Application and advancement of microsphere as controlled delivery system: A review
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Abstract
Of late researchers have been striving hard to scale the requirements to formulate an effective dosage form to simulate controlled drug release. Microspheres have been proved to be a suitable bridge to scale this distance. Microsphere are free flowing solid particle made up of biodegradable and non-biodegradable components, ideally having a particle size less than 200 µm and can be injected by an 18 or 20 number needle. They can be delivered through various routes like oral, nasal, colonic, parentally, ophthalmic and transdermal etc. Various recent advancements like hollow, magnetic, microballons, floating microspheres have been contributed emensely to improve the various hinderances associated with the use of microspheres, which include site specific targeting and improved release kinetics. Current review describes the recent advancements that have been undertaken in the field of microspheres to acheive the controlled drug release, with pre-determined drug release kinetics. Author belives that the review will prove a silver lining for the aspiring researchers, thus helping them to contribute their brick in the castle entitled “microspheres”.

Key-Words: Microspheres, Advancement, Applications, Preparation, Evaluation parameters

Introduction
Previously people have been using conventional dosage form like tablet and capsule for the treatment of acute and chronic disease but these have to be taken several times to maintain the peak plasma concentration. In order to overcome this problem controlled drug delivery system was developed. The main objective of controlled drug delivery is to ensure optimum plasma drug concentration, thus enhancing efficacy and bioavailability of drug with improved patient compliance. Controlled release refers to the use of a delivery system with the objective of releasing the drug into the patient body at a predetermined rate or controlled rate, at specific times or with specific release profiles.[1]
Several problems associated with use of conventional dosage forms for the controlled release includes: The drugs which are hygroscopic in nature are not suitable for filling into capsule because moisture will be absorbed from the shell, make them brittle in nature, leading it to crumble into pieces moreover the dried solution which requires previous dilution are unsuitable for capsule because if administrated as such leads to irritation into stomach.

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Bioavailability problems are associated with tablets because disintegration and dissolution is required before drug is available for absorption and sometimes it also causes gastrointestinal irritation. Various advancements have been made to overcome these drawbacks of conventional dosage form and microsphere is one of them.
Microsphere are free flowing solid particle made up of biodegradable and non-biodegradable material, ideally having a particle size less than 200 µm and can be injected by an 18 or 20 number needle.[2] Microsphere eases sustained drug release and also reduces or eliminates gastrointestinal tract irritation. Microsphere is used to alter the drug release. Drug absorption and side effects due to irritating drugs against the gastrointestinal mucosa is improved because microsphere are made up of small particle size less than 200 µm, which are widely distributed throughout the gastrointestinal tract.[3]

Advantages[4, 5]
- Masking of odour or bitter taste.
- Improve physical stability and gastric enzyme stability.
- Better process ability (improved flowability, dispersability).
- Reduced dose size.
Reduced dosing frequency therefore improves patient compliance.
- Reduced toxicity.
- Absorption window.
- Gastric irritation problem can be overcome by microsphere.
- First pass metabolism is avoided.
- Biological half-life can be enhanced.
- Improve bioavailability.
- Microsphere provides increased therapeutic efficacy and prolonged duration of action.
- Microsphere provides controlled, sustained and targeted drug delivery.
- Microsphere can be injected into body because of small size and spherical shape.

Limitation [4, 6]
- Rate of controlled release dosage form may vary due to certain factors like intrinsic and extrinsic factors.
- There is difference in the rate of release of drug from one dosage form to another dosage form.
- Low drug loading (maximum of 50%) for controlled release parental
- Dumping of dose result in failure of therapy.
- Once injected it is difficult to remove the carrier completely from the body in case of toxic effect or adverse effect.
- Parental delivery of microsphere may interact or form complexes with the blood component.

Material used for preparation microsphere [7]
Biodegradable and non-biodegradable substances are used for the preparation of microsphere. These substances involve polymers of natural and synthetic origin as well as modified natural substances.

Techniques used for preparation of microspheres [5]
Microsphere can be prepared by various techniques such as:
1. Single Emulsion Technique
   A. Heat stabilization method
   B. Chemical stabilization method
   C. Ionic chelation method
2. Double Emulsion Technique
3. Polymerisation Technique
   A. Normal phase
   a. Bulk
   b. Suspension
   c. Emulsion
   B. Interfacial
4. Spray Drying Technique
5. Spray Congealing Technique
6. Solvent Extraction Technique
7. Phase Separation Co-acervation Technique
9. Solvent Evaporation Technique

Single Emulsion Technique [7]
Single emulsion technique is used for the preparation of microparticulate carriers for drug delivery.

Principle: Two steps involved in the preparation of microsphere by single emulsion technique are:
• Natural polymers are dissolved in aqueous solution followed by dispersion in non-aqueous solution.
• Dispersed globule is cross linked by thermal crosslinking method or by chemical crosslinkers (i.e. glutaraldehyde, formaldehyde, butanol, diacid chloride etc) or by ionic chelation method (calcium chloride).

Thermal cross linking method is not suitable for thermolabile drugs, while the disadvantage of chemical cross linking method is the excessive exposure of drug to chemicals if it is added at the time of preparation. Ionic chelation method may have demerit such as salt formation, chelation or counter ion replacement.

Double emulsion technique
Multiple emulsion or double emulsion of type w/o/w is formed during the preparation of microsphere by double emulsion technique. Natural as well as synthetic polymer are used for the preparation of microsphere by this method.

Principle: Aqueous solution of protein or polymer is dispersed in a organic lipophilic continuous phase along with the drug. Homogenization or sonication of the primary emulsion is carried out before addition to the aqueous solution of polyvinyl alcohol, which lead to the formation of multiple emulsion. Once the desired emulsion stability have been obtained, removal of solvent from the emulsion is done by solvent extraction or solvent evaporation process. Microsphere are
separated from the suspending medium by filtration, washing and drying. Incorporation of hydrophilic drug such as leuitizing hormone releasing hormone (LHRH) agonist, vaccines, protein/peptides into microsphere can be done by Double Emulsion Technique. [7]

Example— Genistein chitosan microsphere was prepared by multiple emulsion method of type o/w/o by Wu & Li (2002). [6]

Steps involved in preparation of microsphere-

**Polymerisation technique** [9]
Microsphere can be prepared by polymerisation technique in two ways:

(A) **Normal polymerisation**— Normal polymerisation process involves various methods such as bulk polymerisation, suspension polymerisation and emulsion polymerisation for the preparation of microsphere.

(1) **Bulk polymerisation**— Bulk polymerisation process involves heating of the monomer or mixture of monomer along with the initiator and drug to initiate the polymerisation process. Polymer so obtained is moulded or fragmented as microsphere. Rate of reaction in bulk polymerisation technique can be accelerated by using the catalyst or initiator. Formation of pure polymer is the advantage of bulk polymerisation, but it cannot be used for thermolabile drug as the heat dissipated from reaction may degrade the product.

(2) **Suspension Polymerisation**— Suspension polymerisation is also known as bead polymerisation or pearl polymerisation involves heating of the monomer or a mixture of monomer along with the drug and initiator as droplet dispersion in a continuous aqueous phase. The suspension polymerisation is carried out at low temperature and heat can be easily dissipated out because continuous external phase is normally water. Polymer association with untreated monomer or other additives is the disadvantage of this technique steps used in preparation of microsphere.

(3) **Emulsion Polymerisation**— Emulsion polymerisation differs from suspension polymerisation as initiator is present in the aqueous phase, which further diffuses to the surface of the micelles or on emulsion globule.
Advantage of emulsion polymerisation with respect to bulk polymerisation is that it is used for thermolabile drug because heat can be dissipate out easily and it also produces high molecular weight polymer at faster rate, but polymer association with untreated monomer or other additives is the disadvantage of this technique.

Steps used in preparation of microsphere-

![Diagram of Emulsion polymerization method of formulation of microspheres](image)

**Spray Drying Technique**

In Spray drying process, core material is dispersed in coating solution, in which the coating substance is dissolved and in which the polymer is insoluble, followed by atomisation of the mixture into air stream.

**Principle:** Three steps involved during spray drying process are:
- **Atomisation:** It involves conversion of a liquid feed into fine droplet.
- **Mixing:** Mixing is carried out by passing hot air stream through spray droplets, which causes evaporation of liquid and leaving behind dried particles.
- **Dry:** Dried powder is separated from the air stream and collected.

Feasibility of the process under aseptic condition is the advantage of this method; it is single stage operation, rapid and appropriate for bulk and batch manufacturing.

Disadvantage of this process is the formation of needle shape crystal when caffeine is incorporated into polymer (polylactide) by this technique which leads to incompatibility of drug and polymer (Badmeier & Chen, 1998).

**Example:** Mucoadhesive microsphere of ondanestron for nasal administration is prepared by spray drying technique. (Muchoadhesive microsphere of ondanestron for nasal administration is prepared by spray drying technique).

**Spray Congealing Technique**

Spray congealing technique is similar as that of spray drying technique; the difference between two techniques is only that the dispersion of core material is done in a melted coating substance not in a coating solution followed by atomisation into air stream. Substance such as fatty acid, polymer, waxes, sugars which are solid at room temperature, but can be melted at certain temperature can be used in spray congealing technique.

**Example:** Mucoadhesive microsphere can be prepared by spray congealing technique for the vaginal delivery of Econazole.
Solvent Evaporation Technique - Solvent evaporation technique is one of the oldest and widely used methods for preparation of microsphere. When drug loading is low, this method is used for preparation of microsphere. Example - Solvent evaporation technique is used for the preparation of microsphere of 5-Flurouracil by using dichloromethane and acetonitrile, polyvinyl alcohol is used as processing medium to solidify the microsphere. [16] Steps involved in preparation of microsphere -

- Polymer is dissolved in suitable organic solvent
- Addition of the drug into the solution which is to be encapsulated
- Emulsification in a blender or with a suspended agitator
- Continuous stirring
- Formation of oil phase droplets and emulsion stability
- Evaporation of solvent
- Collection of microspheres
- Filtration, Washed, Dried
- Microsphere

Solvent Extraction Technique - In this process, removal of the organic phase is done by extraction with an immiscible organic solvent. The hardening time for microsphere is decreased by removal of the organic solvent by extraction with water. Rate of solvent removal depend upon various factors such as temperature of water, ratio of emulsion volume to the water and solubility profile of the polymer. [17]

Phase Separation Coacervation Technique - In this process the solubility of polymer is decreased in the organic phase to affect the formation of the polymer rich phase known as coacervates. It is used for the preparation of reservoir type system (encapsulated water soluble drug such as proteins, peptides) and also for matrix type system (hydrophobic drug such as steroids).

Principle: Three steps involved during phase separation coacervation process are -

- Formation of three immiscible chemical phases i.e. a liquid manufacturing vehicle phase, core material phase and coating material phase.
- Deposition of the liquid coating polymer upon the core material.
- Rigidization of the coating by thermal, cross linking or dissolution method.[19]

Evaluation of microsphere - Microsphere is prepared by different methods and under different conditions so that it has various microstructures which determine the release and stability of the carrier. Various parameters are evaluated for microsphere, which are as in table 2.
Advancement in Microsphere

1. **Floating microsphere** - Floating microsphere have bulk density less than gastric fluids, thus they remain floating in the stomach without affecting the gastric emptying rate. Therefore gastric retention time is increased and fluctuation in plasma drug concentration is reduced or controlled by floating microsphere. In addition it reduces dumping of dose, dosing frequency, increases therapeutic efficacy, solubility and dispersability. [34] Floating microsphere is of two types:
   a) **Effervescent type** - Swellable polymers e.g. methylcellulose, chitosan and various effervescent compound e.g. sodium bicarbonate, citric acid, tartaric acid are used for the preparation of effervescent dosage form. Floating microsphere of effervescent type liberates carbon-dioxide gas due to which the density of the system is reduced and remains in floating condition in stomach for a prolonged period of time, this result in release of drug slowly at a desired rate.
   b) **Non-effervescent type** - Highly swellable cellulose type hydrocolloids, polysaccharide and matrix forming polymer such as polycarbante, polyacrylate are used to form non effervescent system. This is prepared by thoroughly mixing the drug and gel forming hydrocolloids. On administration, it swells up when comes in contact with gastric fluid and attain a bulk density i.e, less than 1 g/ml. [35]

2. **Radioactive microsphere** - Radioactive microsphere is used in the same way as non-radioactive microsphere. Delivery of high concentration of drug to the target site does not damage normal surrounding tissue. As compare to drugs, radioactivity substance is not released from the microsphere but proceed from inside a radioactive typical distance. The α emitters, β emitters and γ emitters are used as radioactive microsphere. Radioactive microsphere is used for diagnostic and therapeutic purpose. [37,38]

3. **Hollow Microsphere** - Hollow microspheres also called as microballoons is filled up with the drug in their outer polymer shells and are prepared by emulsion-solvent diffusion technique. The ethyl alcohol: dichloromethane solution of the drug and polymer (enteric acrylic) is transfer into a stirring aqueous solution of PVA which is thermally controlled at 400°C. Gas is generated by dispersing the polymer droplet by evaporation of dichloromethane which leads to formation of an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for a period of more than 12 hours _in-vitro_. Different drugs can be prepared by hollow microsphere by using various materials e.g. polycarbante, calcium alginate, Eudragit S 100 etc. [39,40]

4. **Magnetic Microsphere** - In magnetic microsphere small amount of magnetically targeted drug is delivering to the target site in place of high amount of free circulating drug. Those materials which response to magnetic field are used in the preparation of magnetic microsphere are chitosan, dextran etc [4]. Magnetic microsphere is used for diagnostic and therapeutic purpose. Superamagnetic iron oxides radiolabelled is used as therapeutic magnetic microsphere for imaging of liver metastasis, distinguish loop of bowel from other abdominal structure, whereas iron carbon particles radiolabelled with isotope $^{188}$Re, $^{90}$Y etc are used as diagnostic microsphere for liver tumours. [38]

5. **Muchoadhesive Microsphere** - Muchoadhesive microsphere adhere to mucus layer and release drug at desired rate. In muchoadhesive microsphere the intimate contact time with the mucus surface is increased. This results in an increased drug retention time as well as drug concentration at the targeted site [41, 42]. Muchoadhesive formulation can be administered through various routes such as nasal, gastrointestinal, buccal, Ocular etc [43]. Therapeutic efficacy is improved as well as absorption; bioavailability of normally poorly absorbed drug is improved. [44]
Conclusion
It is concluded from above that microsphere is the promising candidate for sustained and as a targeted drug delivery in GIT, liver, colon, nasal, pulmonary system, and ocular drug delivery etc. These are also used as diagnostic agent and for treatment of cancer too. Several methods of microsphere preparation give various approaches and ease to prepare various types of microspheres with different category of drugs.

References


Table: 1

<table>
<thead>
<tr>
<th>S.No</th>
<th>Target Site</th>
<th>Drug Use</th>
<th>Method Of Formulation</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ophthalmic</td>
<td>Cyclosporine, Acyclovir, Ofloxacin, Indomethacin</td>
<td>Cross linking, Coacervation phase separation,</td>
<td>Polymer hydrogels offer better acceptability. Increase precorneal drug residence time. Increase duration of efficacy of drug by using higher molecular weight polymer.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chitosan, Alginate, Gelatin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Starch, Dextran, Albumin, Chitosan+Gelatin, DSM+LPC</td>
</tr>
<tr>
<td>3</td>
<td>Gastrointestinal drug delivery</td>
<td>Ranitidine hydrochloride, Melatonin, Aceclofenac, Furosemide, Amoxicillin, Prednisolone, Meloclopramid Glipizid</td>
<td>Solvent evaporation, By dissolving drug in polymer Cross linking</td>
<td>Floating and hollow microsphere can be used in drug delivery. Controlled drug release system. Decrease fluctuation in plasma drug concentration. Retention of microsphere in stomach for more than 10 hours.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chitosan, Sodium alginate, Gellan gum</td>
</tr>
<tr>
<td>5</td>
<td>Oral</td>
<td>Diazepam, Insulin</td>
<td>Cross linking method,</td>
<td>Increase patient compliance.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chitosan, Gelatin</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Solvent evaporation method</th>
<th>Multiple unit system can be produced. Avoid the exposure of high concentration of drug to mucosa. Faster drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry in oil, W/O in emulsion system, Combined emulsion</td>
<td>Delivery of therapeutically relevant concentration of drug at tumour site. Increase concentration of drug at tumour site. Decrease in side effect and toxicity of anticancer drugs. Enhance drug concentration in brain. Maximize therapeutic efficacy.</td>
</tr>
<tr>
<td>Gelatin, PLGA, Chitosan, PCL</td>
<td>4,6</td>
</tr>
<tr>
<td>Fluorouracil, Cisplatin, Methotrexate, Oxantrazol.</td>
<td>6 Intra tumoral</td>
</tr>
<tr>
<td>Metronidazole, Acriflamine Methothrexate</td>
<td>7 Vaginal</td>
</tr>
<tr>
<td>Solvent evaporation, By dissolving drug in polymer Cross linking</td>
<td>Treatment of mycolic infection of genitourinary tract. Increase residence time of vaginal mucosa tissue. Adequate release and good adhesion property.</td>
</tr>
<tr>
<td>Chitosan, Gelatin, PLGA</td>
<td>4,6</td>
</tr>
<tr>
<td>Prednisolone, Lidocane hydrochloride, Local anesthetics</td>
<td>8 Transdermal</td>
</tr>
<tr>
<td>Solvent extraction method, Spray drying, Spray coageling method</td>
<td>Relevant packaging Sustained release action improving therapeutic efficacy Biocompatible and biodegradable polymer system can be used.</td>
</tr>
<tr>
<td>Chitosan alginate, Chitosan gelatine, PLGA</td>
<td>4,6,25</td>
</tr>
<tr>
<td>Genes</td>
<td>9 Gene delivery</td>
</tr>
<tr>
<td>Cross-linking method, polymerization method</td>
<td>Highly efficient and have wide range of cell targeting It also causes immune responses and oncogenic effects. Use as a carrier of DNA for gene delivery applications</td>
</tr>
<tr>
<td>Chitosan, Gelatin</td>
<td>4</td>
</tr>
<tr>
<td>Amoxicillin, Ampicillin, Tetracycline, Sulfadiazine, Griseofulv</td>
<td>10 Monoclonal antibodies</td>
</tr>
<tr>
<td>Chitosan, Alginate, PLGA</td>
<td>6,7</td>
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</table>

Table 2: Different evaluation parameters with their methods
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Evaluation Parameter</th>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Particle size and shape</td>
<td>Light microscopy, Scanning light microscopy, Confocal scanning microscopy, Confocal fluorescence microscopy, Laser light scattering, Multisize coulter counter</td>
<td>27, 28</td>
</tr>
<tr>
<td>2.</td>
<td>Flow properties</td>
<td>True density, Tapped density, Bulk density, Carr’s index, Hausner’s ratio, Angle of repose.</td>
<td>29</td>
</tr>
<tr>
<td>3.</td>
<td>Entrapment efficiency</td>
<td>By allowing lysing of wash microsphere %Entrapment= Actual content/ Therotical content×100</td>
<td>30</td>
</tr>
<tr>
<td>4.</td>
<td>Density</td>
<td>Multivolume pychnometer</td>
<td>31</td>
</tr>
<tr>
<td>5.</td>
<td>Angle of contact</td>
<td>Microscope</td>
<td>7</td>
</tr>
<tr>
<td>6.</td>
<td>Isolectric point</td>
<td>Microelectrophoresis</td>
<td>32</td>
</tr>
<tr>
<td>7.</td>
<td>Interaction between polymer and drug</td>
<td>Attenuated Total Reflectance Fourier transform</td>
<td>7</td>
</tr>
<tr>
<td>8.</td>
<td>Chemical analysis</td>
<td>Electron Spectroscopy</td>
<td>31</td>
</tr>
<tr>
<td>9.</td>
<td>Drug release profile</td>
<td>USP Type Dissolution Apparatus(Rotating Paddle Type)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dialysis</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Drug/Polymer used in floating microsphere [36]

<table>
<thead>
<tr>
<th>S.No</th>
<th>Drug</th>
<th>Polymer</th>
<th>Method</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Orlistat</td>
<td>Eudragit S</td>
<td>Solvent evaporation</td>
<td>Increase gastric residence time of over 6 hrs.</td>
</tr>
<tr>
<td>2.</td>
<td>Metformin hydrochloride</td>
<td>Ethylcellulose</td>
<td>Solvent evaporation</td>
<td>Short processing time. High encapsulation efficiency.</td>
</tr>
<tr>
<td>3.</td>
<td>Cimetidine</td>
<td>Hydroxypropyl methylcellulose, Ethycellulose</td>
<td>Solvent evaporation</td>
<td>Prolonged drug release (8 hrs) Remaining buoyant for more than 10 hrs.</td>
</tr>
<tr>
<td>4.</td>
<td>Ketoprofen</td>
<td>Eudragit S 100 with Eudragit RL</td>
<td>Emulsion solvent diffusion</td>
<td>Drug retained in floating microparticles decreases with increased ERL content</td>
</tr>
<tr>
<td>5.</td>
<td>Theophylline</td>
<td>Mixture of cellulose acetate butyrate and Eudragit RL (1:1)</td>
<td></td>
<td>Increased residence time in stomach</td>
</tr>
</tbody>
</table>

Table 4: Radioactive microsphere used as diagnostic purpose
Table 5: Radioactive microsphere used as therapeutic purpose

<table>
<thead>
<tr>
<th>S.No</th>
<th>Application</th>
<th>Radioactive Microsphere</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Bone marrow imaging</td>
<td>$^{99m}$Tc sulphur colloid; $^{99m}$Tc antimony sulphide colloid</td>
<td>37</td>
</tr>
<tr>
<td>2.</td>
<td>Blood flow measurement</td>
<td>Polystyrene microsphere labelled with γ emitters $^{141}$Ce, $^{51}$Cr</td>
<td>38</td>
</tr>
<tr>
<td>3.</td>
<td>Gated blood pool study</td>
<td>$^{99m}$In or $^{51}$Cr labelled red blood cell</td>
<td>38</td>
</tr>
<tr>
<td>4.</td>
<td>Radioembolisation</td>
<td>$^{99}$Tc macro aggregated human serum albumin</td>
<td>37</td>
</tr>
<tr>
<td>5.</td>
<td>Infection localisation</td>
<td>$^{111}$In labelled leukocytes, $^{99m}$Tc labelled liposomes</td>
<td>38</td>
</tr>
</tbody>
</table>

Table 6: Drug / Polymer combination used in mucoadhesive microsphere

<table>
<thead>
<tr>
<th>S.No</th>
<th>Drug / polymer combination</th>
<th>Application</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Insulin / DSM + LPC</td>
<td>Help in delivery of insulin through nasal route</td>
<td>3,35</td>
</tr>
<tr>
<td>2.</td>
<td>Amoxicillin/Ethylcellulose-Carbopol</td>
<td>Therapeutic efficacy of drug is increased</td>
<td>46</td>
</tr>
<tr>
<td>3.</td>
<td>Aceclofenac/Eudragit</td>
<td>Controlled release of drug is increased</td>
<td>47</td>
</tr>
<tr>
<td>5.</td>
<td>Clonazepam/Gelatin-chitosan</td>
<td>High concentration of drug delivery in brain</td>
<td>47</td>
</tr>
</tbody>
</table>