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 Antiasthmatics 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.3
• 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.5,6

Factors Effecting Colonic Drug Delivery are colonic fluid volume, intestinal colonic transit time, viscosity of colonic luminal contents, colon pH, enzymes and metabolism.7

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.8

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.8

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.

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pH declines from the farther region of small intestine to colon and increase gradually in colon as mentioned in Table 1.\textsuperscript{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).\textsuperscript{9} Some evidence suggests that there is substantial changes in gastrointestinal pH are associated with disease like cystic fibrosis, IBD, UC.\textsuperscript{9}

Colon is known to consist over 400 different species of aerobic and anaerobic micro-organisms.\textsuperscript{6} These bacteria contain several hydrolytic and reductive metabolising enzymes.\textsuperscript{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.\textsuperscript{10}

Release triggering mechanism of drug
There are four mechanisms which trigger the drug release is discussed below in Figure 2.\textsuperscript{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 the 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.\textsuperscript{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.\textsuperscript{12}

In this context, micro sponges are at forefront having unique, versatile and novel approach.\textsuperscript{13} It represents a new model of porous polymeric microspheres, which allows the entrapment of a wide range of active moieties.\textsuperscript{14} This promising system has its application in transdermal, oral, ocular, pulmonary and parenteral delivery of bioactive compounds.\textsuperscript{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”.\textsuperscript{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.\textsuperscript{16}

MS act as carriers. Drug entrapment by carrier system results in reduction in particle size, increases active surface area and thus enhances solubilisation.\textsuperscript{17} MDS possess various attractive features given below.\textsuperscript{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 compression properties.\textsuperscript{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 sponge, the bioactive should fulfil the following criteria.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16}

**Novel Drug Carrier Systems with their limitations**
- Microcapsules - Once the wall get ruptured, the rate of drug release cannot be controlled.\textsuperscript{21}
- Liposomes - Lower payload capacities, limited chemical stability, microbial instability and rapid drug leakage.\textsuperscript{21}
- Solid lipid nanoparticles – have insufficient stability, sterilization problem.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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 h25 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.25

### Table 1: pH at various regions of GI tract.

<table>
<thead>
<tr>
<th>Region of GI tract</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>1.5 – 3 (fasted), 2 – 5 (fed)</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Duodenum = 6.1 (fasted), 5.4 (fed)</td>
</tr>
<tr>
<td></td>
<td>Jejunum  6.4</td>
</tr>
<tr>
<td></td>
<td>Ileum     7.6</td>
</tr>
<tr>
<td>Large intestine</td>
<td>Cecum     5.5</td>
</tr>
<tr>
<td></td>
<td>Ascending colon 5.7</td>
</tr>
<tr>
<td></td>
<td>Transverse colon 6.6</td>
</tr>
<tr>
<td></td>
<td>Descending colon 7.0</td>
</tr>
<tr>
<td></td>
<td>Sigmoid colon, rectum anal canal 7.8</td>
</tr>
</tbody>
</table>

### Table 2: pH of commonly used polymers.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>pH</th>
<th>Polymer</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit L 100</td>
<td>6.0</td>
<td>Hydroxypropylmethylcellulose (HPMC) phthalate</td>
<td>4.8</td>
</tr>
<tr>
<td>Eudragit S 100</td>
<td>7.0</td>
<td>HPMC phthalate 50</td>
<td>5.2</td>
</tr>
<tr>
<td>Eudragit’ FS 30D</td>
<td>6.8</td>
<td>HPMC phthalate 55</td>
<td>5.4</td>
</tr>
<tr>
<td>Eudragit’ L 30D</td>
<td>5.6</td>
<td>Cellulose acetate trimellitate</td>
<td>4.8</td>
</tr>
<tr>
<td>Eudragit L 100-55</td>
<td>5.5</td>
<td>Cellulose acetate phthalate</td>
<td>5.0</td>
</tr>
<tr>
<td>Polyvinyl acetate phthalate</td>
<td>5.0</td>
<td>Shellac</td>
<td>7.0</td>
</tr>
</tbody>
</table>

### Table 3: Systems of drug delivery to colon.

<table>
<thead>
<tr>
<th>Primary Approach</th>
<th>Novel Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Coating drug with pH sensitive polymer</td>
<td>1. Pressure Controlled (PCDDS)</td>
</tr>
<tr>
<td>3. Microbi ally triggered</td>
<td>3. Osmotic Controlled</td>
</tr>
<tr>
<td>a. Prodrug approach</td>
<td>4. Pulsatile</td>
</tr>
<tr>
<td>b. Azo polymeric prodrug</td>
<td>a. Pulsinicap</td>
</tr>
<tr>
<td>c. Polysaccharide based systems</td>
<td>b. Port System</td>
</tr>
<tr>
<td></td>
<td>5. Azo Hydrogels</td>
</tr>
<tr>
<td></td>
<td>6. Multparticulate drug delivery</td>
</tr>
</tbody>
</table>

### Table 4: Effect of variables in the formulation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug to polymer ratio</td>
<td>DP ratio has its affect on the particle size.</td>
<td>Vivekanand K Chatap et al. 2018 found increase in DP ratio resulted in particle size reduction.25</td>
</tr>
<tr>
<td>Stirring speed</td>
<td>Low speed leads to form agglomerate and high shear rate causes the breakdown of globules resulting in irregular shape.</td>
<td>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</td>
</tr>
<tr>
<td>Stirring time</td>
<td>The optimum time required for formation of MS</td>
<td>M Orlu et al. 2006 observed that solidification of MS one hour stirring is required for preparing microsponges.29</td>
</tr>
<tr>
<td>Stirring types</td>
<td>Mechanical stirrer with 3 to 4 bladed propellers, centrifugal stirrer are used to provide mechanical shear that results in formation of the globules.</td>
<td>M Orlu et al. 2006 found aggregates were formed when 3-4 bladdled propeller were used. Aggregate amount is low with 2 bladed centrifugal stirrer.29</td>
</tr>
<tr>
<td>Volume internal phase</td>
<td>Optimum volume 3-5 ml. Used to dissolve the drug, polymer and forms the organic phase.</td>
<td>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.28</td>
</tr>
<tr>
<td>Emulsifier</td>
<td>Helps to stabilise the emulsion</td>
<td>Sonali et al. 2014 found increasing in concentration of emulsifier resulted in formation of large irregular shaped MS.27</td>
</tr>
<tr>
<td>Plasticizer</td>
<td>Provide the plasticity to microsponges.</td>
<td>Vivekanand K Chatap et al. 2018 observed that increase in the concentration of plasticizer increases the drying rate of MS.28</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Product Name</th>
<th>Active ingredient with its therapeutic action</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Glycolic Acid Moisturizer w/ SPF 15</td>
<td>Glycolic Acid stimulate collagen synthesis which helps to reduces wrinkles</td>
<td>AMCOL Health and Beauty Solution</td>
</tr>
<tr>
<td>2.</td>
<td>Retin A Micro</td>
<td>Tretinoin helps in treating Acne vulgaris</td>
<td>Ortho-McNeil Pharmaceutical, Berwyn, PA 19312 USA</td>
</tr>
<tr>
<td>3.</td>
<td>Carac Cream, 0.5%</td>
<td>Fluorouracil useful in treating Actinic keratosis a precancerous skin condition</td>
<td>Dermik Laboratories, Inc.</td>
</tr>
<tr>
<td>4.</td>
<td>Line Eliminator Dual Retinol Facia Treatment</td>
<td>Retinol (Vitamin A) rejuvenate skin and reduces the wrinkles</td>
<td>Avon</td>
</tr>
<tr>
<td>5.</td>
<td>Micro peel plus / Acne peel</td>
<td>Salicylic acid Stimulates cells turnover, helps to improve pigmentation and fine lines</td>
<td>Biomedic</td>
</tr>
<tr>
<td>6.</td>
<td>Retinol 15 Night cream</td>
<td>Retinol (Vitamin A) rejuvenate skin and reduces the wrinkles</td>
<td>Sothys</td>
</tr>
<tr>
<td>7.</td>
<td>Retinol cream</td>
<td>Retinol (Vitamin A) keeps the skin healthy.</td>
<td>Biomedic</td>
</tr>
<tr>
<td>8.</td>
<td>EpiQuin Micro</td>
<td>Hydroquinone, Retinol both help in treatment of Hyper pigmentation, also reduces skin irritation</td>
<td>SkinMedica Inc</td>
</tr>
<tr>
<td>10.</td>
<td>Salicylic Peel 20 and 30</td>
<td>Salicylic acid results in Excellent exfoliation</td>
<td>Biophora</td>
</tr>
<tr>
<td>11.</td>
<td>Oil free matte block SPF 20</td>
<td>Presence Vinyl dimethicone, corn starch absorbs oil from the skin. Protects skin from UV rays (Sunscreen)</td>
<td>Dermalogica</td>
</tr>
<tr>
<td>12.</td>
<td>Lactrex™ 12% Moisturizing Cream</td>
<td>Lactic acid, glycerine provides long lasting Moisturization to skin</td>
<td>SDR Pharmaceuticals, Inc., Andover NJ, USA 07821</td>
</tr>
<tr>
<td>13.</td>
<td>Oil Control Lotion</td>
<td>Controls the oil by absorption and also act as Skin protectant</td>
<td>Fountain Cosmetics</td>
</tr>
<tr>
<td>14.</td>
<td>Ultra Guard</td>
<td>Dimethicone helps in Protecting babies skin from diaper rash</td>
<td>Scott Paper Company</td>
</tr>
<tr>
<td>15.</td>
<td>Aramis fragrance</td>
<td>Ultra light powder that can sustain release fragrance used in Anti perspirant spray</td>
<td>Aramis Inc.</td>
</tr>
<tr>
<td>S. No</td>
<td>Drug</td>
<td>Category</td>
<td>Method</td>
</tr>
<tr>
<td>-------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>1.</td>
<td>Aspirin</td>
<td>NSAID</td>
<td>Quasi emulsion solvent diffusion (QESD) method</td>
</tr>
<tr>
<td>2.</td>
<td>Aceclofenac</td>
<td>NSAID</td>
<td>QESD</td>
</tr>
<tr>
<td>3.</td>
<td>Acyclovir</td>
<td>Anti-cancer</td>
<td>QESD</td>
</tr>
<tr>
<td>4.</td>
<td>Albendazole</td>
<td>Anti protozoal</td>
<td>O/O emulsion</td>
</tr>
<tr>
<td>5.</td>
<td>5 Amino salicylic acid/ mesalamine</td>
<td>Anti-inflammatory to treat IBD</td>
<td>QESD</td>
</tr>
<tr>
<td>6.</td>
<td>Carvedilol</td>
<td>Anti-hypertensive</td>
<td>Novel method</td>
</tr>
<tr>
<td>7.</td>
<td>Candesartan cilexetil</td>
<td>Anti- hypertensive</td>
<td>QESD</td>
</tr>
<tr>
<td>8.</td>
<td>Curcumin</td>
<td>Treatment for UC</td>
<td>QESD</td>
</tr>
<tr>
<td>9.</td>
<td>Curcumin</td>
<td>Anti-inflammatory</td>
<td>QESD</td>
</tr>
<tr>
<td>10.</td>
<td>Diclofenac sodium</td>
<td>NSAID</td>
<td>QESD</td>
</tr>
<tr>
<td>11.</td>
<td>Dicyclomine</td>
<td>Anti-Cholinergic</td>
<td>QESD</td>
</tr>
<tr>
<td>12.</td>
<td>Dicyclomine</td>
<td>Anti-Cholinergic</td>
<td>QESD</td>
</tr>
<tr>
<td>13.</td>
<td>Diltiazem</td>
<td>Anti-hypertensive</td>
<td>QESD</td>
</tr>
<tr>
<td>14.</td>
<td>Dutasteride</td>
<td>Benign Prostatic Hyperplasia</td>
<td>QESD</td>
</tr>
<tr>
<td>15.</td>
<td>Flurbiprofen</td>
<td>NSAID</td>
<td>QESD, entrapment method</td>
</tr>
<tr>
<td>16.</td>
<td>5Fluoro Uracil</td>
<td>Anti cancer</td>
<td>Oil in oil emulsion solvent diffusion method</td>
</tr>
<tr>
<td>17.</td>
<td>5 Fluoro Uracil</td>
<td>Anti cancer</td>
<td>Modified QESD using porogen</td>
</tr>
<tr>
<td>18.</td>
<td>5 Fluoro Uracil</td>
<td>Anti cancer</td>
<td>QESD</td>
</tr>
<tr>
<td>19.</td>
<td>Fluconazole</td>
<td>Anti fungal</td>
<td>QESD</td>
</tr>
<tr>
<td>20.</td>
<td>Indomethacin</td>
<td>NSAID</td>
<td>QESD</td>
</tr>
<tr>
<td>22.</td>
<td>Lansoprazole</td>
<td>Proton pump inhibitor</td>
<td>QESD</td>
</tr>
<tr>
<td>23.</td>
<td>Lornoxicam</td>
<td>osteoarthritis</td>
<td>QESD</td>
</tr>
<tr>
<td>24.</td>
<td>Lornoxicam</td>
<td>osteoarthritis</td>
<td>QESD</td>
</tr>
<tr>
<td>25.</td>
<td>Meloxicam</td>
<td>Anti-cancer</td>
<td>QESD</td>
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<tr>
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<td>succinate</td>
<td>QESD</td>
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<td>Potassium channel opener</td>
<td>QESD</td>
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Hari et al.: Microsponges for Colon Targeting

in its natural state Environment Scanning Electron Microscopy is used.

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. The characterization of pores i.e., pore volume and diameter, distribution of pores, total pore surface area etc were carried out.

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

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:

\[
\text{Actual drug content} \% = \frac{\text{Mact}}{\text{MMs}} \times 100 \quad \text{Equation 1}
\]

The effect of drug to polymer ratio, stirring speed, time, type and volume of internal phase in the formulation of microsponges are shown in Table 4.

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 and laser light diffractometer.

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.

ii. Morphology and surface topography of MS

Transmission electron microscope, photon transmission spectroscopy, 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

Figure 1: Anatomy of large intestine.

Figure 2: Mechanism of drug release.
Encapsulation efficiency % = \(
\frac{\text{M}_{\text{act}}}{\text{M}_{\text{MS}}} \times 100
\) \text{ Equation 2}

Here,
\( \text{M}_{\text{act}} = \) drug content in weighed quantity of MS
\( \text{M}_{\text{MS}} = \) weighed quantity of powder of MS
\( \text{M}_{\text{theo}} = \) theoretical amount of drug content.

\% Production yield = \( \frac{\text{Practical Mass of MS}}{\text{Theoretical Mass of Polymer + Drug}} \times 100 \) \text{ Equation 2}

vi. Compatibility studies: The compatibility between the drug and the excipients or adjucnts was studied using Fourier Transform Infra-red 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.,

\[ Q_t = Q_0 + K_0 t \] \text{ --- equation 4}

Where, \( Q_0 \) = amount of the drug at time \( t \)
\( K_0 \) = 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.

\[ \log C = \log C_0 - \frac{Kt}{2.30} \] \text{ --- 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.

\[ Q = Kt^{1/2} \] \text{ --- 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.

\[ W_{t}^{1/3} - W_{0}^{1/3} = kt \] \text{ Equation 7}

\( W_{t} = \) initial amount of drug present in the dosage form
\( W_{0} = \) remaining amount of drug left in dosage form at time \( t \)
\( k = \) Constant”\(^{33}\)

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.\(^{44}\)

\[ \frac{Mt}{M_a} = Kt^n \] \text{ Equation 8}

\( M_t/M_a = \) 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, nanoferrospongs and siRNA.

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

\[ \text{Organic: solvent } + \text{ monomer } + \text{active moiety } + \text{cross linker} \quad \rightarrow \quad \text{Aqueous phase } + \text{emulsifier } + \text{N2} \quad \rightarrow \quad \text{Emulsification} \quad \rightarrow \quad \text{organic: phase } + \text{aqueous continuous} \quad \rightarrow \quad \text{Formation of quasi emulsion droplets} \quad \rightarrow \quad \text{Diffusion of the organic solvents} \quad \rightarrow \quad \text{Solid microsponges} \quad \rightarrow \quad \text{Filtered, washed and dried} \]

\text{Figure 3: Flow diagram of liquid-liquid suspension method.}

\text{Figure 4: Flow diagram of QESD method.}
These NS promises in achieving site specific targeting and controlled delivery of drugs.26

Nanorosponge: Is a novel approach. These are the magnetic nanoparticles having interconnected nanosizes of size ranging from 2-100 nm which serves as a reservoir for various drug moieties. The drug release is controlled by the nanosizes 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 compliance.

Colon targeting of these Microsponges is a de novo method 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.

CONCLUSION

Colon specific oral drug delivery is an effective formulation strategy that improves the oral bioavailability of acid or/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.

REFERENCES

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