



A REVIEW: SUSTAINED RELEASE ORODISPERSIBLE TABLET

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ABSTRACT

In the 1980s, orally disintegrating tablets (ODTs) were introduced in the market becoming one of the most useful techniques of drug delivery. The target populations for ODTs are bedridden pediatric, geriatric, and or disabled patients. Patients with persistent nausea, who are traveling, have little or no accesses to water are also good candidates. Sustained release technology is considered a useful drug delivery method in the pharmaceutical industry, that managed to overcome the limitations of conventional dosage forms and succeeded to improve the therapeutic efficacy, patient compliance and convenience of handling. The basic concept of formulating SR-ODTs involves formulating the drug coated or encapsulated in a matrix to form a multi-particulate drug system These include the use of ion exchange resin systems, microencapsulation, nanoparticles, pellets and stimuli-responsive polymers. Each approach has its own characteristics & use in sustained drug release through the ODT. Sustained release ODT can offer advantages of both, ODT technology and sustained release technology, which provide additional clinical benefits to patients.

KEYWORDS: Sustained Release ODT, Microencapsulation, Ion exchange resin, Pellet, Stimuli-response polymer, Diffucaps.

INTRODUCTION

Orodispersible tablets (ODT) are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue. Orodispersible tablets are also known as Mouth dissolving tablets, Melt in mouth, Orally disintegrating tablets, Fast dissolving drug delivery, Rapimelts tablets, Porous tablets & Quick dissolving tablets. Upon dissolving, ODT dispersion in the oral cavity facilitates pre-gastric absorption of drugs (buccal and pharyngeal cell uptake) and the avoidance of unwanted first-pass metabolism. Pre-gastric absorption reduces dosage requirements and is highly beneficial for drugs that undergo hepatic metabolism and drugs with active ingredients that produce toxic metabolites mediated by first-pass liver and gastric metabolism.

As per United state Pharmacopoeia and European Pharmacopoeia, an ODT must weigh not more than 500 mg and disintegrate in 2.0 mL of available saliva in less than 30 seconds (USP) or 180 seconds (EU), with friability equal to or less than 1.0%. Combining ODTs with specialized functional polymers and coating processes can lead to ODTs with sustained release profiles. goal of sustained release drug delivery systems is to provide the optimum dosage of a drug to reduce side effects and increase the patient compliance and increase efficacy, sustained release formulations enable less frequent dosing of drugs with short half-life.

About 35% of the general population and related with a number of disease conditions like-

1. Dysphagia.
2. Parkinsonism.
3. Motion sickness.
4. Mental disability.
5. Unconsciousness.
6. Unavailability of water etc.

To overcome such problems, new drug delivery systems, like Orodispersible tablets (ODT) having Sustained Release properties has been developed.

Need of sustained release ODT

Both the drug delivery system has their disadvantage. The sustained drug delivery has problem of choking and dysphagia. Whereas ODT has a problem of more frequent dosing of drug having short half life, and currently there is no ODT formulation that delivers the drug at sustained manner so this dosage form will help to overcome the problem related to both drug delivery system. As the drug get disintegrate in small swallowable particle avoiding the risk of choking & dysphagia. Then the polymer coated small particle will disintegrate in mouth releasing small microsphere that gives release for long period of time.

A) Requirement for sustained release ODT^[1,2]**A.1) API (Active Pharmaceutical Ingredient)**

1. Molecular weight should be less than 500 Dalton as more weight cause less diffusion of drug through membrane.
2. Half life should be less than 7 to 8 hr.
3. Dose size should be ≤ 100 mg.
4. Stable at water & saliva.
5. Size of microsphere or microcapsule should not be more than 300 μm .

A.2) Excipients

Drug having poor compressibility should be added into directly compressible excipient to formulate ODT. They

E.g.

Superdisintegrants	Mechanism of action	Commercially available grade
Crosslinked cellulose	Swelling and wicking.	Crosscarmellose [®] , solutab [®] , vivasol [®] .
Crosslinked PVP	Act by capillary action.	Crosspovidon M [®] , kollidon [®] , polyplasdone [®] .
Crosslinked starch (5-20%)	Swelling action.	Explotab [®] , Primogel [®] .
Calcium silicate	Wicking occur.	-
Crosslinked alginic acid	Swelling and wicking.	Algenic acid NF [®] .

A.2.b) Diluent

Diluents are the pharmaceutical inert ingredient that are needed for pharmaceutical preparations. Their range may vary from 5-80% in pharmaceutical formulation. They

E.g.

Diluents.	Use.	Side effect.
Sucrose	Sweetening agent	Dental caries.
Lactose	Act as filler or bulking agent.	Diarrhoea, headache, flatulence & stomach cramps.
Mannitol	Act as diluents in chewable & dispersible tablets	Allergic, hypersensitivity type reaction.
Polyethylene glycol	Act as inert ingredient	High dose cause teratogenicity
Calcium carbonate	Used in dental product	Constipation & loss of appetite

A.2.c) Glidants

Glidant are intended to promote the flow of tablet granulation and powder mixture from hopper to die cavity by reducing friction between them.

E.g. Talc (1-2%), colloidal silica (0.2%), Corn starch (5-10%).

A.3) Disintegration time

Property	Time (second)	Reference
Disintegration time	≤ 180 ≤ 30	European pharmacopoeia FDA & USP

A.a) Advantages^[1,3,4]

1. No or less need of water to swallow the tablet.
2. Can be easily administered to pediatric, elderly and mentally disabled patients.
3. No of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
4. Suitable for sustained/controlled release delivery.

should have good compressibility, flowability and plasticity(plasticizer).

A.2.a) Superdisintegrant

Superdisintegrants are the agent that added in the formulation to enhanced the breakdown of tablet into smaller fragment in an aqueous media. This allow quick dissolution of drug.

are added to the formulation to improve tablet properties like compression, flow ability, bulk of tablet and also to provide palatability.

5. Allows high drug loading.
6. Minimized systemic and local side effects.
7. Good drug utilization.
8. Decrease in amount of total dose of the drug.
9. Prevents fluctuation of plasma drug concentration in body.
10. Improved bioavailability of the drug.
11. Improved efficiency in treatment.
12. Improved patient compliance.
13. Easy taste masking.

A.b) Disadvantages

1. Dose dumping may occur.
2. More production cost.
3. More knowledge and skill person required.
4. The tablets may leave unpleasant taste in mouth if not formulated properly.

B) Formulation of sustained release ODT^[5,6]

When ODT's combined with specialized functional polymer and coating process it gives the sustained release of drug through ODTs. For formulating sustained

release ODTs first the drug is coated with rate controlling polymer. E.g. Ethyl cellulose, HPMC & Eudragits then formed microparticle or microcapsule is directly compressed with super disintegrant and other excipient. The formed tablet will rapidly disintegrate and microsphere or microparticle get easily swallow & release the drug in sustained manner.

B. a) Approaches to develop sustained release ODT

1. Microencapsulation.
2. Ion exchange resin.
3. Pellet.
4. Stimuli-response polymer.
5. Diffucaps.

1) Microencapsulation^[2,7]

Microencapsulation may be defined as the process of surrounding or enveloping one substance within another substance. It is the process in which small droplets of liquid or particles of solid material are coated by a continuous film of polymer or coating material.

1. a) Need of microencapsulation in sustained release ODT

1. Primary reason is for sustained & prolong release.
2. It helps to mask the taste of bitter drug.
3. Improve the stability of drug which are sensitive to oxygen, moisture & light.
4. Alteration in site of absorption.

1.b) Coating material^[19,20]

The release rate of drug from microcapsule is governed by the polymer used as a coating material. The selection of appropriate coating material helps to decide the physical and chemical properties of microcapsules/microspheres. The polymer should be capable of forming a film around core material.

1.c) Properties

1. It should be inert
2. It should be non-hygroscopic, tasteless & stable.
3. Film forming & pliable.

1. d) Example of coating material.

Water soluble: polyvinyl pyrrolidone, starch, hydroxyethyl cellulose, Methyl cellulose (MC), Polyvinyl alcohol (PVA) & Polyacrylic acid.

Water insoluble: Ethyl cellulose, cellulose nitrate, Silicones.

Waxes & lipids: paraffin, carnauba, steric acid & Glyceryl stearate.

1.e) Methods of microencapsulation

1. Spray drying
2. Pan coating
3. Solvent evaporation
4. Coacervation by phase separation

A) Spray drying^[4,16]

Spray drying used as a microencapsulation technique in this active material is dissolved or suspended in a melt (polymer) solution and becomes trapped in the dried particle. Spray drying involves dispersing the core material in a liquefied coating substance and spraying the core coating mixture into some environmental condition, whereby, relatively rapid solidification (and formation) of the coating is affected. Coating solidification in the case of spray drying is affected by rapid evaporation of a solvent in which the coating material is dissolved.

Microencapsulation by spray drying is done by dispersing a core material in a coating solution, in which the coating substance is dissolved and in which the core material is insoluble, then by atomizing the mixture into air stream. Which is usually heated, supplies the latent heat of vaporization required to remove the solvent from the coating material, thus forming the microencapsulated product.

A. a) Advantages

1. Low bulk density product.
2. Porous nature capsule form.
3. Free flowing particles formed.

B) Pan coating^[5,6]

Pan coating process is widely used in pharmaceutical industrial process for forming small particles. The particles are tumbled by using pan while the coating material applied slowly on core. The solid particles of greater than 600 µm in size are generally considered essential for effective coating. The coating is applied using atomized spray for desired solid core material in coating pan. To remove coating solvent warm air is passed over coating material.

B.a) Advantages

1. Most suitable for large particle coating.
2. Easy to handle.

B.b) Disadvantage

1. It is a time-consuming method.
2. High material loss during process.

C) Emulsion solvent evaporation^[1,5,6]

Emulsion solvent evaporation method is widely used and easy to perform.

It's generally consisting of two types i.e. Emulsion solvent evaporation & Emulsion solvent extraction/diffusion method.

C.a) Solvent evaporation

Emulsion maintained at reduced atmospheric pressure, and low agitation due to which solvent gets evaporated.

1. Aqueous solution of drug is prepared
2. Organic phase having polymer solution is added in solvent like chloroform with stirring.

3. Formed emulsion is added top large amount of emulsifier (PVA) to form multiple emulsion.
4. Emulsion is constantly stirred till organic solvent evaporated giving microspheres.
5. Microsphere collected & dried.

C.b) Solvent extraction

The procedure for solvent extraction is same but instead of drying the emulsion transferred to large quantity of water where solvent diffuses out forming microcapsules.

C.c) Procedure

The polymeric material is dissolved in volatile organic solvent. Then the drug which is to be encapsulated dissolve in organic solution to form emulsion, suspension or solution. Then the organic phase was emulsified under agitation in scattering phase consisting of non-solvent of polymer which was immiscible with the organic solvent that contain appropriate amount of surfactant. Then emulsion is agitate to evaporate organic solvent. Then formed microsphere is wash and allow to dry.

C.d) Advantages

1. Encapsulation of both hydrophilic & hydrophobic drug.
2. Simple & easy to perform.
3. Encapsulation of solid & liquid can be done.

D) Coacervation by phase separation^[2,5,18]

1. Formation of three immiscible phases; a liquid manufacturing phase, a core material phase and a coating material phase
2. Deposition of the liquid polymer coating on the core material
3. Rigidizing of the coating material.

Step-A: The first step of coacervation phase separation involves the formation of three immiscible phases:

- A) Liquid vehicle phase.
- B) Coating material phase.
- C) Core material phase.

The three phases are formed by dispersing the core material in a solution of coating polymer, the vehicle phase is used as a solvent for polymer. The coating material phase consists of a polymer in a liquid phase, is formed by using one of the of phase separation coacervation method, i.e. by changing the temperature of the polymer solution, or by inducing a polymer-polymer interaction.

Step-B: It involves the deposition of the liquid polymer coating on the core material. This is done by controlled mixing of core material and liquid coating material. The liquid coating polymer deposited on the core material if the polymer is adsorbed at the interface formed between the core material and liquid phase. The reduction in the total free interfacial energy of the system help to increase the deposition of the coating material, brought by the

decrease of the coating material surface area during coalescence of the liquid polymer droplets.

Step-C: In the last step rigidizing of the coating material done by cross linking desolvation techniques & the thermal. to forms a microcapsule.

e.g. Patil H. et.al formulate the sustained release ODT of domperidone using microencapsulation technique and polymer like Ethocel 10 & superdisintegrant like crosslinked PVP they manage to sustain the drug release for 9 hr.

2) Ion-exchange resins^[6,10,12]

There has been increasing use of ion exchange resins in producing sustained release (SR) systems because of the advantages that it gives. IERs are simple to prepare, as they are not affected by compression force and studies have demonstrated that there was no incidence of drug burst from the coated pellets even during cases of high drug loading.

IERs are water insoluble polymers that contain repeated units of acidic and basic functional groups of the polymer chain. These functional groups can form reversible weak ionic bonds with oppositely charged drug molecules. Such drugs are released from the resin by exchange with charged ions from the surrounding environment According to the nature of the exchangeable ion.

IERs has many applications in formulation since their introduction in the 1950s where IERs were used to stabilize sensitive drugs, in tablet disintegration mask bitter taste of drugs and control rate of drug release. IER are classified into cationic and anionic exchange resins.

E.g. A Complex formation between drugs and ion-exchange resins & the effects of coating by various aqueous polymeric dispersions on the complexes were evaluated for developing new sustained-release fast-disintegrating tablets (FDTs). Complexes of ion-exchange resin and dextromethorphan, a model drug, were prepared using different particle sizes of the resins. Aqueous colloidal dispersions of ethyl cellulose (EC) and poly (vinyl acetate) (Kollocoat SR30D) were used for fluid-bed coating, the coated particles were granulated with suitable tablet excipients and then compressed into the tablets.

2.a) Advantages^[22]

1. Simple method of formulation.
2. Drug loading is high.
3. No uncontrolled burst of drug due to drug & resin complex.
4. Economic and readily available.
5. Eliminate over and under dosing.
6. Drug-resinate can formulate in different dosage form such as tablets, capsule and suspension.

2.b) Clinical advantages

1. Improved patient compliance.
2. Reduced in drug toxicity.
3. Reduction in drug accumulation with chronic therapy.
4. Reduced drug level fluctuation in blood.

2.c) Disadvantages

1. Increase first pass metabolism.
2. Required additional patient education.
3. Cost of single unit is higher than conventional.

3) Pellet^[4,10,12,15]

When pellets coated with rate controlling polymer it gives sustained drug release. Coated micro pellets behave differently than powders under compression. Powders undergo will plastic deformation upon compression hence form strong compacts. Pellets due to their spherical shape undergo elastic deformation giving compacts of low mechanical strength.

E.g. G. Venkatesh et al., formulate sustained release pellets of melprone which were compressed into ODT.

3.A) Methods of pellet formulation^[21]**1) Extrusion spheronization**

It is a multistage process which involves following stages

- 1) Mixing of dry ingredient to achieve homogeneous powder dispersion.
- 2) Wet the mass to form a plastic mass.
- 3) Then wet mass is shaped into cylindrical segment of uniform diameter using extruder.
- 4) The spheronization stage at which the cylindrical mass rolled into sphere shape.
- 5) Finally drying of sphere & sieve to achieve uniform size.

2) Hot melt extrusion

It is a modified method of extrusion spheronization. In this drug and excipient converted into molten mass and subsequently shaped using appropriate equipment to provide solid sphere or pellet.

3) Other methods**A) Layering technique**

- a) Solution layering.
- b) Suspension layering.
- c) Dry powder layering.

B) Balling**C) Globulization**

- a) Spray drying.
- b) Spray congealing.

D) Cryopelletization.**3.a) Advantage**

1. Better flowability.
2. High drug loading capacity.
3. Dust free method.
4. Uniformity of dose.

3.b) Disadvantages

1. It is difficult to compress pellet into tablet due to their rigidity
2. They required highly sophisticated instrument hence increase in cost.

4) Diffucaps^[5,11]

Diffucaps technology involves

- 1) The preparation of drug containing core of immediate release pellet obtain by Layering drug on inert core or extrusion spheronization
- 2) Applying one or more coating with functional polymer
- 3) Combining one or more coated, spherical, multilayer bead into HPMC or blending with rapidly disintegrating granules & compressing it into ODT.

This technique is developed by Aptalis pharmaceutical. This technology of Aptalis use in the development of controlled-release delivery systems for once or twice daily dosing of single or drug combinations that exhibit extreme pH-dependent solubility profile.

4.a) Advantages

1. Useful for the drug having extreme pH dependent solubility.
2. Enhanced absorption of drug throughout GIT.

5) Stimuli responsive polymer^[7,14,17]

The research was performed for production of polymer which could be triggered by environmental changes & can cause change in polymer. These polymers known as stimuli sensitive polymer. Stimuli response polymers shows sharp change in their properties as small change in environmental condition, such as Temperature, Light, Salt Concentration and pH.

Their properties influence by environmental & physiological properties which includes

1. pH
2. Ionic strength
3. Temperature
4. Biological enzyme.

1) Thermo-responsive polymers

They response to change in temperature and their activity is based on very sensitive balance of hydrophilic & hydrophobic group. Polymer can show upper critical solution temperature (UCST) or lower critical solution temperature. (LCST) and below this temperature phase separation is observed.

E.g. poly (N-alkyl substituted acrylamides), poly(N-isopropylacrylamide), copolymers such as poly (L-lactic acid)-poly (ethylene glycol)-poly (L-lactic acid) (PLLA-PEG-PLLA) tri-block copolymers.

2) pH responsive polymers

pH-responsive polymers are affected by a change in the pH where it can trigger alterations in the polymer

structure. The main components of pH responsive polymers are ionizable weakly acidic or basic moieties. These groups, upon ionization produce electrostatic repulsions due to their anionic and cationic groups. This leads to a sudden chain extension.

E.g. Chitosan, polyacrylic acid, albumin etc.

The combination of thermo-responsive monomer like NIPAM with one of pH-responsive monomer gives double-responsive copolymers.

Marketed formulation^[13]

1. Extended-Release Methylphenidate Orally Disintegrating Tablets

Extended-release methylphenidate products, the ODT formulation provides 12 hours of symptom control, giving patients a once-daily dosing in a formulation that does not require swallowing a large tablet or capsule.

In June 2016, Neos Therapeutics received approval from the Food and Drug Administration for their mixed amphetamine salts ODT (Adzenys XR-ODT™). Their extended release ODT formulation of methylphenidate, Cotempla XR-ODT®, was approved on June 20, 2017 for the management of ADHD in children and adolescents from 6 to 17 years of age.

CONCLUSION

Pharmaceutical formulators and manufacturers are continuously seeking to improve and simplify drug delivery. For the patients like pediatrics, geriatrics, and patients suffering from dysphasia and unconsciousness. The fast-dissolving dosage form is the best option for those patient. Current sustained-release technologies incorporated into an ODT to provide a better therapeutic value, by reducing the need for multiple daily doses and improving patient compliance. Several technologies such as stimuli-responsive polymers, ion-exchange resins and lipospheres have emerged to produce better sustained release orally disintegrating tablets (SR-ODT).

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