Journal of Pharmaceutical and Scientific Innovation

www.jpsionline.com (ISSN : 2277 -4572)

Research Article

PREPARATION AND EVALUATION OF ORALLY DISINTEGRABLE TABLETS USING *BORASSUS FLABELLIFER* STARCH, *IPOMEA BATATAS* STARCH AND THEIR MODIFIED FORM AS SUPERDISINTEGRANT

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DOI: 10.7897/2277-4572.06143

Received on: 25/12/16 Revised on: 04/03/17 Accepted on: 10/3/17

ABSTRACT

The objective of the study was to prepare and evaluate orally disintegrable tablets of olanzapine using *Borassus flabellifer* starch and *Ipomea batatas* starch for its superdisintegrant activity. The starches were modified using phosphorylation method with disodium hydrogen orthophosphate anhydrous. DSC analysis revealed that there was no interaction between olanzapine and excipients used in the tablet formulations. Pre-compression parameters were conducted for all formulations blend and were found to be satisfactory. Different concentrations of 3% to 10% of starches were used in the formulation to study the improvement in the ODT parameters. The optimized formulation was compared for its super disintegrant activity with spray dried lactose as diluent and the results were compared but not significantly different. Modified *Ipomea batatas* starch showed better DT of 16 & 19 seconds (9% and 10%) respectively in comparison to unmodified *ipomea* starch showed DT of 33 & 45 seconds (9% and 10%) which mean that there is no significant change in DT and no use of modification of starch. The modified *borassus* starch showed better DT of 20 & 22 seconds (9% & 10%) respectively in comparison to unmodified *borassus* starch showed DT of 99 & 115 seconds (9% & 10%) which was significantly different & here the modification of starch was useful to improve disintegration time. The dissolution parameters of all formulations did not show any significant difference in release profile. The formulations were optimized using ODT parameters such as disintegration time, wetting time, water absorption ratio and other physiochemical evaluation parameters. To conclude, *Ipomea batatas* starch in higher concentration (9% & 10%) can be used as supredisintegrant without any modification unlike *Borassus flabellifer* starch which needs modification to set superdisintegrant activity.

Keywords: Orally disintegrable tablets, olanzapine, super disintegrants, *Borassus flabellifer* starch, *Ipomea batatas* starch.

INTRODUCTION

Schizophrenia is a mental disorder often characterized by abnormal social behavior and failure to recognize what is real. Common symptoms include false beliefs, unclear or confused thinking, auditory hallucinations, reduced social engagement and emotional expression, and inactivity.

Symptoms begin typically in young adulthood, and about 0.3–0.7% of people are affected during their lifetime. The disorder is thought to mainly affect the ability to think, but it also usually contributes to chronic problems with behavior and emotion. People with schizophrenia are likely to have additional conditions, including major depression and anxiety disorders; the lifetime occurrence of substance use disorder is almost 50%. prognosis is based on observed behavior and the person's reported experiences *(Wikipedia 2015)*.

Medications are used for the treatment of acute episodes, prevention of relapses and recurrences, and improvement of symptoms in the interim. Antipsychotic agents are the mainstay of treatment with antidepressants, mood stabilizers or benzodiazepines being useful adjuncts.

Over the past decades, there has been an increased research for novel drug delivery systems (NDDS) to improve safety, efficacy and patient compliance. The discovery of new chemical entity is highly expensive and time consuming, hence pharmaceutical industries are focusing on the design and development of new drug delivery systems for existing drugs leading to better bioavailability, reduced adverse effects and with more patient compliance are very important aspect when considered a formulation of NDDS.

One of such novel technologies is oral disintegrating tablet. This dosage form provides a convenient means of administration of drugs.

In the present study superdisintegrants such as *Burassus flabellifer*, *Ipomea batatas* starch and their modified forms starch should be used to prepare orodispersible tablets of Olanzepine. Excipients such as PVP K-30, lactose, spray dried lactose and should be used in different concentrations to study its effect on ODT parameters.

MATERIALS AND METHODS

Olanzapine was gift sample from RA Chem Pharma Ltd, Hyderabad. *Borassus flabellifer* starch, *Ipomea batatas* starch, Lactose, PVP K.30 from Yarrow Chem. Products, PVP K.30 from Corel Pharma Chem Ltd, Spray dried lactose and Magnesium stearate were purchased from SD Fine-Chem. Limited, India. All the reagents and chemicals used were of analytical grade.

Modification of starch

Preparation of starch phosphate

Starch phosphate was prepared based on the method of Choi *et al* with some modifications. *Borassus flabellifer* (100 g) and di-

sodium hydrogen orthophosphate anhydrous (30 g) were suspended in 100 ml of water and continuously stirred for 20 min. This starch slurry was then filtered and the wet starch mixture was conditioned for 12 h at room temperature (28°C). To enhance phosphorylation, this mixture was heated in a forced air oven at 130°C for 3 h. The product obtained was ground and sized *(Jubril I et al., 2012)*.

Analytical methodology

Standard curve of olanzapine, compendial media of in 6.8 pH buffer was performed to quantify the samples. All the solutions were prepared in fresh before use.

Table 1: Formulation design of tablets

Formulation/ ingredients	F2	F3	F4	F5	F6	F7	F8	F9
	mg							
Olanzapine	10	10	10	10	10	10	10	10
Lactose/ spray dried lactose	37	36.5	36	35.5	35	34.5	34	33.5
Borassus/ ipomea starch (modified/ unmodified)	1.5	2	2.5	3	3.5	4	4.5	5
PVP K-30	1	1	1	1	1	1	1	1
Talc	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Magnesium stearate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Total weight	50	50	50	50	50	50	50	50

Note: F2= starch conc. of 3% to F9= starch conc. of 10%.

Comparative evaluation of optimized formulation with formulation prepared lactose and spray dried lactose.

Comparative evaluations of optimized formulations were compared with formulation prepared with lactose & spray dried lactose *(Mahaveer Khinchi PR et al., 2011)*.

Preparation method for olanzapine oral disintegrable tablets

Uniformly mixed blend was compressed into tablets containing 10mg drug using 4.70mm flat face surface punches on a Rimek-1 rotary tablet machine by direct compression method. Total weight of tablet was kept 50mg.

Evaluation of oral disintegrable tablets

The prepared tablets can be evaluated for various parameters (Shyamala et al, 2002, Bradoo et al 2001, & Makino et al, 1993).

Weight variation

Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated.

Thickness

The thickness of tablet is measured by screw gauge. The thickness of the tablet is related to the tablet hardness. Tablet thickness should be controlled within a ± 5% variation of a standard value. In addition, thickness must be controlled to facilitate packaging. The thickness in millimeters (mm) was measured individually for 10 pre-weighed tablets by using screw gauge. The average thickness and standard deviation were reported.

Hardness

The tablet strength is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester). Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability

Friability of the tablets was determined using Roche friabilator (Electrolab, India). This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. Preweighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula.

$$F\ \% = (1 - W_0 / W) \times 100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test

Wetting time

Five circular tissue papers of 10-cm diameter were placed in a petri dish with a 10-cm diameter. 10 ml of water at 37°C±0.5°C containing eosin, a water-soluble dye, was added to the petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average reading noted.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed.

Water absorption ratio R, was determined using following equation.

$$R = W_a - W_b / W_b \times 100$$

Where W_a = weight of tablet after absorption,
W_b = weight of tablet before absorption

Disintegration time

Disintegration time was measured using a modified disintegration method. For this purpose, a Petri dish was filled with 10 ml of water at 37°C±0.5°C. The tablet was carefully put in the centre of the petridish and the time for the tablet to completely disintegrate into fine particles was noted.

Content uniformity

20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 5mg was weighed and dissolved in 100 ml of phosphate buffer pH 6.8, filtered and drug content analyzed spectrophotometrically at 258 nm.

***In-vitro* release**

In-vitro drug release of oral disintegrable tablets was determined using USP dissolution apparatus II (Paddle type) (Electrolab TDT-08L). The dissolution test was performed using 900 ml 6.8 pH buffer at 37°C ± 0.5°C. The speed of rotation of paddle was set at 75 rpm. 5 ml samples were withdrawn at time points of 1, 3, 5, 7, 10, 12 min and same volume was replaced with fresh media. Absorbance of solution was checked by UV spectrophotometer (ELICO- 164 double beam spectrophotometer, Hyderabad, India) at a wavelength of 258 nm and drug release was determined from standard curve.

Accelerated stability studies

The optimized formulation was subjected to stability studies at 40°C±2°C/75%±2% RH for period of one month. Each tablet was individually wrapped in aluminum foil and packed in ambered colored bottle and put at above specified condition in a heating humidity chamber for one month. The tablets were analyzed for the hardness, disintegration time, drug content and *in-vitro* drug release.

RESULTS AND DISCUSSION

Thermal analysis by DSC

The physical nature of the drug, polymer and optimized formulations were studied by DSC. DSC analysis was performed using Shimadzu DSC-60 differential scanning calorimeter (DSC). The instrument was calibrated with indium standard. 3-5 mg samples were weighed and placed in a closed, hermetic sample pans with pin hole. Thermo grams were obtained by heating the sample at a constant rate 10°C /min. A dry purge of nitrogen gas (50 ml/min) was used for all runs. Samples were heated from 0°C to 350.0°C. The melting point, heat of fusion, disappearance of the crystalline sharp peak of the drug and appearance of any new peak and peak shape were noted**.** DSC of the pure drug showed a sharp peak at 195.7ºC. DSC of drug with excipients showed peak characteristic of the drug with no additional peaks. From DSC, it can be concluded that the drug and carrier showed no interaction.

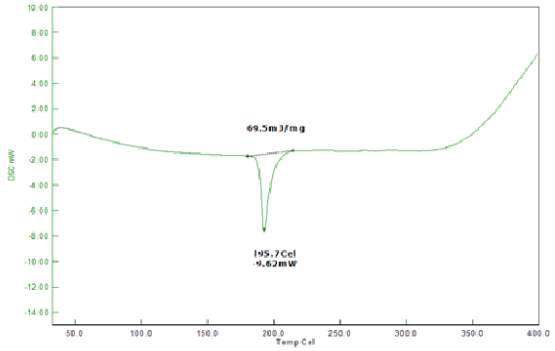


Figure 1: DSC graph of pure drug

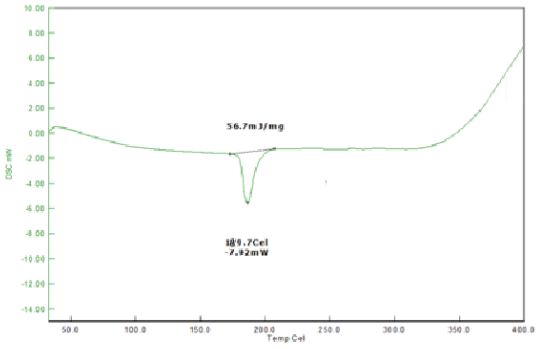


Figure 2: DSC graph of drug with excipients

Evaluation of modified starch
Swelling index

Swelling index was calculated from mean readings of three determinations. The starch of modified *Borassus flabellifer* and *Ipomea batatas* showed least percentage of swelling index than unmodified *Borassus flabellifer* which was shown in the table 3.

Table 2: Swelling index and viscosity of *Borassus flabellifer* starch & *Ipomea* batatas starch

Name of starch	Swelling index (%v/v)	Viscosity (cps)
Borassus flabellifer	16	3.20
Modified *Borassus flabellifer*	60	2.22
Ipomea batatas	20	3.08
Modified *ipomea batatas*	10	2.01

Viscosity

Viscosity of the starch was measured using Brookfield viscometer LVDV-II+ pro (spindle- 62). Modified *ipomea batatas* starch starch was found to be less viscous than unmodified *Borassus flabellifer* & *ipomea* starch. Viscosity of the starch is given in the table 3.

Evaluation ODT of optimized formulations with spray dried lactose

The following table presents the precompression parameters of ODT of modified *Ipomea* starch with spry dried lactose at 9% and 10% concentrations and modified *borassus flabellifer* starch with lactose at 9% and 10% concentrations. The formulations were formulated with spray dried lactose to study the improvement in physicochemical evaluation of ODT of optimized formulations and compared with ODT prepared with natural modified superdisintegrant *ipomea batatas* & *borassus flabellifer* starch. Preformulation parameters of all formulations blend were conducted. The important aspects for the direct compression formula are good flow property and compressibility. A comparison of the bulk density and tapped density provides measure of the relative importance in a given powder; such a comparison is often used as an index of the ability of the powder flow properties.

The powder flow depends on three general areas: the physical properties of the particle (e.g., shape, size, compressibility), the bulk powder properties (e.g., size distribution, compaction), and

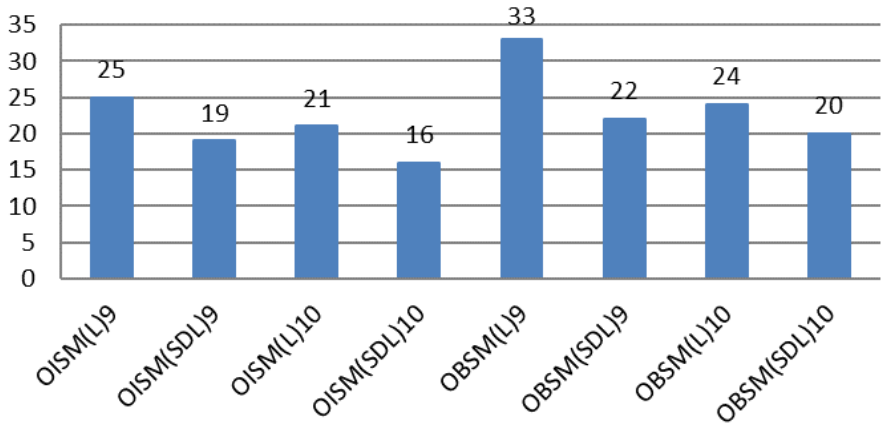
the processing environment (e.g., storage, humidity). The angle of repose <30° indicates free flowing material and >40° with poor flow properties. Values for angle of repose were found in the range of 30° to30.5° showing that the blend of powder was free flowing and can be used for direct compression. The value for carr's index was in between10.90±0.07 to 13.89 indicating that all batches of powder blends were having good compressibility. Hausner's ratio was to be within the limits 1.11 (<1.25). All the formulations showed good blend properties for direct compression and hence tablets were prepared by direct compression technology.

Evaluation of optimized formulations

The olanzapine orodispersible tablets were prepared by using natural super disintegrant namely, modified *ipomea batatas* starch & modified *borassus flabellifer* starch. All the above formulations were evaluated for various parameters like hardness, friability, drug content, wetting time, water absorption ratio, disintegration time and in vitro drug release studies. The hardness of the tablets was found to be 2.5 to 3 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance. The thicknesses of the tablets were found to be 1.09 to 2.1. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e.±10%. The disintegration time was found to be 16 to 20 seconds. These formulations taken for subsequent study. The wetting time was found to be range 17 to 24 seconds. The water absorption ratio was found to be 60 to 61. The drug content was found to be 99.55 to 99.63 %, indicating uniform distribution of drug in the tablets.

Table 3: Evaluation of optimized formulations

Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio	Content uniformity (%)
OISM9	49	3.3	2.2	0.19	19	24	61	99.55
OISM10	51	3.2	2	0.16	16	20	60	99.63
OBSM9	48	3.1	1.9	0.19	22	23	61	99.60
OBSM10	49	2.9	2	0.18	20	17	60	99.59



OISM (L) =formulation with lactose, **OISM (SDL)** =spray dried lactose

Figure 3: Disintegration time of optimized formulations with spray dried lactose Vs formulations with lactose

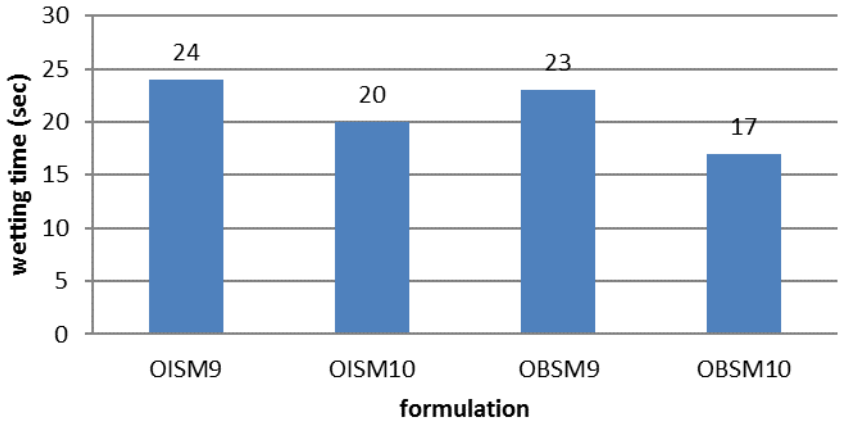


Figure 4: Wetting time of optimized formulations

The above figure presents the evaluation parameters of modified *Ipomea batatas* starch with spray dried lactose at 9% and 10% concentrations and modified *Borassus flabellifer* with spray dried lactose at 9% and 10% concentrations. The formulations were formulated with spray dried lactose to study the improvement in physicochemical parameters of ODT of optimized formulations. All the formulations did not show significant difference in ODT parameters with lactose or spray dried lactose formulations.

The release profiles did not show significant difference in the release pattern when compared to lactose as diluent.

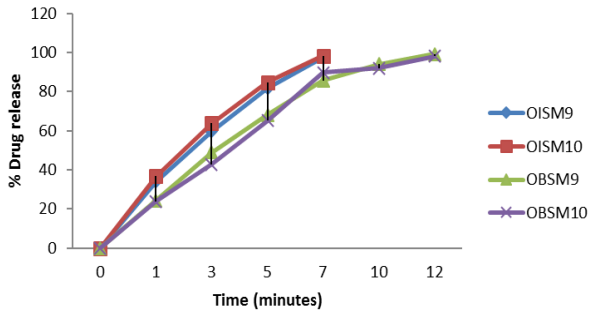


Figure 5: Dissolution profile of olanzapine orodispersible tablets of optimized formulations (with spray dried lactose)

Accelerated stability studies

The accelerated stability studies of optimized formulation did not show significant changes compare to initial values. All the basic physicochemical evaluation parameters of the optimized formulation were retained.

CONCLUSION

Orodispersible tablets of olanzapine was successfully formulated using natural polysaccharides and their modified forms such as *borassus flabellifer* starch and *ipomea batatas* starch for its superdisintegrant activity. The prepared formulations were compared with lactose & spray dried lactose as diluent for improvement in DT and other ODT parameters. FTIR studies revealed that there was no interaction between olanzapine and excipients used in tablet formulations. Precompression parameters were conducted for all formulations blend and were found to be satisfactory. The orodispersible tablets formulated using modified *ipomea batatas* starch with spray dried lactose at concentration of 10% showed better disintegration time compared to unmodified *ipomea* formulations but there was no significant change in DT and other ODT parameter which indicate that no useful of modification of *ipomea* starch to use it as superdisintegrant unlike orodispersible tablets formulated using borassus starch & its modified form which showed significant difference in DT between modified and unmodified form which indicate that the modification of *borassus* starch was useful to set superdisintegration activity & modified *borassus* starch can be used in higher concentration. To conclude, modified polysaccharide such as *Ipomea batatas* starch in higher concentration (9% & 10%) can be used as supredisintegrant without any modification unlike *Borassus flabellifer* starch which need modification to set superdisintegrant activity.

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How to cite this article:
Zeinelabdin Salim M.A, P. K. Lakshmi. Preparation and evaluation of orally disintegrable tablets using *Borassus flabellifer* starch, *Ipomea batatas* starch and their modified form as superdisintegrant. J Pharm Sci Innov. 2017;6(1): 3-7.

Source of support: Nil, Conflict of interest: None Declared