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Microsponges: A *de novo* Method for Colon Targeted Oral Drug Delivery

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ABSTRACT
Colon Targeted Oral Drug Delivery System has gained much importance in recent times in delivering drug substance for the local action against colonic cancers, infections, Ulcerative Colitis (UC) and Crohn's disease and for systemic action of protein peptides and non-peptide drugs include Cardiovascular and Antiasthamatics etc. This article gives an overview about the anatomy, physiology of colon and factors that are having influence on the formulation. Various approaches for colon targeting are specified and micro sponges are at forefront having unique, versatile and novel approach. Micro sponges are highly cross linked porous polymeric microspheres with many interconnected voids loaded with API that are released in a controlled manner. Micro sponges are designed to deliver efficiently at minimum dose with reduced side effects, enhancing the stability and solubility of active pharmaceutical ingredients. Further, the novel techniques in preparation, compiling the present research information with novel applications of drug delivery with micro sponges are highlighted.
Key words: Crohn's disease, Nanosponges, Quasi emulsion, Ulcerative Colitis, Colon, Targeting, Delivery systems.

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INTRODUCTION

Colon-specific oral drug-delivery systems gained prominence in recent years. It helps to deliver diverse drug moieties for local as well as systemic action.[1] The oral route of administration of drugs is well-established and is considered to have high patient compliance. Colon as a site specific for drug delivery has favourable position for, close neutral pH, reduced gastric related enzymatic action, longer transit time and enhanced responsiveness to drug absorption.[2]

Therapeutic advantages of Oral-Colon targeting:

- **Highly desirable in treating local diseases** such as ulcerative colitis, amoebiasis, Crohn's disease, carcinoma and infections, while minimising the side effects that occur due to release of higher drug content in gastrointestinal tract or because of unnecessary systemic absorption.[1]
- Useful in **chronotherapeutic** point of view in delivery of those drugs where a delay in drug release is required, as in case of nocturnal asthma, angina pectoris, rheumatoid arthritis.[1]
- **Avoid premature drug release in upper GIT.** They are designed to selectively release the drug in response to the colonic environment.[3]
- Prevents the drug loss from first pass effect.

Anatomy of Colon

Large intestine is the final section in gastrointestinal tract comprises of caecum colon, rectum and anal canal which is extended from the ileocaecal junction to the anus as shown in Figure 1.[4]

Caecum seamlessly joins up with the colon. Colon is the largest portion of about 1.5 meters long, made up of ascending colon which continue as the transverse colon at hepatic flexure, then as the descending colon at splenic flexure and finally transformed as the sigmoid colon.[4] Distal to ileocaecal sphincter, the bacterial concentration increases sharply and colon has micro flora of 10^{11}-10^{12} cfuml^{-1}.[5]

Factors Effecting Colonic Drug Delivery are colonic fluid volume, intestinal colonic transit time, viscosity of colonic luminal contents, colonic pH, enzymes and metabolism.[6]

Colonic Fluid Volume

Although colon is considered to be having high water absorbing capacity, the fluid volume available in colon estimated to be 1-44 ml. The average volume is approx. 13 ml where, solubility and dose of the drug becomes an important factor for bioavailability in colon.

For example, a highly potent drug Budesonide having a dose of 9 mg is well absorbed in the colon whereas mesalamine even though significantly have higher solubility (3.64 mg/ml) when compared to budesonide (0.24 mg/ml) its absorption at colon becomes rate limiting factor because of having significantly higher dose i.e.,4.8 g daily.[6]

Intestinal Colonic Transit Time

Colonic disease states like ulcerative colitis and Crohn's disease influence transit time.[11] For example patients suffering from UC will have reduced colonic transit time results in reduced exposure to the distal colon this may affect the bioavailability of the drugs in colon.[6]

Viscosity of Colonic Luminal Contents

Viscous colonic contents and decreased intestinal motility restricts fluid movement around the dosage forms and retards dissolution. Reduced motility delays erosion of the drug products.[7]

Colonic pH, enzymes and metabolism

In GIT region pH differs greatly from 1-2 in stomach to 7.5 in distal region of small intestine.

pH declines from the farther region of small intestine to colon and increase gradually in colon as mentioned in Table 1.[2,8]

Colon pH influence the solubility of the drugs in colonic fluid which will have an effect on pharmacokinetic and pharmacodynamic behaviour of colonic drug delivery systems (CDDS).[6] Some evidence suggests that there is substantial changes in gastrointestinal pH are associated with disease like cystic fibrosis, IBD, UC.[9]

Colon is known to consist over 400 different species of aerobic and anaerobic micro-organisms.[6] These bacteria contain several hydrolytic and reductive metabolising enzymes.[10] These enzymes helps in metabolising/ fermenting substance like carbohydrates and proteins. Micro flora activated systems are formulated with polysaccharides such as chitosan, guargum, pectin are promising rate controlling components in colon targeted dosage form. Colon targeting has two approaches Primary and Novel approach as mentioned in Table 3.[10]

Release triggering mechanism of drug

There are four mechanisms which trigger the drug release is discussed below in Figure 2.[11]

1. **pH dependent release:** pH varies along the GIT so dissolution of the polymer at desired site. This can be achieved by using the polymers that have a threshold pH (Table 2) for dissolution at that particular site.
2. **Time dependent release:** Time-dependent formulations are designed to release drug after desired lag time.

   E.g. Delayed release drugs or therapy of disease that depends on circadian rhythms
3. **Pressure based drug release:** In the large intestine, mass peristaltic movements occur 3-4 times in a day for a short duration, resulting in temporary increase in luminal pressure in colon. Basing on this principle pressure controlled systems are designed. The use of gastrointestinal pressure has been proposed as a method of target release in the distal gut.
4. **Drug release by colonic micro flora:** The micro floral enzyme activity provides site specific drug release. E.g. Micro flora activated system that are formulated using non-starch polysaccharide like pectin, remain undigested in stomach as well as small intestine and only degrade by the anaerobic bacteria that are available in colon and thus release the drug.

Much emphasis has been laid recent times on the development of multi particulate dosage forms. Due to the small size and the uniform dispersion, multi particulate system (MPS) easily pass through the GIT and results in increased drug absorption. MPS approach enables the drug to reach the colon rapidly and can retain for a long duration.[1] These MPS include coated pellets, granules, micro particles and nanoparticle that can be converted into a dosage form either by filling into a gelatin capsule or compressed into tablets. These dosage forms can provide modified drug release. Hence, this system is preferred over single unit dosage forms like tablets.[12]

In this context, micro sponges are at forefront having unique, versatile and novel approach.[13] It represents a new model of porous polymeric microspheres, which allows the entrapment of a wide range of active moieties.[14] This promising system has its application in transdermal, oral, ocular, pulmonary and parenteral delivery of bioactive compounds.[15] In the present review, microsponges are considered as a de novo method for colon drug targeting.

"Microsponges delivery system (MDS) also known as solid phase porous microsphere. Microsponges (MS) are highly cross linked, porous polymeric structures, having many inter connected voids impregnated with an active ingredient releasing controlled manner".[16] MS are colloidal in nature and size ranges from 5-300 µm in diameter. A typical 25 µm sphere may have up to 2,50,000 pores and each micro pore comprises a total pore volume of approx., 1ml/g and pore length equiv. 10 ft which results in extensive drug retention. MS method was invented by Richard Won in 1987. The original patents were assigned to Advanced Polymer Inc.[16]

MS act as carriers. Drug entrapment by carrier system results in reduction in particle size, increases active surface area and thus enhances solubilisation.[17] MDS possess various attractive features given below.[18]

- Stability over wide range of pH 1-11 and can withstand up to 130**°C**.
- Higher payload of 50 to 60 % and cost effective.
- Self-sterilization property as the pore size is 0.25 µm where bacteria cannot penetrate.
- Unique dissolution and compressional properties.[19]
- Can be tailored to have controlled release as per need by further incorporating into tablets, capsules, creams, gels, lotions and powders.

Properties of drug

For drug entrapment into micro sponges, the bioactive should fulfil the following criteria.[20]

- It must be fully miscible with selected polymer and water immiscible.
- It should be inert and stable during the process of polymerization.
- Should not increase the viscosity of the mixture during formulation.[18]

Mechanism of Action

MS having the size of < 200 µm may efficiently be taken up by the macrophages that are present in the colon. Thus they exhibit effective localised drug action at the desired site. They can increase lag time for absorption of the drug as these get intact on to the mucosal surface of colon and thus they have the potential for being developed as colon targeted drug delivery.[16]

Novel Drug Carrier Systems with their limitations

- Microcapsules - Once the wall get ruptured, the rate of drug release cannot be controlled.[21]
- Liposomes - Lower payload capacities, limited chemical stability, microbial instability and rapid drug leakage.[21]
- Solid lipid nanoparticles – have insufficient stability, sterilization problem.[22]
- Microspheres and Nano particles - Comparative to micro sponges they are non-porous in nature and have less capability to bind to rough surface of intestinal mucosa.[23]

METHODS FOR PREPARATION OF MICROSPONGES

(1) Liquid liquid suspension polymerization

(2) Quasi emulsion solvent diffusion (QESD)

Liquid-liquid suspension polymerization method: An organic solution prepared using monomer or monomers (combination), a polymerization catalyst, drug which are fully miscible in an inert organic solvent. This organic solvent is suspended in an aqueous solution which contains additives like suspending agents and surfactants to promote the suspension. Polymerization of the reactants was activated using the temperature or by irradiation. Upon completion of the process the rigid porous solid structures were recovered. The pores are formed as a result of the removal of immiscible organic solvent.[24]

Note: Drug loading may be of two steps when the drug is sensitive to the polymerization condition, the polymerization is performed using the substitute porogen and is replaced by the functional substance under mild experimental condition.[24] Schematic representation of the process is shown in Figure 3.[24,25]

"Quasi emulsion solvent diffusion"[25] technique: Internal organic phase when dispersed in aqueous phase it forms the globules; further diffusion of solvent results in leaving the structure porous. The detailed description is given below with schematic representation in Figure 4.[25]

- Preparation of Internal phase: It is an organic solution formed by dissolving drug, polymer and plasticizer in a miscible inert organic solvent. If necessary it is sonicated.[25]
- Preparation of external aqueous phase contains an emulsifier like PVA is generally used to maintain the stability.[25]

The organic solution is added drop wise into the aqueous solution and mixed by using stirrer that provides the mechanical shear results in formation of globules. Stirring is continued until a rigid porous solid particles i.e., MS is formed. They are recovered by filtering through Whatman filter paper 0.45µm and are washed to remove the solvent residues, further dried in an air heated oven at 40°C for 12 h [17] or vacuum oven at 40°C for 24 h.[25]

Generally used materials are

*Solvents: Ethyl Alcohol or Dichloromethane or Acetone or Methanol.

*Plasticizers: Tri Ethyl Citrate or Dibutyl Phthalate.

*Polymer: Eudragit, ethyl cellulose, styrene.

*Emulsifiers: polyvinyl alcohol.

Limitations

The organic solvents used in the process pose an environmental and safety hazard because of flammability of some solvents. The traces of residual solvent is observed in case of bottom up approach and are toxic and hazardous and this can be overcome by employing appropriate quality control measures, process standardization and proper washing after post manufacture.[16]

Table 1: pH at various regions of GI tract.

Region of GI tract		pH
Stomach		1.5 – 3 (fasted), 2 – 5(fed)
Small intestine	Duodenum	≈ 6.1(fasted), ≈ 5.4 (fed)
	Jejunum	6.4
	Ileum	7-8
Large intestine	Caecum	5.5
	Ascending colon	5.7
	Transverse colon	6.6
	Descending colon	7.0
	Sigmoid colon, rectum anal canal	7-8

Table 2: pH of commonly used polymers.

Polymer	pH	Polymer	pH
Eudragit L 100	6.0	Hydroxypropylmethylcellulose (HPMC) phthalate	4.8
Eudragit S 100	7.0	HPMC phthalate 50	5.2
Eudragit® FS 30D	6.8	HPMC phthalate 55	5.4
Eudragit® L 30D	5.6	Cellulose acetate trimellitate	4.8
Eudragit L 100-55	5.5	Cellulose acetate phthalate	5.0
Polyvinyl acetate phthalate	5.0	Shellac	7.0

Table 3: Systems of drug delivery to colon.

Primary Approach	Novel Approach
1. Coating drug with pH sensitive polymer	1. Pressure Controlled (PCDDS)
2. Delayed release	2. Novel Colon Targeted Delivery Systems.
3. Microbially triggered	3. Osmotic Controlled
a. Prodrug approach	4. Pulsatile
b. Azo polymeric prodrug	a. Pulsincap
c. Polysaccharide based systems	b. Port System
	5. Azo Hydrogels
	6. Multiparticulate drug delivery

Table 4: Effect of variables in the formulation.

Variable	Effects	Reference
Drug to polymer ratio	DP ratio has its affect on the particle size.	Vivekanand K Chatap *et al.* 2018 found increase in DP ratio resulted in particle size reduction.[28]
Stirring speed	Low speed leads to form agglomerate and high shear rate causes the breakdown of globules resulting in irregular shape.	Mine orlu *et al.* 2006 found 350-450 rpm caused to form fibrous and aggregates whereas at 500 rpm produces smaller particle size and homogenous distribution. Optimum speed of 500 rpm spherical shape was found.[29]
Stirring time	The optimum time required for formation of MS	M Orlu *et al.* 2006 observed that solidification of MS one hour stirring is required for preparing microsponges.[29]
Stirring types	Mechanical stirrer with 3to 4 bladed propellers, centrifugal stirrer are used to provide mechanical shear that results in formation of the globules.	M Orlu *et al.* 2006 found aggregates were formed when 3-4 bladded propeller were used. Aggregate amount is low with 2 bladed centrifugal stirrer.[29]
Volume internal phase	Optimum volume 3-5 ml. Used to dissolve the drug, polymer and forms the organic phase.	M Orul *et al.* 2006 found that Milky phase formed with high amount of internal phase solvent of 5 and 10 ml. The microsponges could be prepared by decreasing amount of ethyl alcohol to 3ml.[29] Kiwashima *et al.* 1992 described that recovery of microsponges decreased sharply with increase in ethyl alcohol amount.[30]
Emulsifier	Helps to stabilise the emulsion	Sonali *et al.* 2014 found increasing in concentration of emulsifier resulted in formation of large irregular shaped MS.[27]
Plasticizer	Provide the plasticity to microsponges.	Vivekanand K Chatap *et al.* 2018 observed that increase in the concentration of plasticizer increases the drying rate of MS.[28]

Other Preparation Techniques that Recently Developed: Some of the novel techniques which are useful in preparing the porous microspheres are mentioned below.[26]

- **Double emulsion solvent diffusion method (w/o/w)**: Preparation of biodegradable porous microspheres using water in oil in water technique.

  Advantage: Efficient for loading water soluble and water insoluble drugs. This can be used to entrap thermo labile materials such as proteins and peptides.

  Disadvantage**:** Using the water insoluble surfactants might result as residues in resultant microsponges.
- **Addition of porogen:** In this technique, internal aqueous phase contains porogen like hydrogen peroxide or sodium bicarbonate or sodium chloride.[23]

  Advantage: Results in the formation of highly porous structure that are evenly distributed.

  Disadvantage: May cause the disruption in structure.
- **Oil in oil emulsion solvent diffusion**: Volatile organic liquid used in the internal phase and oil (corn or mineral oil) as an external phase. The Volatile organic liquid was allowed to evaporate slowly with continuous stirring thus results in formation of MS.

  Advantage: Surfactant traces were not present

  Disadvantage: to remove the organic solvents vigorous washings must be carried out
- **Lyophilization:** In this method, the microspheres that were formed subjected for lyophilisation to form the pores.

  Advantage: quick and rapid results.

  Disadvantage: Might result in cracking or shrinkage of particles because of rapid removal of solvent.
- **Vibrating orifice aerosol generator (VOAG) method**It is a technique in which the surfactant was evaporated from the formed microdroplets leaving behind the porous structure

  Advantage: This can be used in targeted drug delivery

  Disadvantage: Requires reflux conditions.
- **Ultrasound-assisted production**: It is a modified method of liquid-liquid suspension polymerization.

  Where it utilise the β-cyclodextrin and diphenyl carbonate as the polymers and cross linking agent respectively. Size was controlled by heating and sonicating the reaction mixture. This resulted in formation of porous microspheres.

  Advantage: Quick reproducible results.

  Disadvantage: Irregular structure and may result in entrapment of potentially toxic cross linking agents.

Table 5: Marketed formulations.

S.No	Product Name	Active ingredient with its therapeutic action	Manufacturer
1.	Glycolic Acid Moisturizer w/ SPF 15	Glycolic Acid stimulate collagen synthesis which helps to reduces wrinkles	AMCOL Health and Beauty Solution
2.	Retin A Micro	Tretinoin helps in treating Acne vulgaris	Ortho-McNeil Pharmaceutical,
3.	Carac Cream, 0.5%	Fluorouracil useful in treating Actinic keratosis a precancerous skin condition	Dermik Laboratories, Inc. Berwyn, PA 19312 USA
4.	Line Eliminator Dual Retinol Facia Treatment	Retinol (Vitamin A) rejuvenate skin and reduces the wrinkles	Avon
5.	Micro peel plus / Acne peel	Salicylic acid Stimulates cells turnover, helps to improve pigmentation and fine lines	Biomedic
6.	Retinol 15 Night cream	Retinol (Vitamin A) rejuvenate skin and reduces the wrinkles	Sothys
7.	Retinol cream	Retinol (Vitamin A) keeps the skin healthy.	Biomedic
8.	EpiQuin Micro	Hydroquinone, Retinol both help in treatment of Hyper pigmentation, also reduces skin irritation	SkinMedica Inc
9.	Sports cream RS, Sports cream XS	Acts as anagesic and Anti-inflammatory	Embil Pharmaceutical
10.	Salicylic Peel 20 and 30	Salicylic acid results in Excellent exfoliation	Biophora
11.	Oil free matte block SPF 20	Presence Vinyl dimethicone, corn starch absorbs oil from the skin. Protects skin from UV rays (Sunscreen)	Dermalogica
12.	Lactrex™ 12% Moisturizing Cream	Lactic acid, glycerine provides long lasting Moisturization to skin	SDR Pharmaceuticals, Inc., Andover NJ, USA 07821
13.	Oil Control Lotion	Controls the oil by absorption and also act as Skin protectant	Fountain Cosmetics
14.	Ultra Guard	Dimethicone helps in Protecting babies skin from diaper rash	Scott Paper Company
15.	Aramis fragrance	Ultra light powder that can sustain release fragrance used in Anti perspirant spray	Aramis Inc.

Table 6: Research work on Microsponges drug formulations targeting to colon.

S. No	Drug	Category	Method	Polymers used	Remarks	Ref
1.	Aspirin	NSAID	Quasi emulsion solvent diffusion (QESD) method	Eudragit RS100	Sustained drug release, Reducing side effects	41
2.	Aceclofenac	NSAID	QESD	Ethyl cellulose, Eudragit RS100, Eudragit s100 Eudragit RL100	Controlled drug release with enhancement of stability solubility and flow properties	50
3.	Acyclovir	Anti-cancer	QESD	Eudragit RS100	Controlled drug release	51
4.	Albendazole	Anti protozoal	O/O emulsion	Eudragit RS100	Sustained release	52
5.	5 Amino salicylic acid/ mesalamine	Anti- inflammatory to treat IBD	QESD	Eudragit S100, L100, RS100	Enhanced bio availability of drug targeting to colon	53
6.	Carvidilol	Anti- hypertensive	Novel method	Eudragit RS 100	Avoid first pass metabolism, enhance the solubility	54
7.	Candesartan cilexeti	Anti- hypertensive	QESD	Eudragit RS100, RL100, S100	Avoid first pass metabolism, enhance the solubility	55
8.	Curcumin	Treatment for UC	QESD	Eudragit L100	Enhanced solubility site specific Colon targeting	23
9.	Curcumin	Anti- inflammatory	QESD	Ethyl cellulose	Enhanced solubility site specific Colon targeting	56
10.	Diclofenac sodium	NSAID	QESD	Eudragit L100, RS 100, EPO 100	Enhanced solubility and bio availability	57
11.	Dicyclomine	Anti-Cholinergic	QESD	Eudragit RS 100	Prolonged drug release, Effective local action.	58
12.	Dicyclomine	Anti- Cholinergic	QESD	Eudragit S100	Colon targeting.	59
13.	Diltiazem	Anti- hypertensive	QESD	Eudragit RS100	Controlled release	60
14.	Dutasteride	Benign Prostatic Hyperplasia	QESD	Eudragit S100	Improve the physical properties of drug	61
15.	Flurbiprofen	NSAID	QESD, entrapment method	Eudragit RS100, microsponge® 5640 system	Controlled release.	29
16.	5Fluoro Uracil	Anti cancer	Oil in oil emsion solvent diffusion method	Eudragit RS100	Sustained release, Reduction in the toxicity, Enhanced accumulation at site specific region	62
17.	5 Fluoro Uracil	Anti cancer	Modified QESD using porogen	Eudragit RS100	Colorectal cancer.	63
18.	5 Fluoro Uracil	Anti cancer	QESD	Eudragit RS100	Enhanced, bioavailability reduction of side effects	64
19.	Fluconazole	Anti fungal	QESD	Eudragit L100	Sustained Release	65
20.	Indomethacin	NSAID	QESD	Ethyl cellulose	Reduce gastric irritation and site specific targeting	66
21.	Ketoprofen	NSAID	Modified QESD using porogen.	Chitosan	Site specific drug targeting.	67
22.	Lansoprazole	Proton pump inhibitor	QESD	Eudragit L100, S100	Avoids degradation in acidic media	68
23.	Lornoxicam	osteoarthritis	QESD	Eudragit RS100, RSPO	Sustained drug release	69
24.	Lornoxicam	osteoarthritis	QESD	Ethyl cellulose	Sustained drug release	28
25.	Meloxicam	Anti-cancer	QESD	Eudragit RS100	Colon specific drug targeting	70
26.	Metoprolol succinate		QESD	Ethyl cellulose	Avoid first pass metabolism and increase the bio availability	71
27.	Nicorandil	Potassium channel opener	QESD	Eudragit S100,RSPO, RLPO	Controlled release up to 24 hr	72

28.	Paracetamol	NSAID	QESD	Eudragit S100	Colon targeted	73
29.	Paracetamol	NSAID	QESD	Eudragit RS100	Controlled release.	74
30.	Paracetamol	NSAID	QESD	Eudragit RS100	Sustain release and colon targeted.	75
31.	Piroxicam	NSAID	QESD	Eudragit RS100, RL100, S100	Enhanced solubility and bioavailability.	76
32.	Prednisolone	Corticosteroid	QESD	Ethyl cellulose Eudragit S100	Colon targeting	77
33.	Prednisolone	Corticosteroid	QESD	Eudragit RS100	Controlled drug release, Site specific drug targeting	27
34.	Resveratol	Ulcerative colitis	Modified QESD using porogen W/O/W	Chitosan	Sustained release	78
35.	Terbutaline sulphate	Anti- asthmatic	O/O emulsion solvent diffusion method	Eudragit RS100	Reduced side effects.	79
36.	Valsartan	Anti- hypertensive	QESD	Ethylcellulose	Controlled drug release, enhanced stability and reduced side effects	80

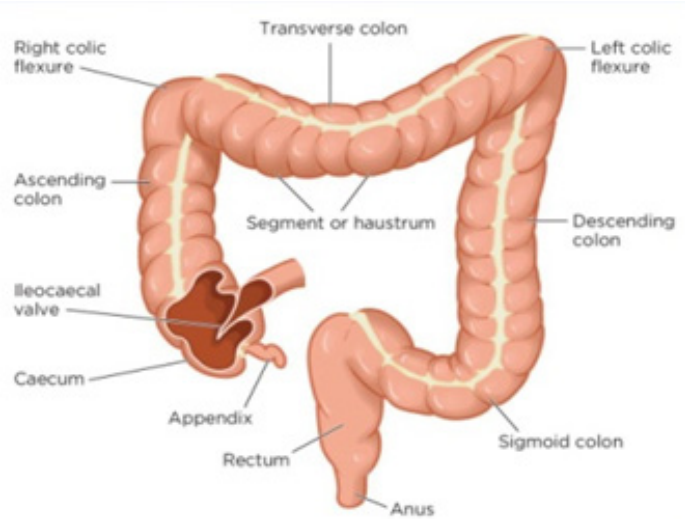

Figure 1: Anatomy of large intestine.

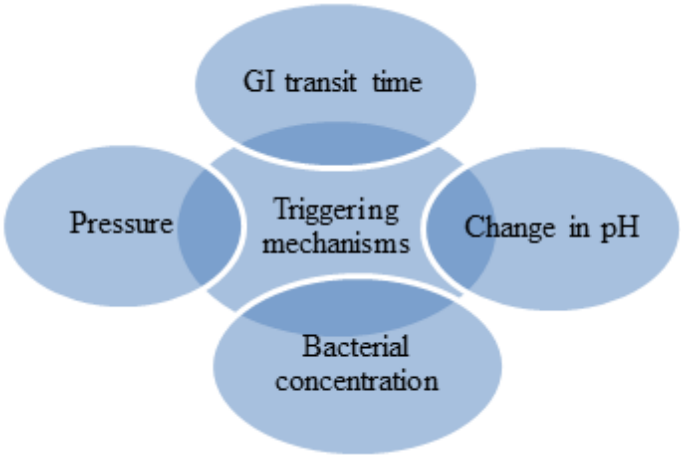

Figure 2: Mechanism of drug release.

The effect of drug to polymer ratio, stirring speed, time, type and volume of internal phase in the formulation of microsponges areshown in Table 4.[27-30]

Evaluation Parameters

i Particle size and size distribution

Particle size and distribution is evaluated by using techniques like zeta seizer, polarizing microscope, optical or electron microscope [25] and laser light diffractometer.[29]

This study is essential because size of the particles have an effect on the texture and stability of formulation. Particles having diameter of about 10-25 µm are found to be free flowing and the particles of diameter greater than 30 impart gritty feeling.[25]

ii Morphology and surface topography of MS

Transmission electron microscope, photon transmission spectroscope, Scanning Electron Microscope is the techniques used for study the morphology of particles.

Most generally used method is SEM analysis where MS are coated with the gold palladium under vacuum. To perform sample imaging in its natural state Environment Scanning Electron Microscopy is used.[31]

iii Porosity: The characteristics feature of MS is its porous nature. Porosity is determined by using two analytical methods, mercury intrusion porosimetry and gas adsorption-desorption method.[32] The characterization of pores i.e., pore volume and diameter, distribution of pores, total pore surface area etc were carried out.[33]

iv. Determination of True Density: Studies were carried out using Ultra-pycnometer and helium gas and is determined on repeated observations.[35]

v. Determination of drug content, encapsulation efficiency and production yield Micro sponges are dispersed in a suitable solvent for the entrapped drug to release. After sufficient time the dispersion is centrifuged and the supernatant is analysed with suitable analytical technique and calculated as per formula. This provides the drug content present in the micro sponges.

The exact drug content (%), loading efficiency (%), production yield of the MS can be calculated according to the following equations: [34]

$$\text{Actual drug content \%} = \frac{\text{Mact}}{\text{MMs}} \times 100 \qquad \text{Equation 1}$$

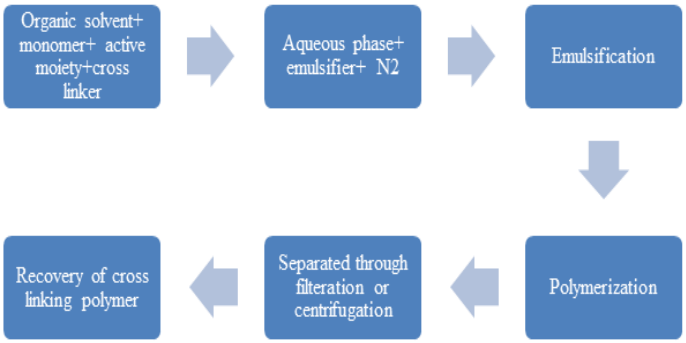

Figure 3: Flow diagram of liquid- liquid suspension method.

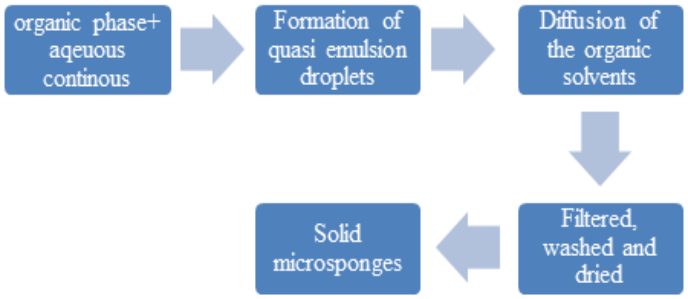

Figure 4: Flow diagram of QESD method.

$$\text{Encapsulation efficiency \%} = \frac{\text{Mact}}{\text{MMs}} \times 100 \qquad \text{Equation 2}$$

Here,

M_{act} = drug content in weighed quantity of MS

M_{MS} =weighed quantity of powder of MS

M_{the} = theoretical amount of drug content.

$$\text{\% Production yield} = \frac{\text{Practical Mass of MS}}{\text{Theoritical Mass of Polymer +Drug}} \times 100 \qquad \text{Equation 2}$$

vi. **Compatibility studies:** The compatibility between the drug and the excipients or adjuncts was studied using Fourier Transform Infrared spectroscopy (FT-IR) and thin layer chromatography (TLC) techniques.[36] Polymerization that may cause change in crystallinity can be studied using X-ray diffraction (XRD) and thermal analysis of drug carried out using Differential Scanning Calorimetry (DSC).[37]

vii. **Polymer or monomer composition:** It controls drug release from MS. The polymer forms a layer around the drug which gets thicken upon increasing in polymer concentration this retards the release of impregnated drug.[38] Different polymers release characteristics can be studied. A graphical plot of percentage drug release against time gives the effect of polymer on rate of release of drug.[39]

viii. **Resiliency:** This indicates the visco-elastic property of formula (MS). It is the study depends on firmness of final formulation. Increased cross-linking might result in retarding the rate of drug release.[40] This test claim to be resilient, if there is no sign of disruption observed even after compression of tablet.[41]

ix. **Dissolution studies:** Dissolution profile of MS is carried out using USP XXIII dissolution apparatus.

Specifications: Modified basket having 5µm stainless steel mesh

Speed of the rotation maintained is 150 rpm.

The dissolution medium is selected by considering *in vitro* analysis of the drug. Samples were withdrawn at specified intervals and analysed using suitable analytical method.[42]

x. **Kinetics of release**: The mode of drug release from the optimised MS formulation can be studied by using the mathematical models as described below:[43]

"Zero Order release kinetics can be measured by using the equation 4 applicable

for modified release dosage forms such as matrix tablets, osmotic systems etc.,

$Q_t = Q_0 + K_0 t$ --- **equation 4**

Where, Q_t = amount of the drug at time t

Q_0 = Initial amount of the drug

K_0 = zero order rate constant.

First order release kinetics are measured by using the below equation 5, Applicable for water

soluble drug present in the porous matrix type of dosage form.

Log C = Log C_0 - Kt / 2.30 --- equation 5

Where, C_0 = initial concentration of drug

C = concentration at time t

K = first order rate constant".

Higuchi Model: Studied by plotting graph with percentage drug release verses square root of time. This relationship is useful in describing the drug release in modified dosage forms.

Q = Kt ½ --- **equation 6**

Where, K= Higuchi dissolution constant

Q= Amount of drug release at time t

Hixson-Crowell model: Studied by plotting cube root of percentage drug remaining in matrix versus time. This is applicable for dosage form like tablets, where the dissolution takes place in planes that are parallel to the drug surface.

$W_0^{1/3} - W_t^{1/3} = \kappa t$ Equation 7

W_0 = initial amount of drug present in the dosage form

W_t = remaining amount of drug left in dosage form at time t;

κ = Constant".[43]

Korsmeyer-Peppas Model: This is applicable to study the drug release from the

polymeric dosage forms. Here the drug release is exponentially related to time.[42]

$Mt/M\alpha = Kt^n$ Equation 8

Mt/Mα = Fraction of drug released at time t

K= Kinetics release rate constant and n is the release exponent

MDS technique currently used in manufacture of over the counter skin care products, cosmetics and prescription products.[44] Some of the marketed products commercially available are given in Table 5.[45,46] MDS applicability for product for oral administration is in research.[47] Research work on Microsponges drug formulations targeting to colon are summarized in Table 6.

New perspectives using MSD technique

In recent times, various advances in MDS were made to form nanosponges, nanoferrosponges and siRNA.

Nanosponges have been developed from cyclodextrin (CD's) cross-linked with organic carbonates like dipheyl carbonate. Drugs that are encapsulated in NS were dexamethasone, paciltaxol, flurbiprofen, doxorubicin hydrochloride, 5-fluoro uracil itraconazole, progesterone, nelfinavir mesylate.

These NS promises in achieving site specific targeting and controlled delivery of drugs.[26]

Nanoferrosponge: Is a novel approach. These are the magnetic nanoparticles having interconnected nanopores of size ranging from 2-100 nm which serves as a reservoir for various drug moieties. The drug release is controlled by the nanopores which have been manipulated by application of external magnetic field.[48]

Novel therapeutic route for siRNA delivery: RNA interference is a process where short interfering RNA (siRNA) strands suppress gene expression that occurs inside the cell. The authors found densely packed sponge like microparticles is an efficient carrier where synthesis and spontaneous assembly of RNA polymers occur. The Microsponge can deliver approx., half a million siRNA precursors per cell where they observed an improved stability and found relatively effective encapsulation of siRNA.[49]

CONCLUSION

Colon specific oral drug delivery is an effective formulation strategy that improves the oral bioavailability of acid or/and enzyme labile drugs. In this review, the physiological changes, pathophysiological changes in the microenvironment of colon that surrounds disease site makes targeting of formula/ drug complicated. Using micro particulate system, such as microsponges holds a great potential in enhancing drug targeting, drug uptake and solubility because of its reduced particle size and porous nature. Microsponges have become a rapidly evolving technology. Colon targeting of these Microsponges is a de novo method that provides significant benefit to the patient in terms of safety, efficacy and compliance.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest among them.

ABBREVIATIONS

UC: Ulcerative Colitis; **MDS:** Microsponge delivery system; **MS:** Microsponges; **HPMC:** Hydroxypropyl methylcellulose; **XRD:** X-ray diffraction; **DSC:** Differential Scanning Calorimetry; **QESD:** Quasi Emulsion Solvent Diffusion; MPS**:** Multi particulate system; **FT-IR:** Fourier Transform Infrared; **O/O:** Oil in Oil.

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