In Vitro Release Study on Capsules and Tablets Containing Enteric - Coated Granules Prepared by Wet Granulation

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ABSTRACT

Wet granulation method was used instead of conventional pan coating or fluidized –bed coating technique to prepare enteric-coated diclofenac sodium granules, using ethanolic solution of Eudragit™ L100 as coating, binding and granulating agent .Addition of PEG400 or di-n-butyl phthalate as a plasticizer was found to improve the enteric property of the coat.

Part of the resulted granules was filled in hard gelatin capsules (size 0), while the other part was compressed into tablets with and without disintegrant.

The release profile of these two dosage forms in 0.1N HCl (pH 1.2)for 2 hours, and in phosphate buffer (pH 6.8) for 45 minutes as well as the release kinetic were compared with that of the enteric film coated Voltadin (R) SDI tablets.

The results of this study show that, the prepared dosage forms have a good enteric property, with faster release of drug from encapsulated enteric-coated granules in comparison with compressed tablets.

الخلاصة

تم استخدام الطريقةالرطبة لتحضيرحبيبات مغلفة معويا بدلا من الطرق الشائعة الأخرى لتحضيرعقار صوديوم دايكلوفيناك و ذلك باستخدام محلول كحولي لمادة اليودراجيت ا ل ١٠٠ كمادة رابطة لتكوين الحبيبات بالأضافة الى كونها مادة مغلفة حيث انها لاتذوب في المعدة ولكن تذوب في أس هيدروجيني اعلى من٦ وقد وجد ان استخدام مواد تزيد من مرونة المادة المغلفة مثل البولي اثيلين كلايكول٤٠٠ ومادة ثنائي بيوتيل فثاليت تحسن من عملية التغليف المعوي.

وقد تم تعبئة جزء من هذه الحبيبات في كبسولات كما تم ضغط الجزء الآخر وتحويله الى حبوب، حيث تم مقارنة كيفية وسرعة تحرر العقار من هذه الأشكال الصيدلانية في وسط ذي اس هيدروجيني١,٢ (حامض الهيدرو كلوريك ذي عيارية قيمتها٠,١) لمدة ساعتين وفي وسط ذي اس هيدروجيني ٦,٨ لمدة ٤٥ دقيقة مع حبوب الفولتادين(المغلفة معويا) من انتاج معمل ادوية سامراء.

وقد اظهرت النتائج جودة التغليف المعوي للأشكال الصيدلانية المحضرة، وأن تحرر العقار من الكبسولات الحاوية على الحبيبات المغلفة معويا كان أسرع من تحرره من الحبوب.

INTRODUCTION

Enteric coated granules encapsulated in hard gelatin capsules as a pharmaceutical dosage form were used to get products with fast onset of absorption and better pharmacokinetic properties [1-3], since this dosage form is less influenced by food intake due to faster gastric emptying of granules after dissolving of hard gelatin shell compared with the retention of relatively large enteric coated tablet in the stomach.

In addition, patients preferred the easily swallowed gelatin capsules on tablets [4].

Different techniques were used to prepare enteric-coated granules or pellets, such as pan coating and fluidized bed coating apparatus [5-8].

The aim of this study is to investigate whether enteric-coated granules could be prepared by ordinary wet granulation method using ethanolic solution of Eudragit™ L 100 as coating and granulating agent.

The non-steroidal anti-inflammatory drug (NSAID) Diclofenac sodium is used as a model drug for this study.

MATERIALSand METHOD

Materials:-

The following materials were used , Diclofenac sodium (Bio Gena.Italy), Eudragit™ L 100 (Rhöm pharma ,GMBH, Weiterstadt, Germany) ,Ethanol 95% ,Polyethylene glycol 400 (BDH chemicals Ltd,Pool England), Lactose ,Hydrochloric acid, (Riedal-De Haen, AG Seelze-Hannover, Germany) ,Microcrystalline cellulose (Avicel PH 102) (FMC Corporation,Pensylvania USA.) ,Trisodium phosphate (Hopkins and Williams Ltd. ,England), Di-n-butyl phthalate (USB ,B. Brussels ,Belgium), Magnesium stearate (Merck ,Darmstadt ,Germany), and enteric film coated Voltadin(R) SDI tablet as a reference.

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Method:-

• Preparation of Enteric-Coated Granules:-

Diclofenac sodium was mixed with lactose and the powder mass was moistened with 2% ethanolic solution of Eudragit™ L100 as a granulating , binding and enteric coating agent [6, 9] until the proper consistency was obtained. The amount of enteric polymer was about 1.25% based on the total weight of the powder mixture. The moist mass was then granulated by passing through a 0.8 mm mesh size sieve. The granules were then dried on trays. Part of the resulted granules was filled in hard gelatin capsules size 0 (25mg/capsule) while the other part was compressed into tablets (25mg /tablet).

• Dissolution:-

The dissolution characteristics of the encapsulated enteric-coated granules, the compressed tablets from the prepared granules and Voltadin(R)SDI tablets as a reference were studied using USP XXIV method for enteric coated products at 50 r.p.m and constant temperature (37± 0.5 °C). One capsule or tablet of each was placed in 750 ml 0.1 N HCl (pH 1.2)and samples were taken for 2 hours, followed by addition of 250 ml of 0.2M trisodium phosphate to the same jar to get phosphate buffer of pH 6.8, then sampling were continued for 45 minutes [10].

Samples were taken at certain time intervals and assayed for diclofenac sodium spectrophtometrically at its λmax 273 nm for the acid medium and at λmax 276 nm for the buffer medium.

• Factors Affecting the Preparation:-

1. Effect of Addition of Plasticizer:-

Two different types of plasticizers were used to study their effect on improving the coating property of Eudragit™ L100. A water-soluble type (PEG 400) and non water-soluble (Di-n-butyl phthalate). 10% of either type of plasticizer calculated on the amount of dry lacquer substance was added to the coating solution [9].

2. Effect of Compressing the Granules:-

Part of the resulted enteric-coated granules was compressed into tablets. The results of dissolution of these tablets were compared with that of encapsulated enteric-coated granules.

3. Effect of Addition of Disintegrant :

10% Avicel PH 102 calculated on the total amount of granules was added extragranularly [11] to the enteric coated granules before compression. The results of dissolution were compared with those of encapsulated enteric-coated granules as well as with tablets prepared from the same granules but without disintegrant.

RESULTS and DISCUSSION

• Dissolution in Acid Medium:-

1. Effect of Addition of Plasticizer:-

The effect of plasticizer was studied by comparing the release of drug from the encapsulated granules coated with Eudragit™ L100 in acid medium with and without addition of plasticizer.

The results show that 15% of the drug was released from the coated granules in the absence of plasticizer in the coating solution, which is not accepted according to the USP requirements for the enteric-coated preparations, which state that not more than 10% of drug dissolves at the end of 2 hours [10].

Addition of either PEG 400 or di-n-butyl phthalate to the coating solution decreased the release of the drug after 2 hours of dissolution in acid medium to 6.2% and 8.5% respectively in comparison with 10% released from the reference Voltadin(R) SDI tablets (Fig. 1), which are all acceptable.

These results indicate that addition of either of the plasticizer can improve the enteric property of the coating polymer which may be due to increasing the mobility of the chain of the polymer at the surface of the granules, so they facilitate the filming property of the polymer [12,13],but since di-n-butyl phthalate is non water soluble, it will decrease the permeability of film to moisture and enhance the stability of the product, so it is preferred for the preparation of this product on PEG 400 [14],therefore the granules prepared with PEG 400 were neglected.

2. Effect of Compressing the Granules:-

Compressing of the granules prepared using di-n-butyl phthalate as plasticizer for the coating material to tablets with and without addition of disintegrant, resulted in decreasing the release of drug in the acid medium of dissolution to 7.4% and 6.3% respectively in comparison with the encapsulated granules (Fig. 1). The decrease in the release of drug may be due to the smaller surface area of the tablets compared to the granules, while the slight difference in the release between the two tablet preparations, may be due to the effect of disintegrant.

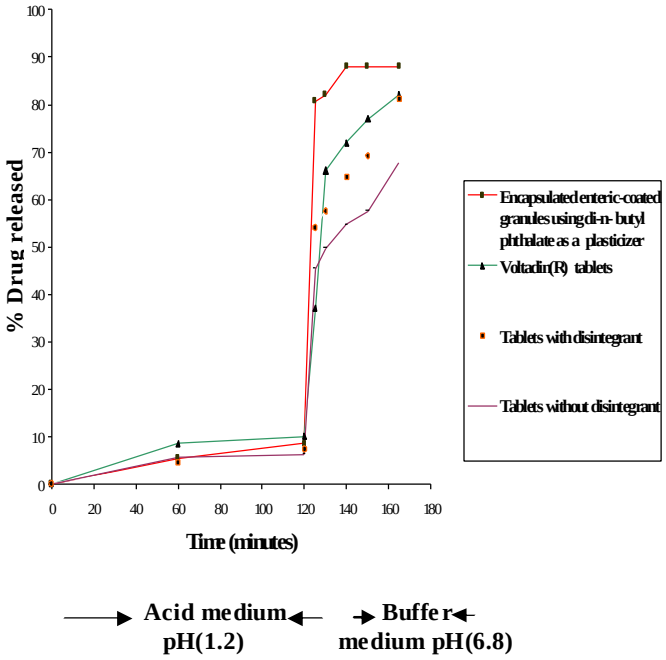

Fig. (1) Dissolution profile of encapsulated enteric-coated granules tablets Prepared with and without addition of disintegrant in comparison with Voltadin(R)SDI tablets

• Dissolution in Buffer Medium:-

As shown in Fig. 1, higher and faster release was obtained from encapsulated enteric-coated granules in comparison with Voltadin(R)SDI tablets and tablets prepared with and without addition of disintegrant, where about 90% of the drug was released from these granules within 20 minutes [8] compared to 72%, 57.5% and 49.7% from the other tablets, respectively.

This high and fast release of drug is mainly due to the larger surface area of the granules compared to the tablets.

In addition, both the encapsulated enteric-coated granules and tablets containing disintegrant as well as Voltadin(R)SDI tablets met the USP specifications for the release of drug in buffer solution (not less than 75%of drug dissolves at the end of 45 minutes) [10] in contrast to tablets without disintegrant.

Kinetics of Dissolution:-

The release characteristics of the drug from encapsulated enteric-coated granules and tablets prepared from these granules in presence of disintegrant as well as that of Voltadin(R) SDI tablets, follow first order kinetics, since plotting the logarithm of the percent remaining versus time gave straight lines with good correlation (r-value range from -0.94 to -1.01) for the acid medium and the two phases in the buffer medium of dissolution as shown in Fig.2.

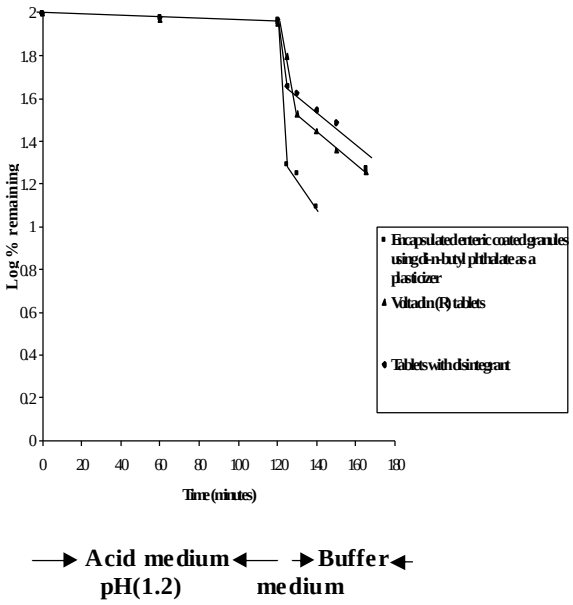

Fig. (2) Plot of the log % remaining versus time for the release of drug from encapsulated enteric-coated granules and tablets prepared with addition of disintegrant in comparison with Voltadin(R) SDI tablets.

The small value of the release rate constant in the acid medium(pH 1.2) (Table 1) gives an indication that the coating material (Eudragit™ L100) when used as granulating and binding agent is effective in preventing the release of drug in acidic pH.

However, the small and slow release of drug at this pH may be either due to the presence of small-uncoated drug or due to the release of drug through the coating and its possible discontinuities [15].

As the pH of the dissolution medium reaches the level critical for the coating pH 6.8 (buffer medium) the film starts to dissolve, thereby increasing the release of drug [9, 15] as shown in Fig.2 and Table 1, in which there is a great increase in the release rate constants of the two dosage forms in the buffer medium mainly at the first phase (more than 100 times) compared to that at acid medium.

In addition, the results of dissolution at the buffer medium give an indication that the release of drug is affected by the dosage form

as well as by the surface area, since the release rate constants for the encapsulated enteric-coated granules are higher than that of compressed tablets.

Table (1)
Release rate constants (K) min^{-1}.of the Prepared Dosage Forms in Comparison with Voltadin(R) SDI Tablets

pH The Dissol-ution Medium	Encapsulated Enteric-coated Granules using di-N-Butyl Phthalate as Plasticizer	Tablets with Disinte - grant	Voltadin(R) SDI Tablets
1.2	$76.75*10^{-5}$	$57.5*10^{-5}$	$88.3*10^{-5}$
6.8			
K_1	0.309	0.143	0.098
K_2	0.031	0.020	0.017

Abbreviations:-

K_1: refers to the dissolution rate constant for the first phase in the buffer medium

K_2: refers to the dissolution rate constant for the second phase in the buffer medium

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