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# Pregelatinized hydroxypropyl pea starch as matrix forming material for lyophilized orodispersible tablets of tadalafil

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ABSTRACT

Oral fast-disintegrating dosage forms, also known as 'fast-disintegrating' or 'fast-dissolving' dosage forms, are a relativelynovel dosage technology that involves the rapid disintegration or dissolution of the dosage form. The objective of present study was to demonstrate pregelatinized hydroxypropyl pea starch as promising soluble matrix forming material in the preparation of orodispersible tablets (ODT) that was easy to administer and provides rapid release of the drug. The ODT was prepared by lyophilizing an aqueous dispersion of tadalafil containing modified pea starch. ODTs were investigated for tablet characteristics including dimensions, hardness, friability, *in vitro* dissolution and *in vitro/in vivo* disintegration time. The best properties exibhited by OTD are wetting time 13.5 ± 1.2 s, disintegration time of 16.6 ± 0.8 s. Results obtained from dissolution studies showed that ODT of tadalafil significantly improved the dissolution rate of the drug compared with the native drug. More than 75% of tadalafil in ODT dissolved within 1 min compared to only 30% of tadalafil native drug dissolved during 60 s. In conclusion the formation of stable and strong lyophilized orodispersible tablet using pregelatinized hydroxypropyl pea starch as sole matrix excipient is investigated. This study suggests that pregelatinized hydroxypropyl pea starch can act as a potential matrix forming material for oral drug delivery.



## 1. Introduction

Oral rapid dissolving dosage forms, also term as fast-melt, fast-disintegrating or fast-dissolving, that are novel dosage forms that involves the rapid disintegration or dissolution of the system, being it is the most common dosage form (i.e. tablet) goes into a solution or suspension in the mouth without the need for water. The dosage form starts to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within few seconds after administration [5,14]. The active ingredient absorbed and provides desired response immediately after the solution containing the active ingredients is swallowed. Among the different approaches for orodispersible tablets lyophilized tablets have been the most widely used because of the simple and low-cost manufacturing process. A variety of polymers are employed as matrix-forming excipients whose characteristics may play a key role and significantly influence the performance of these dosage forms. A promising formulation of a lyophilized tablet were made only of maltodextrin or gelatin [12]. Several ODTS patented technologies like Orosolv, Durasolv, Flash Dose, Flashtab, Wow tab, and Zydis are successful commercially [13]. Numberous lyophilized tablets available in the market. viz: Grazax® and Claritin® (Catalent), Proxalyoc and Loperamide Lyoc® (Cephalon), Remeron Soltab Zomig-ZMT®(CIMA Labs)and Felden® Flash (piroxicam, Pfiser Inc., NY) [12].

Starches are natural polymeric materials having extensive pharmaceutical application such as fillers, binders and disintegrants due to their low cost, non-toxicity and biodegradability [6,7,15]. Recently, new generation of pregelatinized hydoxypropyl soluble starches having optimal amylose: amylopectin ratio (35: 65) has been introduced. These polymers were demonstrated as excellent film forming agent.

In this study chemically modified pregelatinized hydroxypropyl pea starch (Lycoat RS720®) by etherification with the reagent propylene oxide was used as a matrix former for the preparation of ODT using the freeze drying technique will be evaluated. Pregelatinized hydroxypropyl pea starch give up thinned starch with lower viscosity on partially hydrolysing using acids or enzymes. Lycoat RS720 undiformely disperses in cold water and simple heating up to 70° C will develop film forming ability. Due to

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hydroxypropylation solution does not form gelation on cooling (no retrogradation and high stability). Lycoat RS720® specifically developed for the aqueous film coating for immediate release, solid oral dosage forms [10].

Tadalafil was selected as a model drug. Tadalafil is a cyclic guanosine monophosphate (cGMP) specific Type V phosphodiesterase (PDE5) inhibitor for treating erectile dysfunction (ED). Almost half of elderly population above age 75 experience erectile dysfunction [2]. Elderly individuals those with dysphasia have problems in taking medications prescribed in tablet and capsule form. Hence the lyophilized oral dispersible tablet may provide suitable dosage form that is easy to swallow for elderly patients.

This study aims to fabricate and optimise ODTs prepared by freeze drying using modified pregelatinized hydroxypropyl pea starch that not only have sufficient mechanical strength/hardness to withstand manual handling, but also have a rapid disintegration time.

## 2. Materials and methods

### 2.1. Materials

Pregelatinized hydroxypropyl pea starch (Lycoat RS720®) (35.0% of amylose and 65% of amylopectin, Low viscosity grade) was kindly supplied by Roquette Pharma, Mumbai. Tadalafil and flavor (Mix fruit)were gifted by Ajanta Pharmaceuticals, Mumbai. Mannitol was purchased form Lab India. All other chemicals were reagent grade and used as received.

### 2.2. Methods

#### 2.2.1. Preparation of ODTs

Tadalafil ODTs were prepared using pregelatinized hydroxypropyl pea starch (Lycoat RS720®) as a matrix former. The Lycoat RS720® concentration (1%) was selected based on preliminary trials as suitable concentrations for the preparation of lyophilized tablets. Lycoat RS720® and mannitol (0.5%) were first dissolved in distilled water using a magnetic stirrer to obtain the required concentration, and then an accurately weighed amount of tadalafil powder was dispersed in the prepared aqueous solution using a magnetic stirrer to result in a dose of 2.5 mg tdalafil. Magnesium stearate and flavour added to above solution. Then 1 ml resultant solution was then poured in each pocket of a poly vinyl chloride (PVC) blister pack having a diameter of 13 mm and a depth of 3 mm. The tablet blister packs were frozen at −22 °C for 24 h, and then placed in a lyophilizer (Vir-Tis Benchtop, SP Scientific, Warminster, PA) at process conditions: Condensor Temp −45 °C and vaccum < 100 mT.

### 2.3. Characterization of ODTs

#### 2.3.1. General appearance

The general appearance of oral dispersible tablet dosage form and its aesthetic values are of prime importance. Thus, 20 tablets were evaluated for various attributes *viz.* tablet's size, shape, colour, presence or absence of any odor, physical flaws, diameter and thickness was examined using vernier calliper.

#### 2.3.2. Organoleptic evaluation of ODTs in human volunteers

Organoleptic property was conducted on 12 healthy adult human subjects, in the age group of 22–26 years to evaluate taste, palatability of formulation. The gustatory sensation tests, intensity scores were usually applied for overall palatability, for components of palatability (1-good aftertaste) and for the four basic tastes (2-sweetness, 3- saltiness, 4- sourness and 5-bitterness) [9].

#### 2.3.3. Uniformity of weight

The uniformity of weight test was performed as specification given in European pharmacopoeia [8]. Twenty tablets were individually weighed and the average of tablet weights was calculated. Results are presented as the percent relative standard deviation (% RSD) of the tablet mass.

#### 2.3.4. Tablet friability

The tablet friability test was done according to European Pharmacopoeia (8th edition) specifications [8]. Twenty tablets were accurately weighed and placed in the drum of friabilator (Electro lab, India). The tablets were rotated at 25 rpm for a period of 4 min and then removed, dedusted and accurately reweighed. The percentage loss in weight was calculated and taken as a measure of friability.

#### 2.3.5. Wetting time measurement

The wetting times were measured according to the following method. Briefly, tissue papers folded twice to simulate the tongue conditions were placed in a petri dish with a 10-cm diameter. Ten millilitres of water containing amaranth, a water-soluble dye, was added to the petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for colored water to reach the upper surface of the tablets was noted as the wetting time [4].

#### 2.3.6. In vitro disintegration time

In vitro disintegration times of the prepared ODTs were determined using a disintegration tester (Electro lab, India) with six tablets in distilled water kept at 37 ± 0.5 °C according to EP (8th edition) specifications [8]. The disintegration time is the time required for the ODT to completely disintegrate until no solid residue remains or only a trace amount of soft residue remains on the screen of disintegration test apparatus. A digital stopwatch was used to measure the disintegration time to the nearest second. All results are presented as mean value ± SD ($n = 3$).

#### 2.3.7. In vivo disintegration time

The *in vivo* disintegration time of each of the prepared ODTs was evaluated in six human volunteers after getting informed written consent. All volunteers were instructed to clean their mouth with distilled water before commencing the test. Each of the six subjects was administered a coded tablet. Tablets were placed on the tongue and immediately the disintegration time was recorded. The subjects were informed to spit out the tablet residue of the oral cavity after disintegration and rinse their mouth with distilled water. They were also instructed not to swallow the saliva during the test and also saliva rinsed from the mouth after each measurement. The test results are presented as mean value ± SD ($n = 3$) [1].

### 2.4. Drug content

Twenty tablets were weighed and powder equivalent to 2.5 gm was dissolved in 70 ml methanol and was further diluted up to 100 ml using distilled water. This stock solution was carefully filtered and 0.1 ml of this was diluted to 10 ml and absorbance was recorded at 284 nm using UV Visible double beam spectrophotometer (Shimadzu model, 1700).

### 2.5. Dissolution studies

The dissolution profiles of tadalafil lyophilized tablets compared with the native drug were determined using a dissolution tester (Tablet Dissolution Tester, Electro lab India) following the USP paddle method. Test was perform in 900 ml of phosphate buffer (pH 6.6) maintained at 37 ± 0.5 °C with a paddle rotation speed at