CONTROLLED RELEASE SUSPENSION: A REVIEW

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ABSTRACT:
Oral drug delivery is most preferred route of drug delivery. Novel technologies with improved performance, patient compliance, and enhanced quality have emerged in the recent past. Sustained release dosage forms aimed at controlling the rate of release as well as maintaining desire drug level in the blood for long duration. An oral suspension could be the best suitable dosage form for geriatric and pediatric patients. Many therapeutic benefits could be gained by incorporating functions of sustained drug release in to suspension dosage form. They include improvement of rate and extent of drug absorption, higher patient compliance, reduction of side effects and taste masking for bitter drug. A number of techniques to obtain the sustained release oral suspension of a drug are mentioned in the article. The required drug characteristics, the stability testing and characterization of the dosage form as well as the different guidelines to follow are mentioned here. Many patent applications are already granted and many more are published in order to provide an implicit basis for the development of the sustained release suspension dosage forms of the various drugs such as Pseudoephedrine, Paracetamol, Non-steroidal anti-inflammatory drugs, Chloramphenicol, Propanalol etc.

KEYWORDS: Active Pharmaceutical Ingredient, Suspension, Sustained release, Controlled release, Ion Exchange Resin, Micro-encapsulation, Polymerization, Stability Tests.

INTRODUCTION:
Tablets and capsules are unsuitable for administering high doses of Active Pharmaceutical Ingredient (API) since individual large dose is difficult to swallow, or require the administration of several tablets or capsules at a time, making it less patient compliant. Also chewable tablets are also not ideal with pediatric and geriatric patients due to need of chewing, poor taste masking and lack of control release possibility. Oral liquid suspensions are majorly designed for the patients with difficulty in swallowing. But their controlled release form is also tricky due to the chances of premature release of the API in the suspending media during storage. This produces a significant challenge and accounts for the fact that there are few

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sustained release oral suspension formulations. Different methods are mentioned hereafter for overcoming the problem.

**DISPERSION:**
Dispersion system consist of (1)-particulate matter (dispersed phase) (2)-continuous medium (dispersion medium)

**Table 1:** Classification of dispersed systems (based on particle size)

<table>
<thead>
<tr>
<th></th>
<th>Molecular dispersion</th>
<th>Oxygen molecules, glucose solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; 1 nm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Colloidal dispersion</th>
<th>Natural polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1nm-0.5 mm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Coarse dispersion</th>
<th>Suspension and emulsion</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>&gt; 0.5 mm</td>
<td></td>
</tr>
</tbody>
</table>

**SUSPENSION:**
Pharmaceutical suspensions are uniform dispersions of solid drug particles in a vehicle in which the drug has minimum solubility. Particle size of the drugs may vary from one formulation to the other depending on the physicochemical characteristics of the drug and the rheological properties of the formulation. Liquid dosage form is more favored than solid because of the flexible dosage administration and easy to swallow. It’s controlled release form is more patient compliant with lesser side effects and better bio-availability. [1]

A pharmaceutical suspension is a coarse dispersion in which the internal phase is dispersed uniformly throughout the external phase. [1]

**Reasons for suspension:**
a) Drugs chemically unstable in solution are usually stable in suspended form. b) Convenient dosage form for large doses. c) Safe and compliant for infants and children. d) For insoluble or poorly soluble API. [2]

**Challenges in formulation of oral suspension:**
1) Physical stability: the properties of a solid-liquid dispersion system alter the physical stability as well as the absorption rates of the formulation. 2) Acceptable organoleptic properties like taste, is hard to achieve and thus reduces the patience compliance. 3) The preparation of a placebo that looks similar and tastes alike is challenging.

- A suspension containing particles between 1 nm to 0.5 µm in size is called colloidal suspension. When the particle size is between 1 to 100 µm, the suspension is called coarse suspension. Most of the pharmaceutical suspensions are coarse suspension.
- Majority of the marketed suspensions are available as dry powders that must be reconstituted before administration but occasionally some products in the market are ready-to-use. The first products are not very stable once reconstituted; must be used within 7 to 10 days.

**Pharmaceutical applications of suspensions:**
1) Insoluble drug or poorly soluble drugs which required to be given orally in liquid dosage forms (In case of
children, elderly, and patients have difficulty in swallowing solids dosage forms)
2) To overcome the instability of certain drug in aqueous solution
3) To mask the taste: Examples are paracetamol suspension (more palatable) and chloramphenicol palmitate.
4) Some materials are needed to be present as finely divided forms to increase the surface area. For example, Mg carbonate and Mg trisilicate are used to adsorbed some toxins
5) Suspension can be used for topical applications: An example is calamine lotion Bp ⇒ after evaporation of dispersing media; the active agent will be left as light deposit
6) Can be used for parenteral administration as intramuscular (i.m.) injection to control the rate of absorption.
7) In vaccines, inactivated toxins are adsorbed on the porous surface of Aluminum hydroxide.
8) X-ray contrast media: an example is oral and rectal administration of propyliodone

**Qualities of ideal suspension:** A well-formulated suspension should have the following properties:

1) The dispersed particles should not settle readily and the settle should redispersed immediately on shacking. Ideally, the particles in a suspension should not sediment at any time during the storage period. Unfortunately, the present technology does not allow us to prepare such a suspension. Since one cannot completely avoid the sedimentation of particles, it is desirable that the particles should settle slowly. The easy redispersion of sedimented particles in a suspension is important for the uniformity of dose.
2) The particle should not form a cake on settling
3) The viscosity should be such that the preparation can be easily poured. A highly viscous suspension would make pouring difficult.
4) It should be chemically and physically stable
5) It should be palatable (orally)
6) It should be free from gritting particles (external use)

**Innovation in suspension:**

1) Taste-masking: Un-palatability due to bad taste was conquered by different taste masking approaches: Polymer coating of the drug. b) Encapsulation with a basic substance. c) Polymer coated drug with a basic substance. d) Coating with pH control.
2) Nano-suspension
3) Controlled release suspension: It can be of two types: Sustained release: increases the duration of action without affecting the onset of action. Delayed release: Increases the onset of action time. The major advantage of
controlled release is the decrease in dosing frequency. [1]

Latest Advancement in Oral Controlled Release (OCR) Suspension: [6-7]
Over the last two decades, controlled technology has received increasing attention from the pharmaceutical industry and academia. As new technologies emerge, they not only open up a wide range of new therapeutic opportunities, but also offer the benefits of product differentiation, market expansion, and patent extension. By 1998 over 70 chemical entities had been formulated into more than 90 oral controlled release products that were approved for marketing by the U.S. Food and Drug Administration (FDA).

In the 20 years or so, designing of new drug delivery system has gained importance. The main focus of the researchers is a delivery system which is site specific with a required dose and time scale. The development of such a system allows us to conserve and maintain effective drug concentration, eliminate the night time dosage, improve the patience compliance, increase the specificity of action and decrease the side effects.

For example a controlled release suspension of diclofenac sodium is very popular in elderly for the treatment of chronic disease like rheumatic disorders. [8]

Drug in a controlled release-gastro retentive dosage forms can remain in the gastric region for several hours. Thus the gastric residence time of the drug is prolonged, bioavailability is improved and wastage is reduced. [9]

The attempts to develop liquid oral controlled release formulations are usually based on the multiparticulates such as coated pellets or micro particles. Leaching of the drug into the aqueous medium and the interaction with liquid contents, changing the properties during storage is the main problem faced during the development of the formulation.

Some of the earlier strategies included saturated drug solutions as a suspending medium, preparation of dry controlled release syrup for reconstitution before use and ion-exchange resins. Now a day's microspheres, polymer layers, solid liposheres, encapsulations are researched in detail. [10]

A lot of work has already done on the Drug-Ion exchange resin release wherein different methods for delivery of the resins were formulated, such as direct suspension, microencapsulation or coating before suspension, Pennkinetic system, hollow fiber system.

2. Microspheres: [12]
The highly soluble drugs can also be entrapped in polymeric microspheres using different methods such as: oil in water (dispersion or co solvent method) or water in oil (multiple emulsion method) emulsion-solvent evaporation method. Oil in water meltable dispersed phase (MDP) encapsulation method is easy and useful in preparing Beeswax matrix microspheres (liposheres) with drug entrapped without the use of any toxic organic solvent.

Development of the oral controlled release suspension:
The efficacy of the drug depends highly on the path of the drug molecule from site of
administration to target site. Different conditions encountered may change the effectiveness of the drug or affect the amount at the receptor site. A delivery system with physiological stability and optimum bioavailability needs to be formulated.

**Table 2:** Unsuitable characteristics of the drug substance for controlled release suspension

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Unsuitable characteristics</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not effectively absorbed in the lower intestine</td>
<td>Riboflavin, ferrous salts</td>
</tr>
<tr>
<td>2</td>
<td>Absorbed and excreted rapidly, short biological lives</td>
<td>Penicillin G, furosemide</td>
</tr>
<tr>
<td>3</td>
<td>Long biological half-lives &gt;12hrs</td>
<td>Diazepam, phenytoin</td>
</tr>
<tr>
<td>4</td>
<td>Large dose required &gt;1g</td>
<td>Sulfonamide</td>
</tr>
<tr>
<td>5</td>
<td>Cumulative action and undesired side effects; low therapeutic indices</td>
<td>Phenobarbitol, digitoxin</td>
</tr>
<tr>
<td>6</td>
<td>Precise dosage required</td>
<td>Anti-coagulants, cardiac glycosides</td>
</tr>
<tr>
<td>7</td>
<td>No clear advantage for CR</td>
<td>Griseofulvin</td>
</tr>
</tbody>
</table>

**Criteria to be met by drug proposed to be formulated in sustained release dosage forms:** [2, 3, 13, 14]

a) Desirable half-life:
The half life of a drug is an index of its residence time in the body. If the drug has a short half life (less than 2 hours) the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half life of eight hours or more are sufficiently sustained in the body, when administered in conventional dosage from, and controlled release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to four hours.

c) Small dose of the drug product:
 If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undetermined. This is chiefly because the size of a unit dose controlled release formulation would become too big, to administer without difficulty.

d) Desirable absorption and solubility characteristics:
Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into controlled release formulations is therefore unrealistic and may reduce overall absorption efficiency.
e) Desirable absorption window:
Certain drugs when administered orally are absorbed only from a specific part of the gastrointestinal tract. This part is referred to as the ‘absorption window’. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as controlled release dosage form are unsuitable.

f) First pass clearance:
Delivery of the drug to the body in desired concentrations is hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release forms.

3. Microencapsulation: [15-17]
Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material. The product obtained by this process is called as micro particles, microcapsules. Particles having diameter between 3 - 800µm are known as micro particles or microcapsules or microspheres.
Generally Micro particles consist of two components a) Core material b) Coat or wall or shell material.

4. Polymerization by Phase separation methods: [18-22]
The particle size of the resulting microspheres depends on the polymerization conditions, including the monomer/co-monomer composition, the amount of initiator and the total monomer concentration.

Two main types of phase separation methods are available:
a) Aqueous coacervation (Simple and complex) & b) non- aqueous coacervation methods

5. Emulsion–solvent evaporation (o/w, w/o, w/o/w): [23-26]
A) Single emulsion methods: It could be two types, such as oil in water (o/w) or water in oil (w/o) type emulsion.
B) Multiple emulsion methods: It is mainly w/o/w type

6. Ion Exchange Release (IER): [27-34]
Ion exchange is reversible interchange of ions without any radical change in structure or the properties of the solid. The interchange takes place between the two phases; solid and liquid. The solid phase is known as the IER and can be of two types: cationic-exchange resin, anionic exchange resin.
The complex between the drug and the IER is termed as a Resinate. Formulation to site of absorption of the IER is depicted in the fig no. 1.

Fig 1: In-vitro formulation to in-vivo ADME process for Drug-resinates

Physical and chemical properties of IER:
Spherical beads with 0.5 to 1.2 mm diameter, usually yellow in color. The solubility depends on the nature of counter ion and the extent of cross linking of the basic skeleton. Commonly IER swells 2-3 times their original weight. Despite strong swelling, the chemical stability is good. Chemically it consists of a polymer matrix and a functional component to which the counter ion binds.

The structural component is of stable acrylic polymer of styrene-divinylbenzene copolymer, and the functional part can be acidic (sulfonic or carboxylic) or basic (amine).

Ion Exchange Resinates are the most common commercially used complexes for sustained release suspensions. They prevent leaching of the drug in the suspending medium during storage; but the in vivo release profile fluctuate depending on the concentration of counter ions present in GIT.

**Ion-Exchange Resin Characterization:**

1. Particles size:
   - Micro sieves by screening
   - Microscopy
   - Coulter counter

2. Porosity:
   - Nitrogen absorption at -195°C and by measuring the true density (mercury displacement)
   - Scanning electron microscopy
   - Air compression pycnometer

3. Moisture content:
   - Karl fischer titrity

4. Ion Exchange capacity:
   - For Cation-Exchange Resin: The number of moles of Na⁺ which is absorbed by 1g of dry resin in hydrogen form.
   - For Anion-Exchange Resin: measuring the amount of Cl⁻ taken up by 1g dry resin in the hydroxide form.

**Different forms of Controlled release Resinates:** [31-34]

Because of their drug retaining properties, prevention of dose dumping and leaching of the drug from Ion-Exchange resin is an important system in Controlled release resonates complex.

There are majorly four types of resinates:

1. **Simple resinates:** [33]
   These can be directly suspended in liquids. Drug release is faster in comparison with the modified resinates.
   e.g: the release of diclofenac sodium suspension to avoid gastric irritation for the arthritic patients.

2. **Microencapsulated or coated resinates:** [8, 11, 35, 36]
   It provides better control over the drug release due to the rate controlling membrane.
   It involves entry of the counter ions in the drug resinate, release of the drug and diffusion of the drug through the membrane in the surrounding environment.
   Coating materials used are water insoluble such as waxes and ethyl cellulose.
   Release rate is maintained by the thickness of the coat.
Microencapsulation is done by already mentioned Air suspension coating (Wurster process), polymerization, solvent evaporation, pan coating etc.

3. Pennkinetic system: \([37, 38]\) Here the resinate is pretreated with Polyethylene glycol (PEG)-400 to maintain the geometry and this improves the coating process. The resinate is later coated with water insoluble materials. PEG controls the rate of swelling in water and the outer coat controls the rate of diffusion of ions.

4. Hollow fiber systems:
These have the advantage of high surface area to volume ratio, flexibility in loading, permeability and low gastric time.

Functions of a polymer in oral controlled release: \([16,17,18]\)
Diffusion, dissolution and permeation are the important principles applied for a constant rate of drug delivery. The polymers must offer a wide range of properties such as diffusivity, permeability and solubility. It is important to understand the different properties.

FABRICATION TECHNIQUES: \([20, 34-38]\)
This involves either dispersing the drug into a polymeric matrix, or encapsulating the drug containing core or granules with a rate controlling membrane.

Some of the old techniques for encapsulation are as follows;

a) Wet granulation:
Drug is uniformly dispersed into a polymeric matrix using traditional high-shear granulation (HSG) or fluidized-bed granulation (FBG) techniques.

1. high-shear granulation (HSG)
An aqueous or a hydroalcoholic binder solution, such as 5% polyvinylpyrrolidone in water, is sprayed onto a polymeric powder bed, such as 85% HPMC containing the drug. The powder bed is subjected to a very high shear rate to obtain granules incorporating a uniform mixture of drug, binder, and the polymeric excipients. The wet granules could be dried either in a traditional tray dryer, fluidized-bed dryer, or microwave dryer.

2. Fluidized-bed granulation (FBG)
A powder bed consisting of drug, polymer, and other excipients is fluidized in an expansion chamber. The binder solution is sprayed through a nozzle from the top or bottom of the bed depending on the equipment design. The droplet size and the bed humidity are important factors which governs the granule size. Though the granules formed are large in size compare to the requirements and thus the process is no longer used.

b) Spray Congealing
This process consists of suspending the drug particles in a low-melting polymer or wax and pumping the resultant slurry through an atomizer into a spray dryer in which cold air is circulated. The slurry droplets congeal on coming in contact with the air and are collected in the same manner as the spray-dried product. The spray congealing process requires a much higher ratio of coating agent to active material than does spray drying because only the molten coating agent constitutes the liquid phase.
Encapsulation of drug-containing cores and granules (resins) in the manufacture of reservoir-type oral controlled released product can be accomplished by the following coating methods: [19-21]

c) Pan Coating
Pan coaters are one of the earliest types of equipment to be used for encapsulation. Pan coating involves spraying an atomized coating solution through nozzles on a moving bed of tablets. The distribution of the coating is accomplished by movement of the tablets perpendicular to the application of the coating solution. Drying of the coating solution from the tablet bed is accomplished by directing heated airflow from the front to the back of the partially or fully perforated pan.

d) Spray drying
Spray drying has been used to produce microencapsulated and matrix formulations of several drug substances including theophylline, acetaminophen, and sulfa-ethylthiazole.
Process steps involved:
1. Liquid feed is atomized into fine droplets.
2. These fine droplets are mixed with heated gas stream, allowing the liquid to evaporate and leave dried solids powder.
3. Finally, the dried powder is separated from the gas stream and collected. The final product usually has the same size and shape as the atomized droplet.

e) Air suspension coating (Wurster Process) [39]
With the high demand for encapsulated materials in the global market, fluid-bed coaters have become more popular. They are used for encapsulating solid or porous particles with optimal heat exchange the liquid coating is sprayed onto the particles and the rapid evaporation helps in the formation of an outer layer on the particles. The thickness and formulations of the coating can be obtained as desired.
f) Vibration technology \[^{[15]}\]
This technology is based on an ancient principle (Lord Rayleigh, in the late 19th century) which shown that a laminar liquid jet breaks up into equally sized droplets by a superimposed vibration. The parameters are the frequency, the velocity of the jet and the nozzle diameter. To guarantee the production of uniform beads or capsules and to avoid large size distributions due to coalescence effects during the flight, the droplets pass through an electrostatic field to be charged. As a result these droplets don’t hit each other during the flight and will be spread over a larger surface of the gelation bath thus resulting in monodisperse beads.

g) Jet Cutter technology \[^{[15]}\]
The JetCutter is a simple technology for bead production that meets the requirement of producing monodisperse beads originating from low up to high viscous fluids with a high throughput.

Evaluation parameters for container and closures \[^{[1, 8, 11, 34, 35]}\]
- **Multiple internal reflectances**: This test is performed to ensure that the material of the container falls within the range of HDPE or LDPE as specified in the test.
- **Thermal analysis**: This standard determines endotherms and exotherms temperatures. These temperatures should fall within the ranges specified by the standard.
- **Light transmission**: These tests are intended to provide protection from light as specified by the standard.
- **Water vapor permeation.** These tests are intended to provide protection from moisture permeation as specified by the standard. Water vapor permeation tests are performed using aluminum foil for sealing the open end of the bottle if it is used with a closure.

- **Heavy metals.** Under these tests, containers must meet the requirements for heavy metals under Physicochemical Tests — Plastics.

- **Nonvolatile residue.** Under these tests the container must meet the requirements for nonvolatile residue under Physicochemical Tests — Plastics

- **USP 24 <661>** also has test procedures for Polyethylene Terephthalate (PET) and Polyethylene Terephthalate G (PETG).

**Stability studies of the sustained release suspension:**\(^{[1,6,8,34,35,37]}\)

All prepared suspensions were kept at 30°C and 45°C and evaluated for their physical and chemical properties including pH, sedimentation volume, redispersibility, viscosity, drug leaching, drug content and in vitro drug release every 30 days for 120 days.

- **pH:** using a pH meter.

- **Sedimentation value:** Sedimentation volume of suspension was determined by placing 15 ml of suspension into a 20-ml test tube. The sedimentation volume was the ratio of the final volume of sediment to original volume of the suspension before settling.

- **Redispersibility:** redispersibility was evaluated by rotating in screw-capped test tube 360°C at 20 rpm. The number of revolution was recorded till the suspension restored to homogeneity.

- **Viscosity:** using a cone and plate viscometer, the temperature was controlled at 30 ± 1°C and the viscosity was determined at 50 rpm.

- **Zeta potential:** The zeta potentials (Z-potential) were measured at 25°C using a streaming potential analyzer. Values of the Z-potential were calculated from the Helmholtz-Smoluchowski equation.

- **Determination of in vitro drug release:** Five milliliters of uniformly dispersed suspension was taken and placed directly into a dissolution vessel. Then, the solution was agitated and withdrawn at predetermined interval to analyze for drug release by HPLC spectroscopy.

- **Drug leaching and drug content:** Five milliliters of the homogeneous suspension was centrifuged at 3000 rpm for 10 min until the microcapsules were separated. A clear supernatant was transferred to a 25ml volumetric flask. The microcapsules in test tube were washed 3 times with a 5 ml portion of deionized water. All solutions and the supernatant were mixed in a 25ml volumetric flask and adjusted to volume with deionized water. The drug content was assayed by HPLC spectroscopy.

- **Determination of adsorption:** The amount of CMC or D-sorbitol was measured separately, after dialysis of a...
supernatant obtained by centrifugation of a suspension at 1000 x g for 1 min. The supernatant (1.0 ml) and 5.0 ml water were packed into a dialysis tube and incubated for 120 h at 25°C in 1000 ml water (outer water phase), which was replaced daily by a fresh quantity. CMC remained in the tube, and D-sorbitol was dialyzed to the outside. The amounts of CMC and D-sorbitol adsorbed onto the microspheres were determined indirectly from the difference between the initial concentration and the amount found at equilibrium upon analysis after dialysis.

(A) CMC analysis The CMC concentration of the residue in the tube was assayed by the anthrone reaction. 2 ml of 0.1% w/v anthronesulfuric acid was added to 1.0 ml of the residue, and incubated for 15 min at 90°C. After cooling, it was diluted with 60% sulfuric acid aqueous solution. This sample was analyzed photometrically.

(B) D-Sorbitol analysis D-Sorbitol concentration in the dialyzate was assayed by gas chromatography. After dilution of 1.0 ml of the dialyzates with methanol, it was evaporated to dryness at 40°C. 1 ml of the internal standard solution was added to the residual solid. The solution obtained was injected into a gas chromatograph.

- **Drug release test:** Drug release tests on the suspension with microspheres and the original microspheres were carried out by using the paddle method specified in USP XXI. The samples were placed in 900.0 ml of phosphate buffer (pH 6.8). The dissolved drug was assayed spectrophotometrically.

- **Microscopic evaluation of microcapsules:** SEM was used to examine the surface morphology of the aged microcapsules. The suspended microcapsules were isolated by vacuum filtration, freeze-dried and sputter gold coated.

- **Statistical analysis** The statistical significance of the found differences between parameters at the different storage periods was tested by the analysis of the variance (ANOVA) or the non-parametric Kruskall–Wallis test. The least significant difference (LSD) test or Siegel and Castellan test were applied for multiple comparison between formulations. Reference to a significant difference in the subsequent test refers to a level of P<0.01

**REGULATORY GUIDELINES:**

**Production guidelines: (British pharmacopeia Oral liquids)**

During the development of a preparation for oral use whose formulation consists of antimicrobial preservative. The need for and the efficacy of the preservative shall be demonstrated. During development it must be demonstrated that the nominal content can be withdrawn from the container, for liquid preparations for oral use presented in single dose containers.
The microbial quality should be taken care of during manufacturing, packaging, storage and distribution.

In the manufacture of liquid orals containing dispersed particles measures are taken to ensure a suitable and controlled particle size.

**Test:** Uniformity of dosage units should be checked

**Labeling:** The method of preparation of the solution or suspension and condition alongwith duration of storage after reconstitution should be mentioned on the product label.

**ICH Quality test parameter (Topic Q 6 A):**[^43]

Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products are mentioned in the ICH quality guideline and the following tests are needed to be performed;

- Particle size,
- Particle size distribution,
- Dissolution testing,
- Polymorphic forms,
- Redispersibility,
- Rheological properties,

### Table 3: Marketed Formulations

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Brand name</th>
<th>Generic name</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zmax SR</td>
<td>Azithromycin Dihydrate</td>
<td>Pfizer</td>
</tr>
<tr>
<td>2</td>
<td>Delsym</td>
<td>Dextromethorphan HBr</td>
<td>Reckit Benckiser</td>
</tr>
<tr>
<td>3</td>
<td>Paxil</td>
<td>Paroxetine HCl</td>
<td>GSK</td>
</tr>
<tr>
<td>4</td>
<td>Nexium</td>
<td>Esomeprazole</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>5</td>
<td>Micro-K</td>
<td>Potassium Chloride</td>
<td>Ther-Rx Corp.</td>
</tr>
<tr>
<td>6</td>
<td>Tussionex</td>
<td>Hydrocodone and chlorpheniramine</td>
<td>UCB</td>
</tr>
<tr>
<td>7</td>
<td>Dynahist-ER</td>
<td>Chlorpheniramine and pseudoephedrine</td>
<td>Wolters Kluwer Health</td>
</tr>
</tbody>
</table>

**PATENTS ON SUSTAINED RELEASE SUSPENSION:**

1) **Liquid Sustained Release Composition (WO 1990/007344 A1):**[^44]

An orally ingestible liquid composition having suspended therein at least one orally administrable pharmaceutically active composition, composition being releasable over an extended time period comprising:

a) about 30 to about 90 parts by weight of a member selected from the group consisting of at least one triglyceride or propylene glycol ester of a medium chain length alkanoic acid wherein the acid has between 8 and 10 carbon atoms in the chain and acetylated monoglycerides; caprylic or capric acid.
b) about 2 to about 15 parts by weight of a liquid, high HLB polyglyceryl ester, c) about 1 to about 6 parts by weight of colloidal silicon dioxide and d) about 0.5 to about 5.0 parts by weight of a material soluble or dispersible and capable of being insolubilized by a pharmaceutically acceptable polyvalent cation; lecithin and alginate salts of potassium.

[^43]: http://www.ijpi.org
[^44]: http://www.ijpi.org
weight of a solid pharmaceutically acceptable salt containing the cation required in ii) and iv) about 0.1 to about 40 parts by weight, to a total composition of 100 parts by weight of said at least one pharmaceutically active composition, to a total of 100 parts by weight. The ester is one of these: hexaglyceryl monooleate, octaglyceryl monooleate and hexaglyceryl dioleate. The monoglyceride has an hydroxyl value of 0-15, an acetylation level of at least 95% and a melting point between about 4°C and about 12°C.


An oral pharmaceutical composition comprising ion exchange resin particles having particle sizes from about 30 microns to about 500 microns; at least one pharmaceutically active drug releasably bound to the particles to form a drug-ion exchange resin complex, wherein the drug-ion exchange resin complex is coated with an aqueous based diffusion barrier which comprises from about 1% to about 60%, by weight of the resin particles, of a water-permeable film-forming polymer which contains no substantial traces of an organic solvent. The water-permeable film-forming polymer is ethylcellulose. The drug-ion exchange resin complex contains a solvating agent, polyethylene glycol. A drug particle suitable for forming a sustained release oral pharmaceutical composition comprising a drug-ion exchange resin complex, a solvating agent, and a water-permeable diffusion barrier surrounding at least a portion of the drug-ion exchange resin complex; wherein the diffusion barrier comprises a film-forming polymer and is free or substantially free of traces of organic solvents.

CONCLUSION:
The basic goal of any treatment is to ameliorate the sign and symptom of disorders and provide comfort to the patients. One aspect of such therapy is the sustained administration of an effective dose of drug for an extended period of time. Sustained release is more advantageous since patient's side effects arising out of administering an immediate release therapy are substantially reduced and frequency of the dosage administration is reduced which leads to improve patient compliance. Sustained or prolonged-release dosage forms of various drugs are known. To get sustained release liquid suspension, the drug is complexed with an ion exchange resin forming a drug-ion exchange resin complex particle. After administration of this liquid SR suspension, the drug is slowly released from the complex over a period of time thereby providing a continuous delivery of drug to the patient. In some cases, the drug-ion exchange resin complex particle is coated with a diffusion barrier made of a water-permeable film. Such coated particles, however, have one or more drawbacks, for example, they may involve difficult or expensive to manufacture, e.g., requiring multiple steps and a polymer coating step wherein the polymer must be dissolved and applied from a non-aqueous solvent, a significant quantity of which may remains in the final product as a residual solvent. Alternatively, high loadings of the drug in the ion exchange resin are required to maintain the integrity.
of the coating and to provide satisfactory therapeutic performance.

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