Comparative study for the dissolution of Isosorbide dinitrate tablets in commercial products

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الخلاصة:

ان دواء الايسوسوربيد دايناينتريت يحضر باشكال صبدلانية صلبة مثل الحبوب وهو موجود قي السوق الدوائية اما بشكل حبوب تحت اللسان او حبوب تؤخذ عن طريق الفم وبجرعة 10 ملغم. لقد خضع هذا المستحضر الفموي لدراسة الانحلالية في هذا البحث ,كما يتظمن هذا البحث دراسة الأنحلالية لعدة مستحضرات تجارية لحبوب الأيسوسورباید داينترايت وفق طريقة دستور الادوية البريطاني التي تتظمن استعمال الكروماتوغرافيا السائلة في القياسات الكمية. ان الرسم البياني لمعدل الأنحلالية مع الوقت لجميع المستحضرات التجارية وكذلك الوجبة التحريبية الاؤلى لحبوب الايسوسوربيد دايناينتريت قد جرى تقيمها بالمقارنة مع معدل الانحلالية لمستحضر مرجعي (منشأ أوربي) لهذا الدواء.

لقد اظهرت نتائج المقارنة ان مستوى التكافؤ الحيوي للمستحضرات التجارية كان دون مستوى المستحضر المرجعي وعليه فقد تم وضع صيغة محسنة لحبوب الايسوسوربيد دايناينتريت باستعمال تقنية الضغط المباشر لصناعة الحبوب مما ادى الى ارتفاع معدل الانحلالية وزيادة ثبوتية المادة الفعالة

Abstract:

Isosorbide dinitrate is prepared as a solid dosage forms, and found in the market as a sublingual tablet or conventional tablet of 10mg for oral administration which is subjected to the dissolution study.

In this present work, different commercial products of Isosorbide dinitrate tablets were subjected to dissolution test according to USP method which includes an HPLC determination. The dissolution profiles of three commercial products of isosorbide dintrate tablets and preformulated product were evaluated by comparing with that of reference standard (European product. Actavis Co.) .

Due to low bioequivalenceis of all the commercial products relative to the reference standard, attempts were made to improve the formula of the experimental batch of isosorbide dinitrate tablet by enhancing the dissolution rate and increase the stability of the active substances via the Using of a direct compression method in manufacturing of isosorbide dinitrate tablet which on testing showed a high dissolution rate with optimal physical properties of tables.

Introduction:

Isosorbide dinitrate is a vasodilator with general properties similar to those of glyceryl trinitrate. It is used in the management of angina pectoris and of heart failure [1].

Isosorbide dinitrate tablet is characterized with a low bioavailability after oral administration due to pre systemic clearance. Isosorbide dintrate was prepared as sustained release tablets and its bioavailability were studied [2,5]. Isosorbide dinitrate is very slightly soluble in water which leads to low dissolution, and as a resuult low bioiavailability. The using of β-cyclodextran by japanish workers with Isosorbide mononitrate in a mixture 1: 1 tends to increase the stability and obviously increased the dissolution of tablet preparation[6].

Investigations for the loss in Isosorbide dinitrate concentration which might be attributed to degradation were also carried by a selective HPLC method [7]. However, many HPLC method have been described for determination of isosorbide dinitrate and its derivative mononitrate in solid dosage forms and in human plasma[8,14] .

Isosorbide dinitrate is supplied as 25% diluted powder, mixed with stabilizer since it is sensitive to light and atmosphere, therefore, should be stored in airtight containers. The manufacturing process of Isosorbide dinitrat tablet should be carried in such method to avoid using moisture, due to its instability in aqueous solution.

The British pharmacopoeia discussed the method of measuring the dissolution of Isosorbide dinitrate tablet in 0.1M HCL for 45 minutes .The results were compared with that of reference product (Actavis Co). Most of the generic products of Isosorbide dinitrate tablets used in this work have showed lower dissolution than that of reference tablet. This study, in fact, revealed the necessity of improving the bioequivalency of the commercial products of Isosorbide dinitrate by the precise selection of raw materials and the using of proper solublizing excepients and method of manufacturing.

Materials and apparatus:

Isosorbide dinitrate tablet 10 mg (Actavis Co.), Epico ,DAD,SDI, Solvents; HCL Conc, (Reagent grade),,methanol (HPLC grade), Lactose DC, Avesil 102 ,PEG6000 and Isosorbide dintrate 25% diluted (USP) from (Furate pharm,Ind,).

Dissolution apparatus (kaneur Co.), HPLC appratus (Schimadzo Co.) consists of UV-Visible detector,dual system pump, and software programmer for quantitativework .

Procedure:

Dissolution system: by using the USP solvent (900 ml of 0.1 M HCL), 50 RPM, and the measuring is carried by HPLC for withdrawn samples at different

intervals; 5,10,15,20,30,45 minutes. The dissolution tests were carried for the following samples of isosorbide dinitrate tablets;

Isosorbide dinitrate tablet 10 mg of; (Actavis co.) European origin which is used as reference standard, DAD Co. Jordanian, Epico Co. Egyptian, SDI Co.Iraqi, and experimental batch.

Chromatographic conditions:

Column: ODS (25 cm length), Mobile phase; Methanol: water (50:50) filtered and degassed, Detection; at 222 nm, flow rate; 1 ml per minute.

Formulation of Isosorbide dinitrate tablet 10 mg:

The formula consists of the following ingredients; Diluted Isosorbide dinitrate powder equivalent to 10 mg of Isosorbide dinitrate, Lactose DC (60 mg), Avecil 102 DC (40 mg), PEG-6000 (20mg), magnesium strearate (2mg). The average weight of tablet is 132 mg which is manufactured by direct compression.

Results and discussion:

The results of dissolution tests for the commercial products of Isosorbide dinitrate tablets with their constructed dissolution profiles are shown in figure (1) which indicated that the levels of dissolution of all the commercial products are lower than that of reference standard product. In other hand, the percents of dissolved isosorbide dinitrate after 45 minutes were acceptable (USP requirements is not less than 70%), however their bioequivalencies relative to the reference standard are considered low.

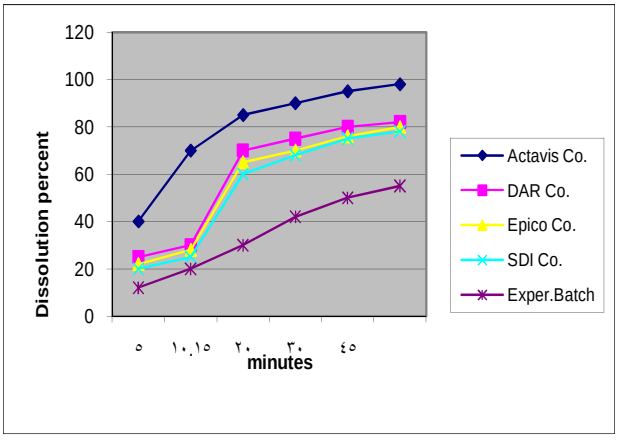


Figure-1: dissolution profiles of different commercial products of isosorbide dintrate tablets compared with reference standard (Actavis Co.).

The quantitative determinations were carried by HPLC method (Figure-2)and the results were quite confidential, since The relative standard deviation of

five injections was less than 1.2% and straight line relationship was obtained between the peak areas and standard dilutions with confidence limit (r^2= 0.999) .

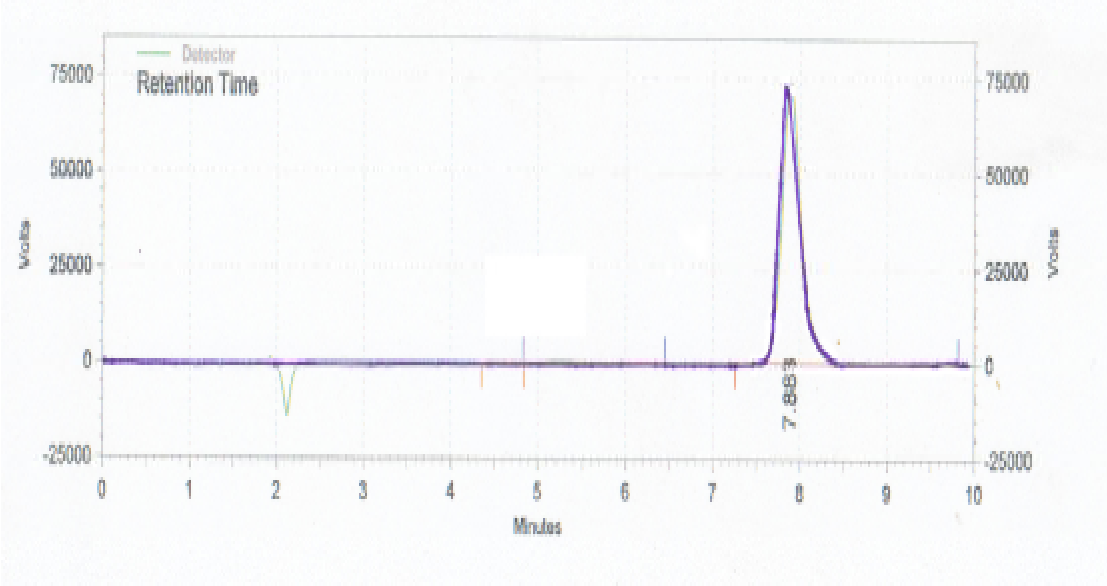
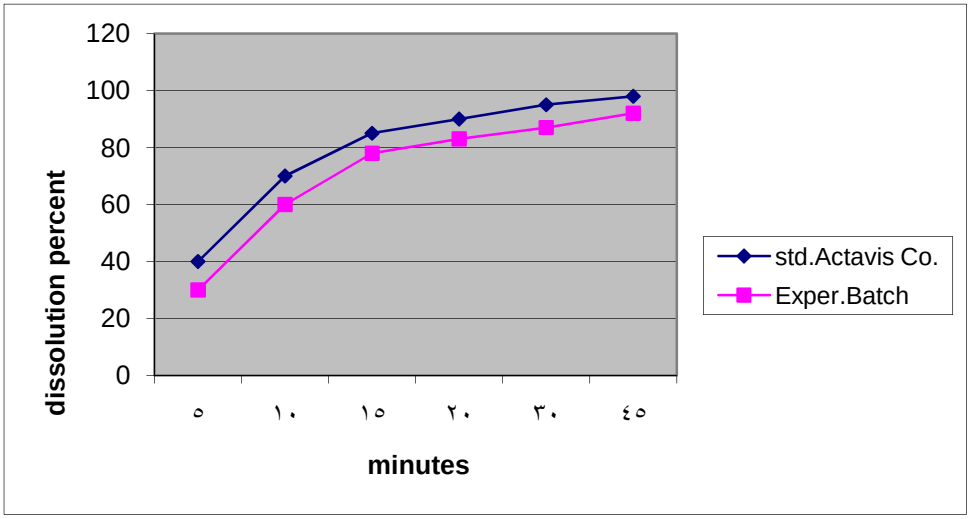


Figure -2: chromatograme for standard isosorbide dinitrate solution 0.001 w/v, retention time = 7.8 min.

For new formulated experimental batch of isosorbide dintrate tablet which is prepared by direct compression the physical properties of tablet were extremely optimized and the results were as following; for disintegration test within 15 second and friability zero. In addition, the dissolution profile was significantly enhanced and this product proved to be bioequivalent to the reference standard.



Dissolution profile of the new formula isosorbide dinitrate tablet Compared with that of reference standard (Actavis Co).

Conclusion:

This work revealed that the different commercial products of isosorbide dinitrate tablets are different in their bioequivalencies, which were evaluated by

their dissolution profiles and the best method of manufacturing this tablet is by direct compression with the use of PEG6000 as a solubilizing agent.

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