was expected due to higher surface area and spongy nature of microsponges and occlusive effect because of the based gel formulation of microsponge thus enhancing residence. Further, in vivo studies were performed which include skin irritation study using Draize test and determining skin localisation index. When skin localisation index was compared for commercial product and microsponges for focusing on targeted drug release at site of action, it was found that microsponge formulation had lower fraction of drug reaching systemic circulation promoting high deposition of drug, almost 5.2 fold higher than commercial formulation. Hence, better localization index of microsponge based gel formulation of 5-FU than commercial product.[37]

Colorectal cancer among the life threatening cancers are caused by chronic inflammation due to dysbiosis. Even mutations in specific genes may cause colorectal cancer which are broadly classified by sporadic (70% of colon cancers), inherited or familial. Candidone, a flavone found in Derris indica, is found to have cytotoxic effect on human cancer cells. Candidone can be safely given through oral route for long term effects. Candidone treats HepG2 cancer cells through blocking the production of p65 phosphorylation, Bcl-xl, Mcl-1, Bcl2 and surviving, activating caspase-3 and caspase-9. In the case of multi drug resistance, candidone acts as chemosensitizer. Since microsponges are polymeric based porous drug delivery system of size less than 200mm are taken up by colon macrophages giving a successful localized drug activity. Upon performing in vitro screening against cancer cell lines HT-29 colon cancer cells, it was found that there is dose dependent reduction in viability of colon cancer cells treated with candidone ranging in different concentrations from 0-800mcg/ml for 24 hours. Because of the efficiency of candidone constituent towards colorectal cancer, microsponges based formulation was prepared for candidone using eudragit RS-100 along with triethyl acetate as plasticizer by quasi emulsion solvent diffusion method. For preparing optimized microsponges 32 factorial design (3 factors studied in 2 levels i.e., high and low levels) was employed to study independent variables (eudragit RS-100 and stirring speed) effect on 3 dependent variables (entrapment efficiency, zeta potential and article size). After the preparation of the microsponges it was observed that optimized microsponges with particle size 44.26-55.77 µm. As we know, with decrease in particle size surface area increases making drugs to be easily absorbed from the formulation. The formed microsponges have negative charge providing excellent stability according to the obtained zeta potential result. The cumulative drug release profile of the microsponges formulated was studied, and obtained result was 3.32-8.12% at first 2 hours at pH 1.2, 8.03-16.25% at next 4 hours at pH 6.8 and followed by 16.25-94.25% at next consecutive 6 hours at pH 7.4.When compared it was observed that at pH 7.4 there is high drug release which is mainly due to polymer used eudragit which is pH sensitive polymer. The release profile of the formulation follows Higuchi model(R2 =0.9921) with diffusion as primary mechanism for drug release. Finally, through the usage of eudragit RH-100 as polymer for preparing microsponge it promotes targeted release at the site of colon avoiding release in upper gastric tract with pH ranging between 1.2 to 6.8.[20]

Another example of anticancer agent delivered using microsponge as a microcarrier is curcumin which has the ability to prevent cancer that is resistant to multiple drug treatment and it is also immune restorer. But it has bioavailability issues due to its poor solubility of about 0.456 µg /ml in aqueous solution, low tissue distribution, rapid metabolism and elimination from body hence a shorter half life. The curcumin is observed to get degraded in intestinal pH i.e., in alkaline environment. For the effectiveness of the curcumin there is a need to develop efficient drug delivery system for specific delivery in stomach with high loading capacity. Hence, microsponges can act as an effective microcarrier. In order to provide specific delivery in stomach it is important to formulate low density gastro retentive system for which feasibility of microsponges as floating drug delivery system was explored. Curcumin based floating microsponges were prepared using biocompatible, safe and inexpensive polymers ethyl cellulose and eudragit RS 100 by quasi emulsion technique using sodium chloride solution as porogen. Buoyancy of microsponges when determined in terms of in vitro in different studies, it was found that correlation of low density (0.4g/cc) of ethyl cellulose with buoyancy of microsponges. Also in other study it was found that with increase in PVA less dense microsponges were formed and with decrease in PVA highly dense microsponges were formed. But when buoyancy of curcumin microsponges were observed with decrease in particle size there was increase in buoyancy. The density of microsponges was observed to be less than stimulated gastric fluid i.e., 1.004g/cc which imparts buoyancy to it. Thus, providing specific delivery of drug in stomach with sustained release and high bioavailability. [19]

Other formulations based on microsponges prepared for the cancer treatment are mentioned below in tabular formula:

DRUG	**REMARK**
CURCUMIN [32]	The microsponges are prepared using ethyl cellulose and poly vinyl alcohol and optimized to prepare targeted floating curcumin microsponges for gastroretentive potential. Optimized formulation gave results with entrapment efficiency 90.7%, buoyancy 82.0% and cumulative drug release of 85.2%. SEM revealed spherical porous microsponges (as shown in figure below the table). Through invitro studies it was observed that curcumin permeate through

DRUG	**REMARK**
	mucin and reach targeted site of gastric cancer. Also, increase in bioavailability of 10 fold increase when compared to native curcumin.
ERLOTINIB HYDROCHLORIDE [33]	Microsponge was optimized and composed using ethyl cellulose and pectin using quasi emulsion solvent diffusion process. The formulation gave result of entrapment efficiency of 82.36% and release of drug for 12 hrs of about 85.49%. when compared to erlotinib aqueous suspension, microsponge formulation has been found to have higher C_{max} thus improving the bioavailability and therapeutic efficacy of drug.
METHOTREXATE[34]	Sustained release microsponge formulation was prepared using quasi emulsion solvent diffusion method which gave result of encapsulation efficiency of 87.191% and sustained drug release of 85.71% . the prepared microsponge particles are filled in Eudragit-S-100 coated hard gelatin capsule depicting release only in colonic region.
IFOSPHAMIDE [35]	Microsponge was prepared using Eudragit RS 100 through oil in oil emulsion solvent diffusion method. The formulation gave entrapment efficiency of 85%. This formulation provided enhancement of accumulation of drug in tumor region and reduced toxicity.

CONCLUSION:

Microsponges represent a promising advancement in drug delivery system especially in terms of cancer therapy by offering controlled release, targeted release, reduced toxicity and delivery of drug along with improved patient compliance. Their preparation methods are adaptable towards commercialization. For effective delivery of drug formulation and other method based parameters can be optimized. Continuous research and development regarding development of microsponges for cancer therapy is needed in terms of surface modification followed by functionalization promoting enhancement in targeted drug delivery along with reducing side effects. Also, promoting personalized and effective cancer therapy. Hence, there may be chances for microsponges to be next generation oncological treatment strategy

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