

NOVEL MELT GRANULATION USING SUGARS FOR METOCLOPRAMIDE HYDROCHLORIDE ORALLY DISINTEGRATING TABLET

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Orally disintegrating tablets (ODTs) are a rapidly growing category of dosage form in the pharmaceutical industry which has received ever-increasing demand during the last decade. They especially find application in target category like geriatrics and pediatrics. Further the ODTs are challenging to formulate if the active drug substance has an unpleasant taste. Metoclopramide hydrochloride is recommended in dose of 10 to 15 mg four times a day for getting relief from nausea, vomiting, stomach pain and reflux oesophagitis. It finds application in all the categories of patients. However its unpleasant taste makes patient reluctant to adhere to the dosage regimen. This necessitated taste masking to be carried out. The taste masking of Metoclopramide hydrochloride was carried out by forming complex with indion 244 using batch process. Further this complex was formulated into ODT using melt granulation technique. A blend of low melting and high melting sugar was used in this technique. The method resulted into tablets which disintegrated in 20 seconds and gave a drug release of $92 \pm 3\%$ at the end of 30 minutes. The tablets were also evaluated for other parameters like hardness, friability, wetting time and in vivo disintegration by subjective evaluation. Thus the present work explores a novel technique of formulating a palatable ODT which gave better balance between disintegration time and hardness of the tablet.

Keywords : Orally disintegrating tablet, taste, sugars, melt granulation.

INTRODUCTION

The demand for orally disintegrating tablets (ODT) has been growing during the last decade especially for elderly and children who have swallowing difficulties. For this reasons, tablets that can dissolve or disintegrate in oral cavity, have attracted a great deal of attention. Also, possibilities of missing out the doses will be minimized because this dosage form will encourage the patient to adhere to dosage regimen and provide patient compliance. The use of orally disintegrating tablets would facilitate dose administration even during traveling or in cases where there is no access to water. ODTs are solid dosage form that dissolves or disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water. ODT can be prepared by various methods such as freeze drying, sublimation of volatile salts, addition of superdisintegrant, wet compression method and use of sugar based excipients. The problem of certain ODT is their low physical resistance and high friability. This work describes a new approach to prepare ODT with sufficient mechanical integrity, involving the use of sugars by melt granulation technique. Sugars not only have good compactability but also have good solubility which will help in faster disintegration.^{1,2} Metoclopramide is recommended in dose of 10 to 15 mg four times a day for getting relief from nausea, vomiting, stomach pain and reflux oesophagitis. It has a half life of 4.5 hours. As it is an antiemetic, the ODT tablet form would be preferred by the patients during emetic conditions due to its

administration without aid of water. Also, it would be conveniently consumed during traveling. Also such patients need immediate onset of action with ease of administration which would be provided by orally disintegrating tablets.³⁻⁵

Hence, the use of this drug in immediate release form would be well justified under these conditions. Moreover the drug has a very bitter taste, so taste masking of the drug should also be carried out.

EXPERIMENTAL

Materials

The drug Metoclopramide Hydrochloride was a generous gift sample from Cosme Pharmaceuticals, Mumbai. The resin was obtained as gift sample from Ion Exchange India Ltd. Xylitol and Pearlitol was procured as gift sample from Signet chemicals. All other excipients used were of pharmacopoeial grade.

Methodology

Preformulation

The drug was subjected to various preformulation tests like identification using melting point, pH solubility profile and hygroscopicity. Differential scanning calorimetry was carried out for checking the drug excipient interaction.^{6,8}

Taste masking of the drug

The taste of metoclopramide hydrochloride is very bitter which necessitates taste masking. The methodology

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involves initially taste masking of the drug, by forming complex with ion exchange resin Indion 244 by batch process.⁹⁻¹²

Preparation of tablet

By Direct compression method

The resinate was mixed with sugars and directly compressed using 8 mm punch on a single station tablet machine.¹³⁻¹⁸

TABLE- 1 Various formulations containing different concentrations of Pearlitol and Xylitol

Formulation Code	Ingredients (in mg)				
	Resinate (equivalent to 10 mg drug)	Pearlitol	Xylitol	Talc (mg)	Weight (mg)
F 1	31.33	50 %	50 %	4	185.33
F 2	31.33	50 %	30 %	4	155.33
F 3	31.33	30 %	50 %	4	155.33
F 4	31.33	30 %	30 %	4	125.33
F 5	31.33	40 %	30 %	4	140.33
F 6	31.33	40 %	50 %	4	170.33
F 7	31.33	50 %	40 %	4	170.33
F 8	31.33	30 %	40 %	4	140.33
F 9	31.33	40 %	40 %	4	155.33

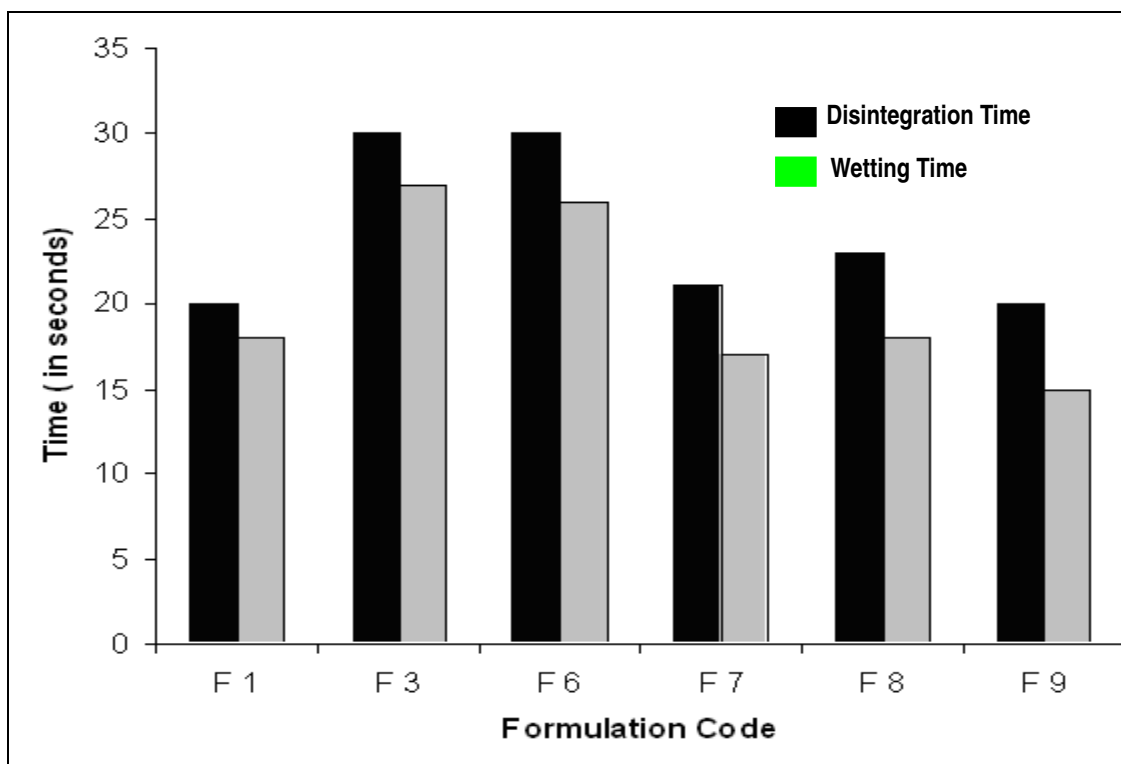


FIGURE 1. Wetting time and disintegration time of various formulations.

By melt granulation method

Mannitol (melting point 166°C) was used as the higher melting point sugar alcohol and xylitol (melting point 97°C) was used as lower melting point sugar alcohol. The resinate was mixed with the sugar alcohols and kept in mantle maintained at 100°C, where the lower melting point sugar alcohol melted. The mass was then passed through mesh # 8 and dried. The dried granules were then passed through mesh # 18 and retained over mesh # 36. The

TABLE- 2 Disintegration times of various formulations

Formulation	In vitro Disintegration Time (sec)
F 1	20 ± 2
F 2	No proper granulation observed
F 3	30 ± 2
F 4	No proper granulation observed
F 5	No proper granulation observed
F 6	30 ± 2
F 7	22 ± 2
F 8	23 ± 2
F 9	20 ± 2

granules were lubricated with talc and compressed using 8 mm punch on a single station tablet machine.

The following trials were carried out Evaluation of tablets

Five tablets were selected randomly from each formulation batch and tested for tablet hardness, disintegration time, and wetting time.¹³⁻¹⁸

Hardness : The fracture strength, which is defined as the force, required to break a tablet by radial compression, was measured with a Monsanto tablet hardness tester.

Friability: Friability was determined using Roche Friability tester.

Wetting time : To measure tablet wetting time, a piece of tissue paper placed in a small culture dish(i.d.= 5 cm) containing 6 ml of water, a pre-weighed tablet was put on the paper, and the time for complete wetting was measured.

In vitro disintegration: Tablet was placed in 6 ml of simulated saliva and the time required for the tablet to disintegrate into dispersion was noted down.

In vivo disintegration : The test was carried out in 5 healthy volunteers from whom informed consent was first obtained. The tablet was held in the mouth for 60 seconds and then spat out. The time required for disintegration was noted down. The method was approved by institutional ethical committee.

In vitro drug release : The drug release from the tablet was studied using 1.2 pH HCl buffer using the paddle method at 37 ± 0.5 °C under sink conditions. After suitable

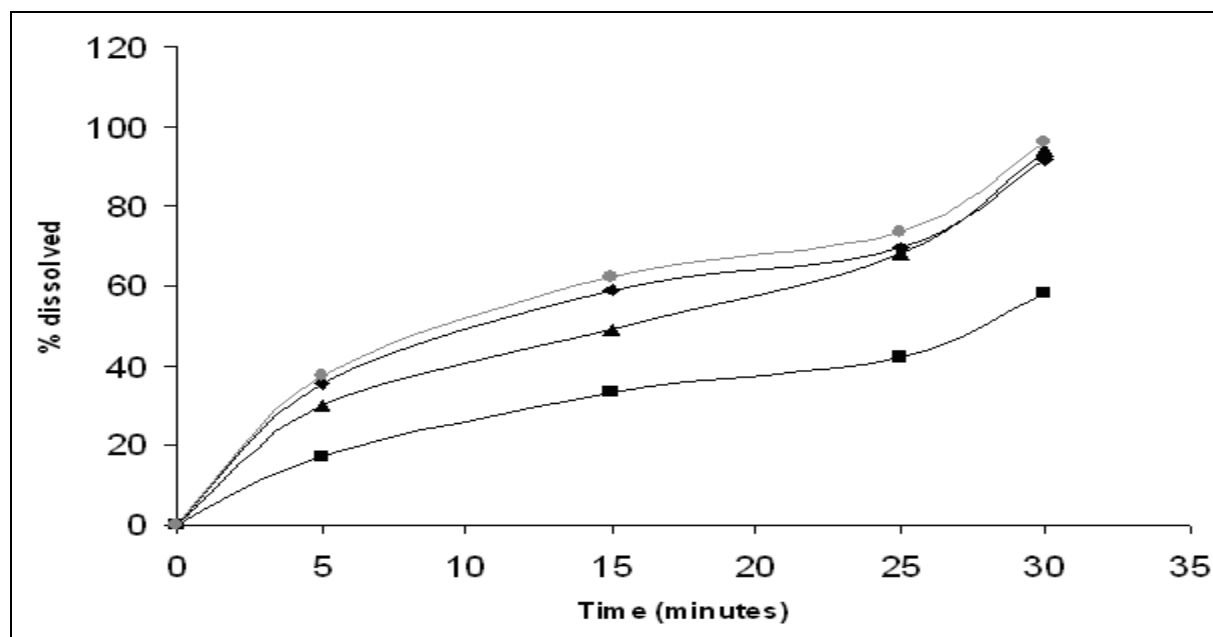


FIGURE 2. Drug release studies in various media (▲- 0.1 N HCl, ■ - SGF (Simulated Gastric Fluid), ▲ - 1.2 pH HCl buffer, ○ -Marketed)

dilution, the samples were analyzed spectrophotometrically at 274 nm.

Assay : Tablets in five were crushed and powder equivalent to one tablet was taken and extraction was carried out. The concentration was determined spectrophotometrically against appropriate blank.

Statistical Analysis : The drug release of the best formulation was compared with that of the marketed immediate release formulation of dose 10 mg and student test was applied at 0.05 level of significance for comparison.

RESULTS

The tablets obtained from direct compression showed a longer disintegration time, low hardness and high friability of 1.2 %. Hence method of granulation was adopted for formulating tablets with sufficient hardness. Since the sugar mixture used was mixture of low melting and high melting sugar, the low melting sugar can be melted to get a granulating mass for preparation of granules. Formulations containing different concentrations of low melting and high melting sugars were formulated and assessed for the granule formation and disintegration ability. The results were as shown in Table- 2.

F 2, F 4 and F 5 did not yield proper mass for granulation due to lesser percentage of low melting xylitol. The formulations which were successful in obtaining granules were also assessed for the wetting time and disintegration time. It is usually considered that the disintegration time of oral cavity directly relates to the wetting time of water into tablet. So, the disintegration time of tablet in oral cavity was examined using healthy volunteers. The wetting ability and disintegration time for the different formulations were as shown in the Figure 1.

F 3 and F 6 showed comparatively greater disintegration time due to greater percentage of Xylitol being present. Out of the remaining four formulations F 1 and F 9 showed least disintegration time. But F 9 showed the effect at lower concentrations, (i.e. 40 % Xylitol and 40 % Pearlitol), hence was finalized for the work. Further F 9 was assessed for various parameters the results of which are shown in Table-3.

The tablet contains resinate which can release the drug only in the presence of ions. Hence the release of the drug from the tablet was greater in 1.2 pH HCl buffer as compared to 0.1 N HCl. The drug release was also carried out in simulated gastric fluid (without pepsin). The drug release studies as shown in Fig 2 indicated that the release in 1.2 pH HCl buffer was comparable to the marketed formulation.

DISCUSSION

The tablets prepared by melt granulation technique showed sufficient hardness and low friability as compared to the directly compressed tablet. There is formation of interparticle bonds induced by melting of xylitol and its subsequent solidification upon cooling imparts hardness and integrity to the tablets. The water soluble nature of the sugars helped in faster disintegration of the tablet.

CONCLUSIONS

This article proposes a new technique of preparing orally disintegrating tablet employing sugars. Here tablets are produced by compressing the granules formed by melt granulation. It was proved that the tablet hardness was related to the increase of interparticle bonds induced by melting and subsequent solidification of the low melting sugar. The prepared tablets containing 40 % xylitol and 40 % Pearlitol was found to be effective in showing a lesser disintegration time, sufficient hardness and good palatability.

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