

Influence of Raw Materials Nature on the Biological Activity of Generic Products of Drug Using Atorvastatin and Isosorbide Dinitrate Tablets as a Model Drugs

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الخلاصة

في هذه الدراسة تم تحضير صيغتي حبوب لدواء الاتورفاستاتين و صيغتين لدواء ايزوزوربايد داي نايتريت في الدوائين كانت الصيغة الاولى لدواء بلوري و الثانية لدواء غير متبلور بطريقة الكبس المباشر. كانت جميع متغيرات عملية التحضير متطابقة ليتم التركيز على دور الشكل البلوري للمادة الاولية في تحرر العقار. بالمقارنة مع النوع المتبلور أظهرت الحبوب المحضرة بأستخدام غير المتبلور من عقار الاتورفاستاتين أداء أفضل في الذوبانية و التحرر في المحلول. بالاضافة الى ذلك كانت حبوب الايزوزوربايد داي نايتريت المبلورة أفضل و اسرع بالتحرر و الذوبانية من غير المبلورة. تلمح هذه النتائج الى ان امتصاص دوائي الاتورفاستاتين ذا المادة الاولية غير المتبلورة و الايزوزوربايد البلوري يكون اكبر من النوعين الاخرين مما يدعم ضرورة الاهتمام بتحليل المواد الاولية الخام بالاضافة للادوية المسوقة عندما يكون هنالك اختلاف بين مختلف المصادر الدوائية لنفس الدواء في عملية الذوبان و التحرر النهائي.

Abstract

In this work, two tablet formulas of amorphous and crystalline atorvastatin calcium beside two formulas of crystalline and amorphous isosorbide dinitrate from different raw materials manufacturing companies were prepared by direct compression method. The process variables were identical in order to concentrate on the effect of the crystalline form of the drugs on the release behavior of the prepared tablets. Compared with crystalline atorvastatin calcium, amorphous form tablets were of better performance in solubility and dissolution, resulting in higher solubility and faster dissolution rate. In addition, the dissolution rates of crystalline isosorbide dinitrate tablets were highly increased in comparison with tablet prepared with amorphous ones. The results imply that the absorption of atorvastatin calcium and isosorbide dinitrate after oral administration was remarkably higher when using the crystalline forms compared to the amorphous ones. These results recommend the attention towards analysis of raw materials of drugs when different brands of same drug shows dissimilar release disposal.

Introduction

The rate and extent of drug absorption can both be influenced by the pharmaceutical dosage form in which the drug is administered. The bioavailability of a medicine is the rate at which the drug becomes available to the body and the extent to which the dose is ultimately absorbed after administration.

The bioavailability of a drug is dependent upon the formulation of the medicine containing the drug. Inappropriate formulation can result in an unacceptable product which releases the drug at too slow rate, or fails to release a proportion of the contents.

Release of drug from conventional tablets follows their disintegration in the stomach and small intestine. The disintegration and dissolution properties of tablets can be altered by changes in their formulation and manufacture. For a tablets these variables includes: Nature and quantity of diluents, disintegrant, lubricant, and the size of granules and their method of manufacture. Also the compression pressure used in tableting and the conditions of storage and age of the finished product. After release of the drug particles the dissolution rate depends on: their wettability by the fluids, particle size, and the polymorph used (for drugs having more than one crystalline form). Example of some drugs for which variable absorption has been observed are shown in table-1 ⁽¹⁾

Therefore, alteration of release of drug in GIT could be achieved by several means like: Reduction of particle size of drug, use of salt in preference to the weak acid or base, use of water soluble prodrug derivative and selection of metastable crystalline form, if the compound exhibits polymorphism ⁽²⁾

The aim of our study is to design and prepare 2 tablet formulas of both atorvastatin calcium and isosorbide di-nitrate. The raw materials of each are from different sources. Then we perform measuring the release profiles of each with time and assemble comparative analysis of the difference if any. Atorvastatin is a member of the drug class known as statins, used for lowering blood cholesterol. It also stabilizes plaque and prevents strokes through anti-inflammatory and other mechanisms. Atorvastatin works by inhibiting HMG-CoA reductase, an enzyme found in liver tissue that plays a key role in production of cholesterol in the body. ⁽³⁾ Isosorbide dinitrate is a nitrate used pharmacologically as a vasodilator, e.g. in angina pectoris but also for anal fissure, a condition which is known to involve decreased blood supply leading to poor healing. It is also used as a direct vasodilator to treat congestive heart failure. ⁽⁴⁾

Materials and methods

Materials: Atorvastatin calcium crystalline and amorphous forms were obtained from Actavis Company. Ltd UK. Isosorbide dinitrate, crystalline form obtained from SDI, Iraq and amorphous one from Gnauzhou Linuo Pharmaceutical Co., Ltd China. Excipients used were a kind gift from alfurat drug factory in Iraq they involve croscarmellose sodium which is an internally cross-linked sodium carboxymethylcellulose used as disintegrant, lactose as diluents, magnesium stearate as glident, and avicel PH 101 (microcrystalline cellulose D.C) as binder and diluent. All other materials used were of analytical grade.

Instruments: UV spectrophotometer (shimadzu, Japan). Tablet machine manual (Indian co.) Hardness tester (Monsanto hardness tester). Dissolution apparatus (Copley Scientific Co, England). HPLC (shimadzu, Japan, column, C18).

Methods:

Preparation of Tablets: 2 tablet formulas of atorvastatin each containing 20 mg and excipients with a total weight of tablet of 120 mg were prepared by direct compression method. The 1st containing crystalline form (F1) and the 2nd containing amorphous form of the drug (F2). On the other hand, another 2 tablet formulas each containing 10mg isosorbide dinitrate [crystalline (F3) and amorphous (F4) forms] and Excipients with a total weight of tablet of 120 mg.

In Vitro Release Studies: the dissolution test of atorvastatin tablet was carried out using USP paddle method. The dissolution medium was 900 ml of phosphate buffer pH 7.2 at 50 RPM, 37 °C. At regular time intervals 5 ml of samples were withdrawn (replaced by equal volume of buffer), filtered through membrane filter, and determined by UV at 240 nm. ⁽⁵⁾ Isosorbide dinitrate tablet (10 mg) assayed using paddle type dissolution apparatus. The dissolution medium is water 1000 ml at 75 RPM 37 °C. Samples were withdrawn at certain intervals (replaced by equal volume of water), filtered through membrane filter, and determined by HPLC, USP method. ⁽⁵⁾

Statistical Analysis

The results of experiments (release profiles at different time intervals) are given as a mean of 3 analyses and between different formulas; statistical analysis was done according to the one way analysis of variance (ANOVA) at the level of ($p < 0.05$).

Results and Discussion

Assay regarding content uniformity of the prepared tablets reveals that the amount of drugs ranged between 95-99%. This indicates that the chosen drugs are stable under the preparation condition and showed an acceptable compatibility with other materials (Excipients) which represent the bulk of the prepared tablets structure.

The hardness of tablets are within the acceptable range of the pharmacopoeia, (Figure-1), although the similarities in the preparations variables of different formulas makes the general characteristics of tablets away from the comparison point of view.

There is a highly significant difference ($P < 0.05$) in the release profile of atorvastatin between the two formulas (F1, F2) as shown in (Figure 2). The difference in the release profile of many drug preparations is always attributed to the amount of release retardant or accelerators present in the formulas. In our study the crystalline state of the drug determines the difference in its dissolution behavior, since the additives and the preparation methods are similar. Amorphous atorvastatin (F2) has higher solubility and dissolution rate (95 % after 60 minutes) than the crystalline form (F1) (75% after 60 minutes). Our results are in agreement with the results of Kim, M et al.⁽⁶⁾ where they confirm the higher solubility of the amorphous atorvastatin compared to the crystalline form. Furthermore, several literatures mentioned the possibility of transformation of amorphous atorvastatin to crystalline form after formulation^(7,8). This supports the value of continuation in studying release profile and follow up of marketed pharmaceutical products. Concerning isosorbide dinitrate, also, a statistically significant difference in the release profile was observed between the two formulas (F3, F4) as shown in (Figure 3). (The formula containing the crystalline form of the drug (F3) has the higher dissolution rate profile (88% after 60 minutes) than the amorphous one (F4) (65% after 60 minutes)

The difference in the solubility and physicochemical characteristics between crystalline and amorphous forms of medications is not a new subject in the procession of the preformulation and pharmacokinetics. However, for drugs of narrow margin of safety and for life saving drugs, like isosorbide dinitrate (used to treat angina) and atorvastatin (used to treat hyperlipidemia) where crystalline configuration demonstrates significant differences in important parameters that may affect the bioavailability and bioactivity of medication. Therefore, the consideration of raw materials resources and their properties should be established in analysis in order to verify the precise outline of dissolution profile among different manufacturers of the same drug.

Conclusion

In this study, 4 tablet formulas were successfully prepared by direct compression method and were evaluated for its dissolution properties. The results characterize that amorphous atorvastatin exhibited enhanced dissolution rate and high saturation solubility in comparison with crystalline atorvastatin. For isosorbide dinitrate, the enhancement in drug dissolution rate and solubility was observed in the crystalline form of the drug. These results can be expected to have a large impact on the oral bioavailability of these two drugs. This study demonstrated the usefulness of the consideration of raw materials characteristics in the analysis of the marketed drugs in order to explain the solubility, stability and release differences among different generics.

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Drug	Observation	Cause
Chloramphenicol	Inactive suspension	Use of inactive polymorph
Tolbutamide	Loss of diabetic control	Poor dissolution of drug from one brand
Digoxin	Enhanced activity of tablets	Change in the method of production
Cortisone acetate	Change in brand of tablet-disease intense	Drug particles in ineffective tablets were aggregated and dissolved only very slowly

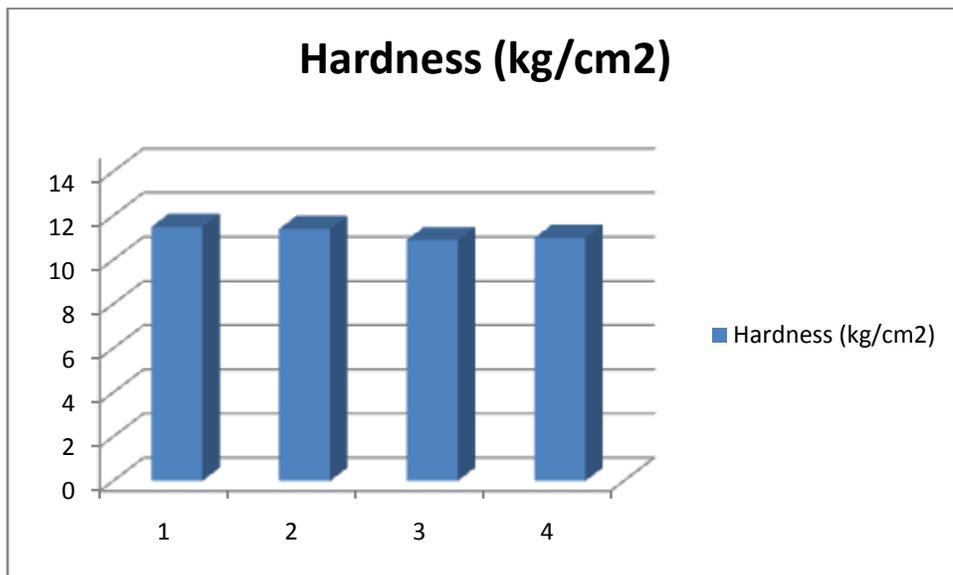


Figure 1: The Tablet Hardness of formulas 1-4

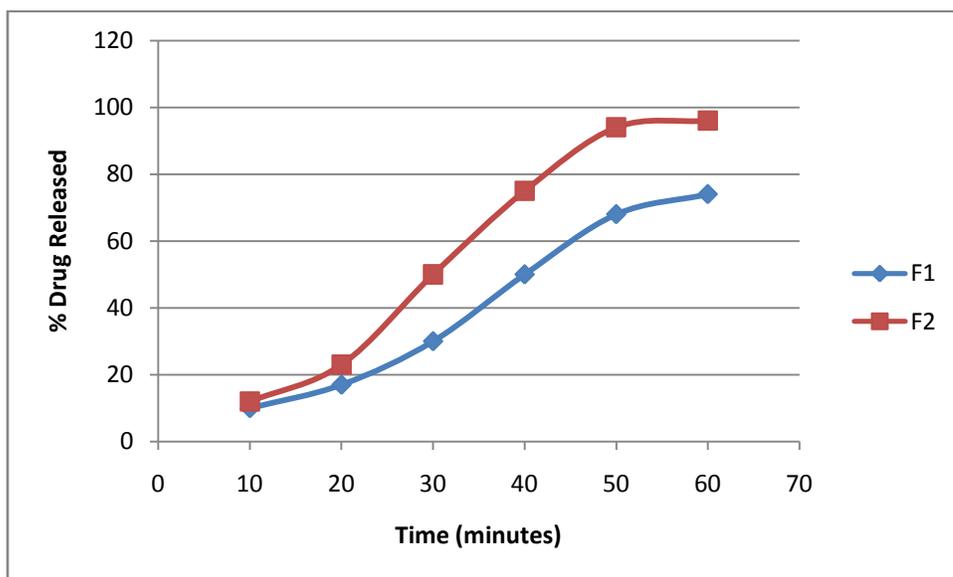


Figure 2: Dissolution Profile of Atorvastatin Tablets

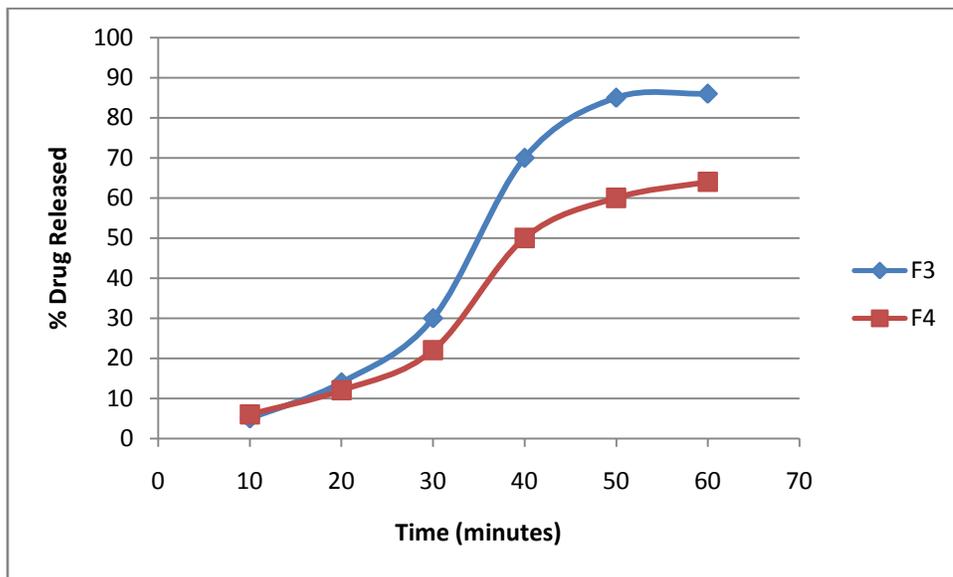


Figure 3: Dissolution Profile of isosorbide dinitrate Tablets.