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Formulation development and in vitro evaluation of oral dispersible tablets of Olanzapine by direct compression

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Abstract

The objective of the present work was to formulate mouth dissolving tablet enriched with taste masking agent to provide rapid onset of action of olanzapine increasing its therapeutic efficacy and also increase the compliance amongst geriatric, pediatric and uncooperative patients. Precompression blends of the ODTs were prepared and evaluated for its micromeritic properties. Total four formulations of ODTs were prepared using direct compression (OLODT1 to OLODT4) method. The concentration of the super-disintegrant was varied for formulating the blends. Mannitol was used as the binder as well as sweetener while saccharin sodium was used as the additional taste masking agent in the formulations. All the formulations were subjected to post compression evaluation test and the results indicate that the formulation had hardness of 3 Kg/cm^2, thickness of 3 mm, weight variation in the range of 4.1-5.3 %, friability of less than 1 %, drug content in the range of 97.8 to 98.8 %, wetting time from 28 to 47 seconds with water absorption ratio of more than 75 %, disintegration time of less than 30 seconds and a drug release of more than 80 % over a period of 5 minutes. The formulations were found to be stable under accelerated conditions for a period of 3 months with almost negligible change in the critical parameters.

Keywords: Olanzapine, oral dispersible, tablets, direct compression, formulation, Mannitol

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Introduction

The idea of delivery of drug in the oral cavity or wet mucosa originated back when sublingual or buccal tablets were formulated for delivery of drugs.[1] These sublingual or buccal tablets presented a basic disadvantage as the patient's impulse to crunch and swallow the tablet. The initial ODTs utilized effervescence as the technology of disintegration and were designed especially for children to take vitamin pills.[2] Since then a number of studies on formulation and evaluation of ODTs have been carried out by various researchers using various methods of formulation.[3-9] Olanzapine is a synthetic derivative of thienobenzodiazepine with antipsychotic, antinausea, and antiemetic activities. As a selective monoaminergic antagonist, olanzapine binds with high affinity binding to the following receptors: serotoninergic, dopaminergic, muscarinic M1-5, histamine H1, and alpha-1-adrenergic receptors; it binds weakly to gamma-aminobutyric acid type A, benzodiazepine, and beta-adrenergic receptors.[10] The onset of action of olanzapine has been reported to be 1 hour post oral administration and this presents a therapeutic challenge for obtaining relief from the symptoms of the allergies. Difficulty in swallowing (dysphagia) is a very general problem with patients of all age groups, especially with the pediatrics and elderly.

Owing to these challenges it was envisioned that a mouth dissolving tablet enriched with taste masking agent would be a probable solution to provide rapid onset of action of olanzapine increasing its therapeutic efficacy and also increase the compliance amongst geriatric, pediatric and uncooperative patients.

Material and Methods

Olanzapine was obtained as gift sample from Medibios Laboratories, Tarapur. All the other reagents and chemicals were procured from Oxford Fine Chemicals, CDH, Qualigens and Fisher Scientific.

Physical characterization, melting point and solubility

The procured sample of Olanzapine was observed for its appearance, color and taste in order to characterize the physical parameters. Melting point of the sample was determined by open capillary method. In order to check the solubility qualitative method was used. A small amount of the procured sample was taken in test tubes and 1 mL of different solvents was added to the tubes. The tubes were agitated to allow for solubilization of the drug and were physically observed for presence or absence of the sample particles in them.

Preparation of ODTs of Olanzapine

The ODTs of Olanzapine were prepared by direct compression method according the batch formula given in Table 1. All the ingredients were separately sifted through 60 mesh sieve. The drug and microcrystalline cellulose were mixed in small portions of both and blending it to get a uniform mixture. This mixture was kept aside for blending. All the other ingredients were accurately weighed and

mixed in geometrical order and tablets and blended in a double cone blender. The blend was compressed to tablets of 8 mm sizes using flat round punch using Sentwin compression Machine.[11]

Table 1 Batch formula per tablet using direct compression method

Ingredient (mg)	Formulation code			
	OLODT1	OLODT2	OLODT3	OLODT4
Olanzapine	5	5	5	5
Crospovidone	7	14	21	28
Sodium starch glycolate	10	10	10	10
Saccharin Sodium	12	12	12	12
D-mannitol	114	107	100	93
Avicel PH-102	54	54	54	54
Methyl cellulose	3	3	3	3
Talc	3	3	3	3
Magnesium stearate	2	2	2	2
TOTAL	**200**	**200**	**200**	**200**

Precompression evaluation the formulation blends[12]

All the prepared blends (OLODT1-4) were subjected to determination of the micromeritic properties like angle of repose, bulk & tapped densities, Hausner's ratio and Carr's Index.

Evaluation of ODTs[12]

The ODTs were subjected to evaluation of the post compression parameters according to guidelines.

Hardness test

The hardness of the formulated tablets was tested using Monsanto type hardness tester. Three tablets from each batch of formulation were randomly taken and the force required to break the tablets was measured using hardness tester.

Friability test

The friability test of the formulations was performed using a Roche type friability test apparatus. Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by the formula

$$\% \text{ Friability} = \frac{W_{initial} - W_{final}}{W_{initial}} X\ 100$$

Weight variation test

20 tablets were randomly taken and weighed to calculate the average weight of the tablets. Each of these tablets was individually weighed and the difference from average weight was calculated. The percent weight variation was calculated to determine the deviation from the average weight.

Thickness

The thickness of randomly selected tablets from each batch of formulation was measured using a digital vernier caliper.

Drug content

Five tablets from each formulation were weighed to determine the average weight. These tablets were crushed in a mortar then the amount of powder equivalent to 20 mg of drug was transferred in 20 mL of 0.1N HCl. 10ml from this stock solution was withdrawn and diluted up to 100 mL with 0.1N HCl. 0.6 mL from this stock solution was pipetted out and

diluted to 10 mL. Absorbance of the resulting solution was measured at 258 nm using UV spectrophotometer.

Wetting time

A piece of tissue paper folded twice was placed in a small petri dish (i.d. = 6.5 cm) containing 10 mL of water, a tablet was placed on the paper, and the time for complete wetting was measured.

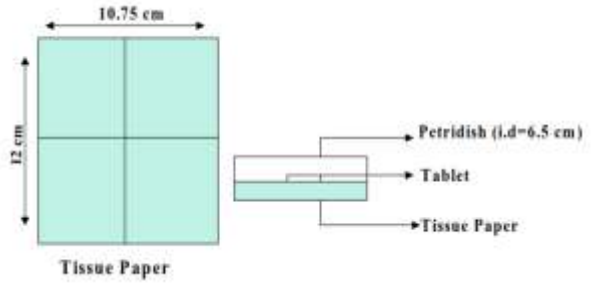

Figure 1 Diagrammatic representation of determination of wetting of tablet

Water Absorption ratio

A piece of tissue paper was folded twice and placed in a Petri dish containing 6 mL of 0.5% v/v amaranth solution (as a coloring agent) in water. A tablet was placed gently on the tissue paper, and the wetted tablet was reweighed. The water absorption ratio R was determined according the following equation

$$R = \frac{W_a - W_b}{W_b} X\ 100$$

Where W_a is the weight of tablet after water absorption and W_b is the weight of tablet before water absorption.

In vitro disintegration time

The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. One tablet was placed in each of the 6 tubes of the basket and a perforated disc was placed over each tablet. The assembly was raised and lowered at 30 cycles per minute in the pH 6.8 buffer maintained at 37±2°C. The time required for complete disintegration of the tablet with no palpable mass remaining in the apparatus was recorded.

In-vitro dissolution

The USP type II paddle apparatus with a paddle speed of 50 rpm was used for dissolution testing for the formulated ODTs. The dissolution media used consisted of 900 mL of 0.1 N HCl and distilled water. 5 mL of samples were collected at time points of 5, 10, 15, and 30 min and the media was replenished with the same volume of fresh media. The free drug concentration was estimated using a UV spectrophotometer at a wavelength of 258 nm.

Short term stability study

The formulated ODTs were randomly selected and subjected to three month stability study at 25°C/ 60% and 40°C /75 % RH. After the end of the study period, some critical parameters were evaluated.

Results and Discussion

The physical characterization of the drug obtained as gift sample was carried out in order to confirm the identity of the drug and the results of physical

characterization, melting point and qualitative solubility studies are presented in Table 2

Table 2 Physical characterization of olanzapine

S. No	Test	Specification	Observation
1	Color	Yellow	Yellow
2	Taste	Bitter	Bitter
3	Appearance	Crystalline powder	Crystalline powder
4	Melting Point	189-195°C	192-194°C
5	Solubility	Insoluble in water, soluble in 0.1N HCl	Slighlty soluble in water, soluble in 0.1N HCl

All the formulations were subjected to preformulation testing of the blends in order to ascertain their suitability for compression. The bulk and tapped density, angle of repose, Hausner's ratio and Carr's Index are used to determine the compressibility and flow properties of the blends. The angle of repose is a measure of the frictional forces in the loose powder blend that may hinder the flow property of the blend making it unsuitable for feeding through the hopper of the tablet machine. The angle of repose of all the formulation blends ranged from 29°89' to 30°31'. A θ value of less than 30° of powder or blends is known to exhibit excellent flow properties.

The results of precompression evaluation of the formulation blends are presented in Table 3. From the results it is evident that all the blends possessed the capability to flow freely and may present no hindrance in compression or tabletting process. The values of Hausner's ratio and Carr's Index are found to be within the specifications of good flow property of powders.

Table 3 Precompression parameters of blends

Formulation Code	Bulk density (g/cm^3)	Tap density (g/cm^3)	Angle of repose (°)	Carr's Index (%)	Hausner's Ratio
OLODT 1	0.367	0.401	29.89	8.48	1.09
OLODT 2	0.379	0.423	30.03	10.40	1.12
OLODT 3	0.391	0.432	30.01	9.49	1.10
OLODT 4	0.381	0.425	30.31	10.35	1.12

Evaluation of ODTs

The tablets formulated after compression were evaluated for various quality control tests of solid dosage forms (tablets) in order to ensure that all the products meet the requirements of mouth dissolving tablets. The results of all the physical parameters of the tablets formulation are presented in Table 4.

Table 4 Post compression parameters of MDT formulations

Formulation Code	Hardness (Kg/cm^2)	Thickness (mm)	Average Weight variation (%)	Friability (%)	Drug content (%)
OLODT 1	3	3	4.6	0.51	97.90
OLODT 2	3	3	5.3	0.55	97.80

OLODT 3	3	3	3.8	0.51	98.80
OLODT 4	3	3	4.1	0.50	97.80

The wetting time and water absorption ratio are the indicator of the efficiency of the superdisintegrants. They exhibit the capacity of the disintegrants to absorb water and wet the tablet completely within the shortest time duration. The quick wetting and high water absorption ratio help in swelling of the ODTs and its rapid disintegration and dissolution in the oral cavity. The wetting time of the formulations ranged from 28 to 47 seconds with water absorption ratio of more than 75 % for the formulations (Table 5). The results reveal that all the formulations possessed the ability to quickly disintegrate and dissolve.

It has been already discussed that the prescribed limit of disintegration for ODTs is 30 seconds and in certain cases for fast dissolving tablets it can be up to 3 minutes. All the formulations exhibited of less than 30 seconds in the *in vitro* test ranging from 19.1 to 29.4 seconds (Table 5).

In vitro dissolution test

In vitro dissolution study was performed to evaluate the release profile of the drug from various formulated ODTs. The results of the study are used to relate the percentage of drug release from its dosage form as a function of time. The addition of super-disintegrants to the formulation aids in the quick disintegration of the formulation promoting the quick dissolution of the particles which in turn enhances the release of drug from the dosage form ultimately causing enhance bioavailability and quick onset of action of the drug. The objective of the study was to achieve quick onset of action and peak plasma concentration of drug for management of allergic episodes. The amount of drug that was released from the formulations over a period of 5 minutes was determined using UV spectrophotometer at 258 nm.

All the formulations were found to release more than 80 % of the drug within a period of 5 minutes (Table 5). While OLODT2 exhibited the lowest release of drug (81.8 %), the highest amount of drug was released from OLODT3 (97.8 %).

Table 5 Wetting, water absorption, disintegration and drug release of MDTs

Formulation Code	Wetting time (seconds)	Water absorption ratio	Disintegration time (seconds)	Drug release (%)
OLODT1	47	75.8	27.2	98.30
OLODT2	40	81.2	29.4	87.80
OLODT3	36	75.1	19.1	98.90
OLODT4	28	83.4	23.6	98.10

Crospovidone containing tablets usually present high capillary activity and pronounce hydration and oppose gelling thereby causing rapid disintegration and drug release. The tablets have low hardness and their porous structure is responsible for rapid water uptake, thereby facilitating the wicking action of methyl cellulose in bringing about faster

disintegration.The cumulative release of drug from ODTs as a function of time is presented in Figure 2.

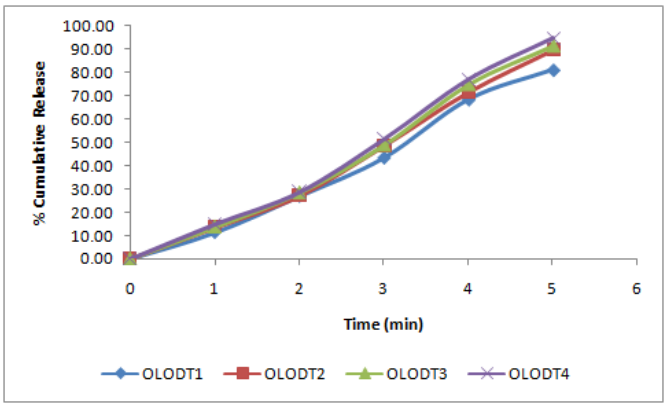

Figure 2 *In vitro* drug release from formulations

Stability Study

Accelerated stability testing was performed on 15 tablets of all formulations by storing them in amber colored stoppered vials at specified conditions of temperature and humidity for a period of 3 months. At intervals of one month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time. The results of stability study are presented in Table 6.

A very small change in disintegration time, drug content and friability was observed in almost all the formulations under the conditions of the study.

Conclusion

It can be concluded from the study that mouth dissolving tablets of olanzapine could be easily formulated using super-disintegrants and sublimating agents in order to achieve a rapid onset of drug action and peak plasma concentration over short period of time. The ODTs formulated using could be highly beneficial for the management of acute allergic episodes that require immediate attention.

Table 6 Results of accelerated stability study

Formulation Code	Time (days)	Hardness (Kg/cm^3)	Friability (%)	Drug content (%)	Disintegration time (seconds)
OLODT1	30	3	0.51	97.81	27.2
	60	3	0.52	97.76	27.3
	90	3	0.52	97.71	27.3
OLODT2	30	3	0.55	97.23	29.3
	60	3	0.55	97.18	29.4
	90	3	0.56	97.18	29.4
OLODT3	30	3	0.50	98.75	19.1
	60	3	0.51	98.71	19.3
	90	3	0.52	98.60	19.2
OLODT4	30	3	0.50	97.80	23.7
	60	3	0.49	97.76	23.6
	90	3	0.52	97.75	23.6

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