Review: ODT's drug containing Spironolactone

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ABSTRACT

Orally disintegrating tablets (ODTs) have emerged as one of the popular and widely accepted dosage forms, especially for the pediatric and geriatric patients. To obviate the problem of dysphagia and to improve patient compliance, ODTs have gained considerable attention as preferred alternatives to conventional tablet and capsule formulations In the present study, an attempt has been made to prepare orally disintegrating tablet of the drug Spironolactone using superdisintegrants crosspovidone, crosscarmellose sodium and sodium starch glycolate by direct compression technique. Various scientific techniques including freeze drying, moulding, spray drying, sublimation, direct compression, cotton candy process, mass extrusion, melt granulation etc. have been employed for the development of ODTs. The prepared tablets were evaluated for pre and post compression parameters i.e. angle of repose, car's index, hausner's ratio, hardness, friability, wetting time, weight variation, *in vitro* disintegration and *in vitro* dissolution study.

Keywords: Orally disintegration tablets, Spironolactone, Superdisintegrants, Enhanced bioavailability.

Introduction

There are many patients of different age groups complaint of some solid conventional dosage forms such as tablets and capsules due to difficulty in swallowing[1]. In order to overcome this problem and improve patient acceptance and compliance, the development of solid dosage forms that disintegrated rapidly or dissolve even when taken orally without water[2]. The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30-50 s after administration[3]. The solution containing the active ingredients is swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect. Tablet is the most widely used dosage form because it's taken easily in term of self-administration, compactness and no difficulty in manufacturing[4]. The basic approach to the development of ODTs is the use of superdisintegrants such as Crosscarmellose sodium, Crosspovidone and Sodium starch glycolate.

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (To accommodate various types of drug candidates) and most importantly, patient compliance.

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Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture.

Spironolactone is a potassium-sparing diuretic (water pill) that prevents your body from absorbing too much salt and keeps your potassium levels from getting too low. Spironolactone is used to diagnose or treat a condition in which you have too much aldosterone in your body.

Important ingredients that are used in the formulation of ODTs should allow quick release of the drug, resulting in faster dissolution. This includes both the pharmacologically active ingredients (drug) and the excipients (additives).

Selection of drug candidate

Several factors may be considered while selecting an appropriate drug candidate for development of orally disintegrating tablets. The ultimate characteristics of a drug for dissolution in mouth and pregastric absorption from fast dissolving tablets include.

1. Free from bitter taste
2. Dose lower than 20mg
3. Small to moderate molecular weight
4. Good solubility in water and saliva
5. Partially unionized at oral cavity pH
6. Ability to diffuse and partition in to the epithelium of upper GIT (log >1, or preferably>2)
7. Ability to permeate oral mucosal tissue.

There are no particular limitations as long as it is a substance which is used as a pharmaceutical active ingredient. Researchers have formulated ODT for various categories of drugs used for therapy in which rapid peak plasma concentration is required to achieve the desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, antiallergic, anti-epileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction.

In contrast, the following characteristics may render unsuitable for delivery as an orally disintegrating tablet:-

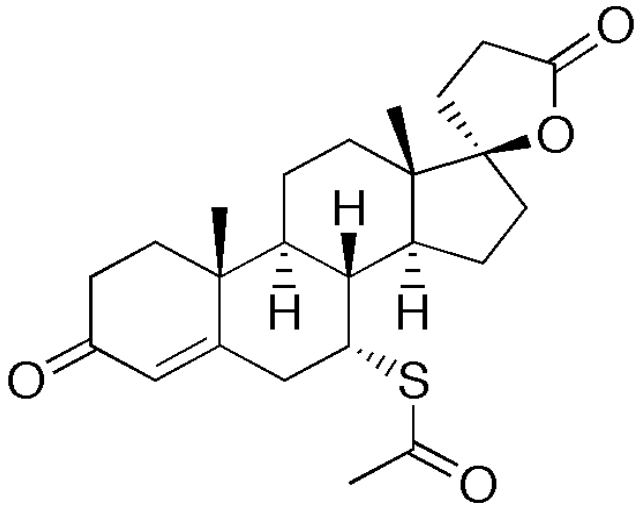
1. Short half life and frequent dosing.
2. Very bitter or otherwise unacceptable taste because taste masking cannot be successfully achieved.
3. Require controlled or sustained release.
4. Combination with anticholinergics.

Selection of excepient

Mainly seen excipients in ODT are as follows at least one disintegrant, a diluent, a lubricant, and optionally, a swelling agent, sweeteners, and flavoring agents etc. Ideal bulk excipients for orally disintegrating dosage forms should have the following properties :

1. Disperses and dissolves in the mouth within a few seconds without leaving any residue.
2. Masks the drug's offensive taste and offers a pleasant mouth feel.
3. Enables sufficient drug loading and remains relatively unaffected by changes in humidity or temperature.

The role of excipients is important in the formulation of fast-melting tablets. The temperature of the excipients should be preferably around 30–350C for faster melting properties.



Structure of SPIRONOLACTONE

Techniques for preparation of ODTs:

The fast dissolving property of the ODTs requires quick ingress of water into tablet matrix thus requires some basic approaches such as maximizing the porous structure of the tablet, incorporation of suitable disintegrating agent and use of highly water-soluble excipients in the formulation. Excipients use in ODTs contain at least one superdisintegrant (having mecnanism of wicking, swelling or both), a diluent, a lubricant and optionally a swelling agent, a permeabilizing agent, sweeteners and flavorings.

Important criteria for excipients would be used in the formulation of ODTs can be identified as ability of disintegrates quickly, not interfere in the efficacy and organoleptic properties of the ODTs due to individual properties, not interact with drug and other excipients, do not negatively affect the desired final integrity and stability of the product and having melting points of range between 30-350C.[2] Type, examples and amounts in general use of various excipients are presented in **Table 2.**

Table 2: Type, examples and range in use (% in weight) of various excepient use in ODTs

Type of the Excipients	Examples	% (w)
Superdisintegrants 15%	Croscarmellose sodium, Crospovidone, Sodium starch glycolate, Microcrystalline cellulose, Carboxy methyl cellulose, Modified corn starch, Polacrilin potassium, etc.	1-
Binder 10%	Polyvinylprolidone, Polyvinylalchol, Hydroxy propyl methylcellulose, etc.	5-
Antistatic agent 10%	Sodiumlaurlysulfate, Sodiumdoecylsulfate, Polyoxyethylene sorbitan fatty acid esters, Polyoxyethylene steartes, etc.	0-
Diluents 85%	Mannitol, Sorbitol, Xylitol, Calcium carbonate, Magnesium carbonate, Calcium sulfate, Magnesium trisilicate, etc.	0-

Superdisintegrants can be classified as synthetic, natural and co-processed.

1.**Synthetic superdisintegrants**: Sodium starch glycolate, croscarmellose sodium, cross-linked polyvinylpyrrolidone, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, partially pregelatinized starch, cross-linked alginic acid and modified resin[3].

2. **Natural superdisintegrants**: Mucilages and gums are obtained from plants can be exemplified with Lepidium sativum seed mucilage, Plantago ovata seed mucilage, Trigonella foenum-graceum seed mucilage, Hibiscus rosa-sinesis linn. mucilage, Ocimum americanum seed mucilage, Aloe barbadensis Miller mucilage, Linum usitatissimum seed mucilage, Cucurbita maxima pulp powder, Banana powder, Gellan gum, Locust bean gum, Xanthan gum, Guar Gums, Gum Karaya, Cassia fistula seed gum, Mangifera indica gum, Agar from Gelidium amansii and other red algaes, Soy polysaccharide and Chitosan.

3. **Co-processing**: Co-processing is the novel concept in which two or more excipients are incorporate to improve their individual properties and obtain a superdisintegrant. Ran Explo-S TM (microcrystalline cellulose, silica and sodium starch glycolate), PanExcea MH300GTM (microcrystalline cellulose, hydroxylpropyl- methyl cellulose and crospovidone), etc are some commercial and complexation of chitosan and alginate, combination of croscarmellose sodium and crospovidone and corporation of rice starch: PEG 1500: Aerosil are some latest research examples of coprocessed superdisintegrants.[5]

Various preparation **techniques** have been developed on the basis of different principles, thus present different properties of ODTs by means of mechanical strength, stability, mouth feel, and taste, swallow ability, dissolution profile and bioavailability.

Freeze drying/ Lyophilization

This process is based on solvent removal from a frozen drug solution or suspension which contains structure forming excipients. The process generally resulted as very light and highly porous form in nature.

Spray drying

This process is based upon to use of a particulate support matrix prepared by spray drying. Support matrix and other components containing aqueous composition form a highly porous and fine powder, and then disintegration and dissolution improve by adding effervescent components and finally spray dried to yield a porous powder.

Molding

This process is achieved by using water soluble ingredients mostly sugars. Drug and excipients powder blend is pushed through a very fine screen then moistened with a hydroalcoholic solvent and moulded into tablets under pressure, the process ended by evaporating of the solvent by air drying.

Phase transition process

In this process, tablets which contain sugar alcohols having high and low melting points are prepared by

compressing; following heating to enhance bonding among particles resulted as sufficient hardness of tablets.

Melt granulation
In this process powders are efficiently agglomerated by the use of binder which can be liquid or melting during the process by using high shear mixers, and temperature is raised above the melting point of the binder.

Sublimation
For accomplishing this process some inert volatile substances like urea, camphor etc. is added to other tablet excipients and blend is compressed into tablet. Subsequently removal of volatile substances by sublimation generates a porous structure.

Mass extrusion
This process based on softening of the active blend by using a solvent mixture of water soluble polyethylene glycol and methanol. Following expulsion of softened mass through the extruder or syringe to get a cylindrical shaped, they cut into segments by using heated blade to form tablets.

Cotton candy process
This process based on formation of matrix of polysaccharides or saccharides which are partially recrystallized and attain better flow properties and compressibility by concurrent action of flash melting and spinning. Then matrix is milled and blended with active ingredients and excipients, soon after compressed to form tablets .

Direct compression
The basic principle of this technique is addition of superdisintegrants in optimum concentrations to tablet formulation in which powdered blend compress directly to form tablets. In the light of developments in ODTs domain, new patent applications have been done and various recent patents in the field of ODTs.

EVALUATION OF ODTs
Evaluation parameters of tablets mentioned in the Pharmacopoeias need to be assessed, along with some special tests. The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulation and process variables involved in mixing and all these can affect the characteristics of blends produced.

A. **Evaluation of blends before compression**

The various characteristics of blends to be tested before compression are

Angle of repose
Angle of repose is determined by using funnel method. The accurately weighed blend is taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug (as solid dispersion)-excipient blend is allow to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

$$\text{Tan } \Theta = h/r$$

Where h and r are the height of cone and radius cone base respectively. Angle of Repose less than 30 ° shows the free flowing of the material.

Bulk density:
Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight. Bulk density can be calculated by using following formula:

Bulk density = Weight of the powder / Volume of the packing.

Tapped density:
It is determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping is continued until no further change in volume is noted. Tapped density can be calculated by using following formula:

Tapped Density = (Weight of the powder / volume of the tapped packing)

Compressibility index
The Compressibility Index of the blends is determined by compressibility index. Compressibility Index can be calculated by using following formula:

Compressibility Index (%) = [(TD-BD) X 100] / TD]

Hausner's ratio
A similar index to indicate the flow properties can be defined by Hausner's ratio. Hausner's ratio can be calculated by using following formula:

Hausner's ratio = (Tapped density x 100)/ (Poured density)

Void Volume: The volume of the spaces is known as the void volume "V" (Yoshio .et al) and is given by the formula

$$V = Vb - Vp$$

Where, Vb = Bulk volume (volume before tapping)
Vp = True volume (volume after tapping)

Porosity

The porosity € of powder is defined as the ratio of void volume to the bulk volume of the packaging. The porosity of the powder is given by following formula:

$$€ = Vb – Vp / Vp = 1- Vp/Vb$$

Porosity is frequently expressed in percentage and is given as:

$$\%€ = (1 – Vp / Vb) X 100$$

The porosity of powder indicates the types of packaging a powder undergoes when subject to vibrations, when stored, or in tablet machine when passed through hopper or feed frame.

B. Evaluation of Tablets

All the formulated ODTs were subjected to the following quality control tests):

Weight variation

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation. Table 9 depicted USP Specification for uniformity of weight.

Hardness

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester etc.

Friability test

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of the tablets. Weigh the 20 tablets from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes. Dedust the all tablets and weigh again. The percentage of friability can be calculated using the formula

$$\% \text{ Friability} = [(W1-W2)100]/W1$$

Where, W1= Weight of tablet before test, W2 = Weight of tablet after test

Disintegration test

The USP disintegration apparatus contains six glass tubes that are “3 long, open at the top, and held against 10” screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 2 °C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Mechanical strength

Tablets should possess adequate mechanical strength to bear shocks of handling in manufacturing, packaging and shipping. Crushing strength and friability are two important parameters for the determination of mechanical strength. Crushing Strength or Tablet Tensile strength is the force required to break a tablet by compression in the radial direction, it is important to note that excessive crushing strength significantly reduces the disintegration time. The crushing strength of the tablet is measured by using Pfizer hardness testers. Tensile strength for crushing (T) is calculated using equation

$$T = 2F / \pi*d*t$$

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet respectively.

Uniformity of dispersion

Keep the Two tablets in 100ml water and stir gently for 2 minutes. The dispersion is passed through 22 meshes. The tablets will consider passing the test if no residue remained on the screen.

Wetting time

The wetting time of the tablets is measure by using a simple procedure. Place the five circular tissue papers of 10 cm diameter in a petridish containing 0.2% w/v solution (3ml). A tablet is carefully placed on the surface of the tissue paper. The time require for develop blue color on the upper surface of the tablet is noted as the wetting time.

Water absorption ratio

A small piece of tissue paper folded twice is placed in a small petridish containing 6 ml of water. Put a tablet on the paper and the time required for complete wetting is measured. The wetted tablet is then reweighed. Water absorption ratio, R is determine by using following formula

R= 100 x Wa-Wb / Wb

Where, Wb is the weight of tablet before water absorption
Wa is the weight of tablet after water absorption

Taste/ Mouth sensation: Mouth-feel is critical, and patients should receive a product that feels pleasant. One tablet from each batch is tested for the sensation by placing the tablet on the tongue. The healthy human volunteers are used for evaluation of mouth feel. Taste evaluation is done by a panel of 5 members using time intensity method. Sample equivalent to 40 mg i.e. dose of drug is put in mouth for 10 seconds and record taste instantly and then after 10 secs, 1, 2, 4 and 6 minutes. Volunteer's opinion for the taste is rated by giving different score values i.e. 0 = good, 1 = tasteless, 2 = slightly bitter, 3 = bitter, 4 = awful.

***In -Vitro* disintegration test**

In-vitro disintegration time is measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation are randomly selected and *In Vitro* dispersion time is carried out.

***In-Vivo* disintegration test**

The test is carried out on 2 or 3 tablets in the mouth and the time in second taken for complete disintegration of the tablet is measured.

***In-Vitro* dissolution test**

In-vitro dissolution study is performed by using USP Type II Apparatus (Paddle type) at 50 rpm. Phosphate buffer pH 6.8, 900 ml is used as dissolution medium which maintained at 37±0.5℃. Withdraw aliquot of dissolution medium (10 ml) at specific time intervals (2 min) and filter. The amount of drug dissolved is determined by suitable analytical technique.

Stability Studies

The optimized formulation of ODTs is subjected to stability study as per ICH guidelines to assess their stability with respect to their physical appearance and release characteristics.

Conclusion

ODTs offer numerous significant advantages over conventional dosage forms because of improved efficacy, bioavailability, rapid onset of action, better patient compliance and acceptance. Pediatric and geriatric patients are primary concerns, as both the groups find these dosage forms convenient to administer as compared to the conventional dosage forms. As a conclusion ODTs presenting many pharmaceutical and clinical advantages including availability of the oral delivery of protein and peptide-based active agents, improved efficacy, improved safety and commercial advantages including enlarged product diversity, extended patent life.

Source of Support: Nil
Conflict of Interest: None

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