Some Variables Affecting the Formulation of Pentoxifylline (PTX) as a Solid Sustained Release Dosage Form

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Abstract

An inert matrix that is used to control the release of (PTX) was prepared using Eudragit RL100 and RSPM types as matrix forming agent . The matrices were prepared by either dry granulation(slugging) , or wet granulation method using chloroform as a solvent evaporation vehichle. The cumulative release was adjusted by using polyvinylpyrollidone (PVP) or ethylcellulose (EC) polymers .The results indicated that both methods of preparation were valid for incorporation PTX as a sustained release granules .Moreover ,the results revealed that best polymer used was Eudragit RSPM in 3:20 polymer drug ratio .Besides to that , the results indicated that the release profiles were affected by pH- medium , PVP and EC addition as an enhancer or retardant polymer used respectively. As well as to the method of preparation .

Key words : Pentoxifylline Sustained Retease , Eudragit RS , RL .

الخلاصة

القالب الغير فعال المستخدم للسيطرة على تحرر عقار البنتوكسيفلين قد حضر بأستخدام اليودراجيت نوع ار.ال100 و كذلك ار.اسب م , لقد تم تحضير القالب بأستخدام طريقة الحبيبات الجافة)الاقراص(و الحبيبات الرطبة بأستخدام الكلوروفورم كمادة طيارة في طريقة التحضير .لقد اشارت النتائج الى أن كلا الطريقتين كانتا صالحة لأدخال العقار كحبيبات بطيئة التحرر علاوة على ذلك فأن النتائج أظهرت ان افضل بوليمر استعمل هو يودراجيت أر.اسب م بنسبة20:3 بوليمر :عقار .كما اشارت النتائج الى ان الأوساط الحامضية مختلفة الأس الهايدروجينى لها تأثير على تحرر العقار .اضافة الى البولي فينيل بايروليدون و الاثيل سلليلوزكمواد مسرعة او مبطئة على التوالي .علاوة على طريقة التحضير .

Introduction

Tablet dosage form can be defined as a unit dose of medication containing one or more of medicinal agents, with or without diluents, made by molding the mixture in a suitable compressible shape[1].Sustained release dosage form having drug release features based on the time or location designed to accomplish convenience and therapeutic not offered by conventional release form [2]. An inert matrix was used to control the drug release , and this can be adjusted by using the enhancers such as microcrystalline cellulose , polyvinylpyrrolidone or surfactants .Eudragit RL100 and RSPM ,are methacrylic copolymers introduced as a coating materials with different permeabilities [3] , depending on functional ionized or neutral groups .They are commonly used in sustained release dosage forms [4]. The distinguishing letters RL and RS related to the initial letters of German words " Leihtduchlassig " freely permeable and Schwerduchlassig , slightly permeable . Pentoxifylline (PTX) also called oxpentifylline is one of the xanthine vasodilator derivative [5] ,that improve with its active metabolite peripheral aterial circulation, and enhance tissue oxygenation The apparent plasma half life of the drug and its metabolite is 2-3 hours . On the bases of using PTX as drug of choice in chronic occlusive aterial diseases , therefore ,it is of a wise candidate drug to be formulated in Sustained release oral dosage form. The usual dosage form of PTX in controlled release tablet from available maintained one is one tablet (400mg.) twice daily . The objective of this study is to prepare controlled release PTX matrix tablets , utilizing dry and wet granulation technique by using Eudragit RL and RS types with PVP and EC polymers as enhancer and retardant materials respectively , to control the release of PTX for extended period [6] .

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Received : 9/11/2007

Accepted : 5/3/2008

Materials and Methods

Materials

Pentoxifylline supplied by slovakopharma , Slovenia , Aceton,acetic acid,chloroform ,ethylcellulose , PVP,from BDH chemicals ,Ltd.Liverpool , England Disodium hydrogen phosphate , HCL ands Lactose from Reidal De Haen Ag Seelz Hanover , Germany (GER) , Eudrait RL100 and RSPM , from Rhom pharma GMBH Weiterstadt GER. ,All other reagents were of analytical grade .

Equipments

Dissolution apparatus ,Copley dissolution DIS 8000 , Copley Scientific , Ltd , UK , Hardness tester , Stokes Monsanto Corporation Limited ,England ,pH-meter ,Hanna Instrument pH 211 Microprocessor , Italy,Oven , Water bath , Memert UL 80 , Rostfrei, Schwach , Germany . Friabilator , Sieves , Roche type Moore and Wright ,Sheffield , England ,Sartorious Balance , Werk-GmbH ,Type 1265 MD , 2854 MD,Germany ,Spectrophotometer , Carry win UV , Varian , Australia ,Tablet Machine double punch , Korsch , type EKO , Erweka ,GmbH, Kr , Offenbach Main , Germany

Methods :

Preparation of Eudragit Solutions :

Eudragit solutions RL100 and RSPM were prepared separately at a concentrations 5 ,10 ,15% by dissolving the desired amount of Eudragit RL100 and RSPM with the desired volume of chloroform , the mixture was shacked for 15 minutes in 25°C until homogenous clear transparent solution was resulted [7]

Wet Granulation :

Different formulas (table 1) were prepared by weighing the drug and excipient equivalent to 30 tablets after drying , then blending the powder and mixed with binding solution of Eudragit polymers used gradually , until proper ball test consistency was result ,The wet mass was screened through 12 mesh sieve and dried in pre warmed oven maintained at 50°C for 2 hours , the dry granules were reduced in size by screening them through 16 mesh size sieve . Then an equivalent weight of granules that contain 400 mg. PTX was mixed with calculated amount of magnesium stearate 0.5% w/w for one minute and compressed into a tablets using 10mm. biconcave double punch compression tablets machine at 11ton compression force

Table (1) . Different Formula of Pentoxifylline with Different Physical Properties of Compressed Tablets

Frmula	PTX (gm)	Eudragit RL(mg)	Eudragit RS(mg.)	PVP (mg)	EC (mg)	Lactose (mg.)	Magnesium stearate (mg.)	Total weight (mg.)	Friability %	Hardness (mg.)	APPEARA
F1	400	20				127.25	2.75	550	3.0	17.1	Friable , Wdusty
F2	400	40				107.25	2.75	550	2.8	17.2	Friable , Wdusty
F3	400	60				87.25	2.75	550	1.5	19	Friable , Wdusty
F4	400	80				67.25	2.75	550	1.0	>20	Friable , Wdusty
F5	400		20			127.25	2.75	550	3.0	17.2	Friable , Wdusty
F6	400		40			107.25	2.75	550	2.7	17.4	Friable , Wdusty
F7	400		60			87.25	2.75	550	1.5	18.4	Friable , Wdusty
F8	400		80			67.25	2.75	550	0.9	>20	White Accepte
F9	400		60	13.8		73.45	2.75	550	0.67	>20	Gray Accepte
F10	400		60	27.6		59.65	2.75	550	0.54	>20	Faint yellow Accepte
F11	400		60	41.4		45.85	2.75	550	0.32	>20	Faint yellow Accepte
F12	400		60		13.8	73.45	2.75	550	0.66	20	White Accepte
F13	400		60		27.6	59.65	2.75	550	0.42	20	White Accepte
F14	400		60		41.4	45.85	2.75	550	0.34	20	White Accepte

Dry Granulation :

The method of dry granulation was introduced as an alternative method for a selective formula (F14) , this was briefly done by weighing the drug and another excipients that equivalent to 30 tablets,then blending and compressed by means of wide single punch machine into 22mm. diameter slugs. These slugs were reduced in their sizes by milling and sieved by 16 mesh size sieves , the resulted particles were mixed with calculated amount of magnesium stearate 0.5% (w/w) and compressed into 10mm. double punch compression tablet machine at the same compression force .

Assay of Total PTX in Prepared Sustained Release (SR) Tablets:

An accurate weight of powder of triturated tablets equivalent to 400mg. of PTX was added to 500ml. of distilled water and shacked for 15 minutes and filter 1ml. of filtrate was diluted to the appropriate concentration (8µg/ml) with distilled water , the absorbance of the final solution was determined spectrophotometrically at 274nm wave length[5] This procedure was performed for those tablets prepared in all methods mentioned before .

Assay of Total PTX in Reference SR- Tablets (TRENTAL 400mg):

Ten tablets of the reference product were weighted individually to get the net weight of each tablet , and then triturated together , An accurate weight of triturated powder equivalent to 400mg. PTX was dissolved in 500ml. distilled water , the final solution was diluted to maintain PTX concentration at 8µg/ml by distilled water , the absorbance was measured using UV-spectrophotometer at 274nm. wave length [5] .

Friability and Breaking Strength Measurement

This measurement was carried out for all prepared formulas using Roche friabilator . the loss in weight of 20 tablets tested before and after rotation should not exceed 1% of total weight of tablet [8] .On the other hand the hardness of the prepared tablets were examined by means of Monsanto hardness tester .

Dissolution Behavior:

Dissolution of the PTX from prepared tablets was carried out using USP basket method maintained at 37°C temp. , and 75 r.p.m speed for 500ml.of buffer solutions (pH 1.2 ,4.6,and 6.8). Samples of 5ml. were withdrawn at 1 hour time intervals for 6-10 hours then the samples filtered and diluted, then cumulative drug release was measured at 274nm. for triplicate samples .

Results and Discussions

Formulation of PTX as A SR- Tablets :

All the powders blend and granules were intended for compression successfully into shiny look appearance . the breaking strength were varied from friable to hard (20kg.) hardness. This variation may be referred to the polymer type and concentrations [9 , 10] . as shown in formula 4 and 8. On the other hand PVP presence gave harder granules (formula 12) compared with others [11] . The same results obtained when ethylcellulose was used as retardant material , since both PVP and EC act as binding and consolidating agents in tablets formulation [12 ,13] .

Dissolution Behavior

Effect of Eudragit Polymer :

Figures (1 and 2) illustrate the cumulative release of PTX from various polymer-drug ratios in phosphate buffer (pH6.8) , the results indicated that the drug release is increased as a function of increasing this ratio for both Eudragit types used , this behavior referred mainly to the thickness of the polymer around drug particles, that results in a delayed permeation of water inside drug particles and dissoluted drug outside stagnant layer of PTX particle [14] .On the other hand the cumulative release of PTX from two polymers used (fig.3) revealed that after 10h. of dissolution, the percent of drug release from formula 3 is 88% compared with 60% in formula 7 , while the reference tablet (Trental400) gave 51% drug release after same period of dissolution . This difference may be attributed to the presence of highly basic quaternary ammonium groups (1:20 and 1:40)ratios for both Eudrait RL and RS types ,respectively which they undergo more solubilization in acidic medium, then the over all solubility of the drug within deaggregated polymer is increased [15] .

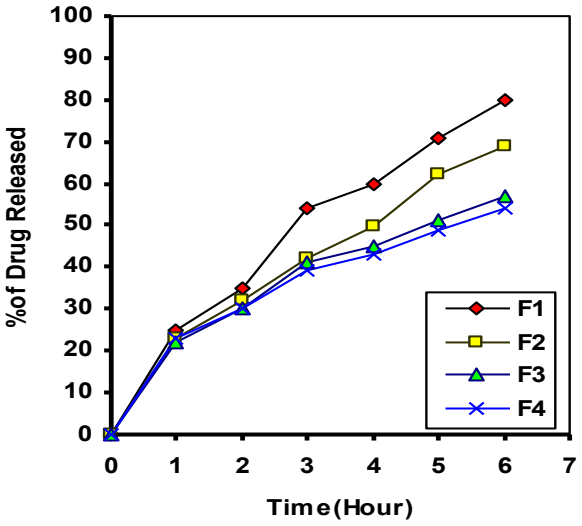

Figure 1. The percent of PTX released from different formulas at phosphate buffer pH 6.8 using Eudragit RL100 polymer.

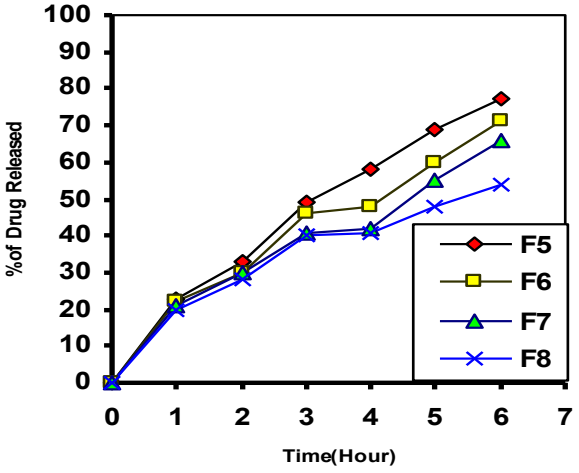

Figure 2. The percent of PTX released from different formulas at phosphate buffer pH 6.8 using Eudragit RSPM polymer.

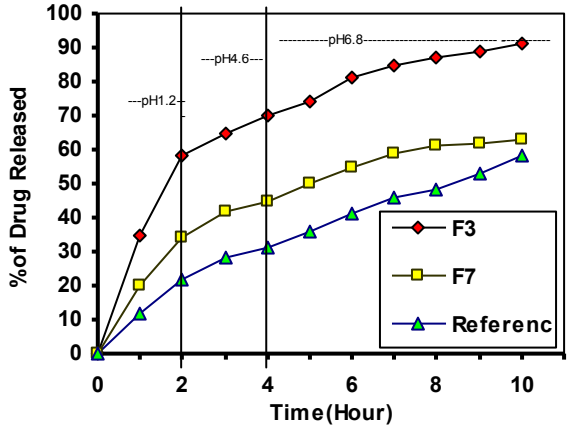

Figure 3. The cumulative percent of PTX released from formulas 3,7 and Reference (Trental 400 mg.) at different pH-medium.

Effect of Polymer Type :

Concerning the type of Eudragit used , fig.3 demonstrate that the time for 50% drug release extended for 2 hours compared with more than 5 hours for both Eudragit RS and RL , respectively . the illustration for this variation related to the higher permeability of Eudragit RL than that of RS polymer type[16] .

Effect of PVP Addition :

Based on the results obtained as shown in fig .4 , It was shown that addition of PVP in formula 7 made of Eudragit RS type , enhance the cumulative release to about 96% when 7.5% w/w PVP used , compared with 50% for reference one this effect may be referred to the higher solubility of PVP in different media mainly at pH 5-7 medium [17] .

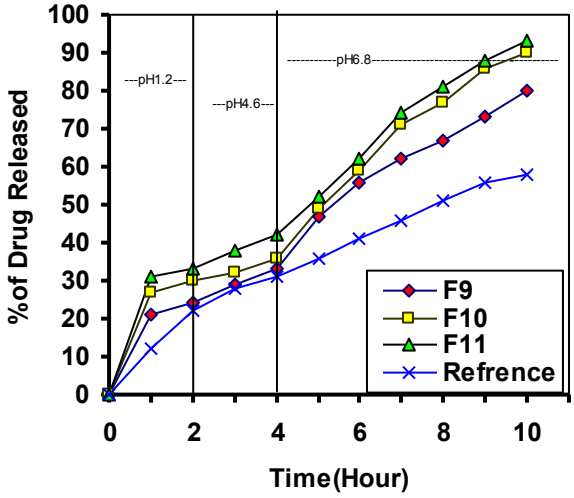

Figure 4. Effect of PVP addition on the cumulative released of PTX from tableted matrix at different pH-medium.

Effect of EC Addition :

The influence of addition 2.5 ,5 and 7.5% w/w of EC to the matrix formulation of formula 7 was illustrated in fig. 5 ,which represents the cumulative release of PTX ,It was seen that when EC incorporated as a retardant material, a slight less or more in drug release was resulted compared with that of reference one (Trental) , and in an appreciab decrease in drug in drug release compared with the other formulas free from EC , which is attributed to the insolubility of EC in water, besides rigid consolidation of Eudragit RS and EC polymer that retain drug in matrix , this phenomena is in a consistent with results obtained by Aldermann [18] and Sreubel [19] .

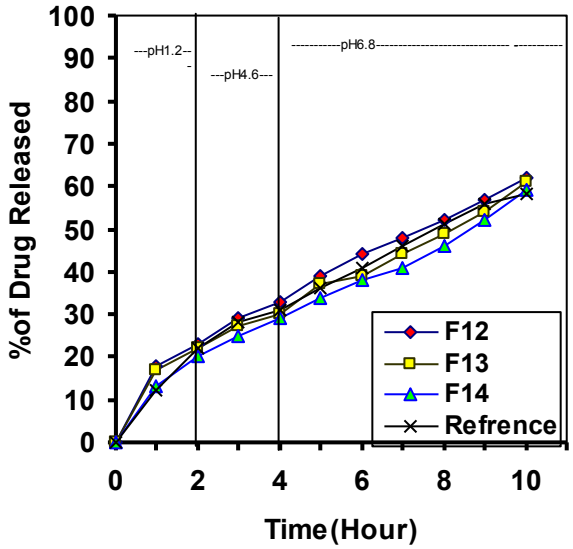

Figure 5. Effect of Ethylcellulose (EC) addition on the cumulative released of PTX from tableted matrix at different pH-medium.

Effect of Granulation Method :

The selected formula 14 was reformulated again using dry granulation method , the results indicated that cumulative drug release by this method gave 75% , compared with 59% for wet granulation after 10h. , as shown in fig. 6 , this behavior may be referred to the solvent effect (chloroform vehicle) that used in a later method help in a formation of more Van Der Waal"s forces among polymer used and PTX (20) . these bonds make a matrix more rigid and delayed drug release through them.

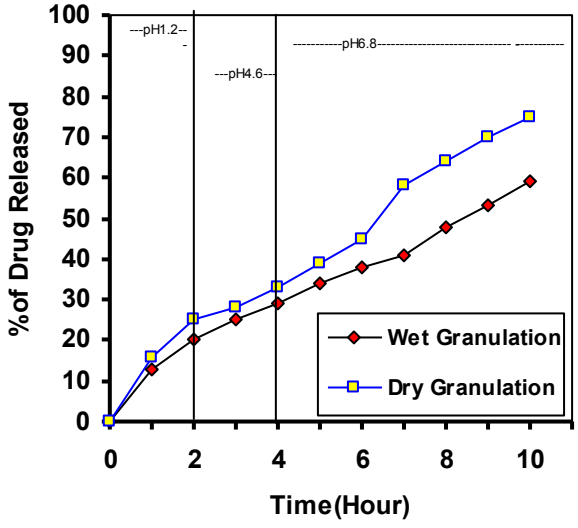

Figure 6. Effect of preparation method on the cumulative release of PTX from selected formula 14 at different pH medium.

Conclusion :

- Concerning the method used , the study demonstrate that both methods were valid for formulation of PTX as promised acceptable SR- granules. But wet method is preferred .
- Both Eudragits used RL100 and RSPM were succeeded in a formation of delayed release matrix .
- Eudragit RS is best to be used in 3:20 polymer :drug ratio for SR granules to utilize PTX as SR matrix similar to (Trental400) .
- The dissolution behavior of PTX from prepared granules varies with different pH-medium , and coating materials .
- Generally , the release of PTX is affected by addition of PVP and EC mainly for matrix made of Eudragit RS(PM) type in a concentration 7.5% w/w.
- Best formula when EC was added to formula 7 represented formula 14 .

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