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A COMMERCIAL VIABLE PROCESS FOR THE PREPARTION OF SUBSTANTIALLY PURE AMORPHOUS FORM OF PROTON PUMP INHIBITORS

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ABSTRACT

A commercially viable process is being developed for the prepartion of substantially pure amorphous form of proton pump inhibitors such as of sodium, calcium, magnesium and potassium salts of rabeprazole, pantoprazole, omeprazole and lansoprazole. The process consist of performing ball-milling of crystalline proton pump inhibitors such as of sodium, calcium, magnesium and potassium salts of rabeprazole, pantoprazole, omeprazole and lansoprazole. The amorphous form of proton pump inhibitors such as of sodium, calcium, magnesium and potassium salts of rabeprazole, pantoprazole, omeprazole and lansoprazole is being characterized by powder X-ray diffraction pattern.

Keywords: polymorphism, proton pump inhibitors, rabeprazole, pantoprazole, omeprazole, lansoprazole and amorphous form .

INTRODUCTION

The proton pump is a molecule in certain cells of the stomach. It "pumps" acid into the stomach. It takes a non-acidic potassium ion out of the stomach and replaces it with an acidic hydrogen ion. This hydrogen ion is what makes things acidic. By putting more hydrogen ions into the stomach, the pump makes the contents of stomach more acidic. The acid secretion into the stomach can be stopped by stopping the action of the pump. Proton pump inhibitors[1] (or "PPI"s) are a group of medications that prevent the release of acid in the stomach and intestines. Examples of proton pump inhibitors include sodium, calcium, magnesium and potassium salts of rabeprazole[2], pantoprazole[3], omeprazole[4] and lansoprazole[5].

Polymorphism[6] is the ability of a solid material to exist in more than one form or crystal structure. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. The amorphous form is generally more soluble than the crystalline form and thus contributes more in the bioavailability of proton pump inhibitors.

The present authors have invented a commercially viable process for the prepartion of substantially pure amorphous form of proton pump inhibitors such as of sodium, calcium, magnesium and potassium salts of rabeprazole, pantoprazole, omeprazole and lansoprazole.

EXPERIMENTAL

Instrumentation

Ball milling was performed using a Retsch centrifugal ball-mill S-100 equipped with a 250 ml stainless steel milling chamber and twenty seven 10 mm diameter stainless steel balls as milling media.

Powder X-ray diffraction ("PXRD") analysis was performed using a SCINTAG powder X-ray diffractometer model XTRA equipped with a solid-state detector. Copper radiation of λ=1.5418 Å was used. The sample was introduced using a round standard aluminum sample holder with round zero background quartz plate in the bottom.

Preparation

Crystalline rabeprazole sodium[13-15] and twenty seven 10 mm diameter stainless steel milling balls were loaded into the milling chamber of the ball mill. The chamber was weighed and the mill was balanced according to the weight. The mill was operated at 600 rpm with the mill's reversing system on for 1 hour. The build-up material was scraped from the chamber walls into the bulk, and the mill was again operated for 4 hours, with cleaning of build-up every 10 minutes. Finally, the material was separated and was analyzed by PXRD and found to be substantially pure amorphous form.

The same process was repeated for preparing substantially pure amorphous form of calcium, magnesium and potassium salts of rabeprazole, pantoprazole, omeprazole and lansoprazole and sodium salt of pantoprazole, omeprazole and lansoprazole and in each instance substantially pure amorphous form was obtained.

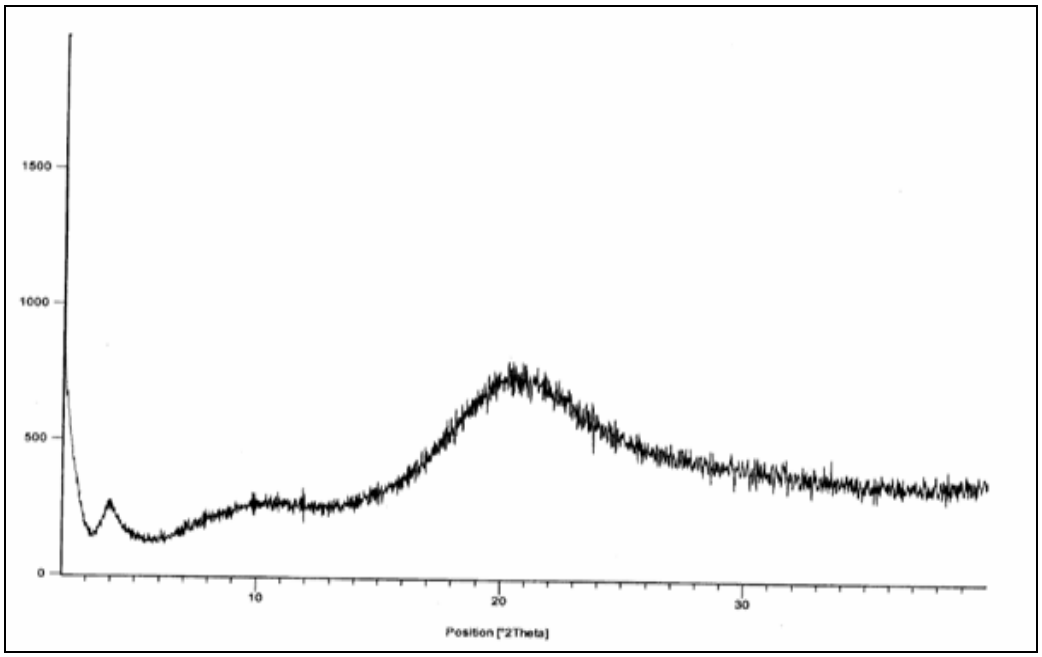

Fig.-1: Depicts substantially amorphous form of rabeprazole sodium

RESULTS AND DISCUSSION

The amorphous form of sodium, calcium, magnesium and potassium salts of rabeprazole, pantoprazole, omeprazole and lansoprazole is generally prepared by spray-drying[7], heat drying[8], lyophilization[9], agitated thin film drying[10] techniques and crystallization[11-12] in an organic solvent.

The processes reported for the preparation of amorphous form of sodium, calcium, magnesium and potassium salts of rabeprazole, pantoprazole, omeprazole and lansoprazole does not consistently yields pure amorphous form. Instead, it always gives some contamination of crystalline forms, which cause the lower solubility of drug hence make the drug less bioavailable.

The spray-drying, freeze drying and lyophilization processes for preparing amorphous form of sodium, calcium, magnesium and potassium salts of rabeprazole, pantoprazole, omeprazole and lansoprazole are not commercially viable due to the requirement of expensive equipments.

The present authors have found that ball-milling of any crystalline forms of proton pump inhibitors such as of sodium, calcium, magnesium and potassium salts of rabeprazole, pantoprazole, omeprazole and lansoprazole yield substantially amorphous form of uniform particle size, which is more soluble and thus are more bioavailable.

The amorphous form was confirmed by X-ray diffraction pattern as depicted in Figure 1, which shows no peaks and has a plain halo, demonstrating the amorphous nature of the solid. The purity of amorphous form was analyzed quantitatively by the internal standard method wherein a known quantity of a reference powder is added to an unknown powder, which is being measured.

CONCLUSION

The preparation of substantially pure amorphous form of proton pump inhibitors such as sodium, calcium, magnesium and potassium salts of rabeprazole, pantoprazole, omeprazole and lansoprazole by ball milling of crystalline forms is a commercial viable process, which can be operated at large scale production without any contamination of crystalline form in an amorphous form.

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