Formulation of Metoprolol Bilayer Tablets as an Oral Modified Release Dosage Form

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Abstract

Metoprolol is a β_1 adrenergic blocker used in treatment of heart diseases. Metoprolol (100mg) tablets was formulated as a modified release oral system utilizing the concept of bilayer system, first layer contained (30mg) as immediate release and the other (70mg) in the sustained release matrix. The immediate release layer consisted of lactose or microcrystalline cellulose as diluents with sodium starch glycolate or sodium croscarmellose as disintegrants. The result showed that the layer contains microcrystalline cellulose and 2% sodium starch glycolate gave disintegration time similar to that of conventional metoprolol tartrate tablet. This result was subjected in the subsequent preparation of the bilayer tablet. The sustained release layer was prepared using three polymers: ethylcellulose (EC), Hydroxypropyl methylcellulose (HPMC) and hydroxyl ethylcellulose (HEC) as retardant materials. It was found that the combination of EC with HPMC in ratio of 2:1 in F11 was best formula because of it's release profile and the tablet integrity and dimensions were conserved for the period of the test, but according to similarity factor (f_2), F15 (which contained EC:HPMC in ratio 2:1 with polyvinyl pyrrolidone (PVP) as a binder) was the best formula showed higher (f_2) among all other formulas and equals to 72.3 comparing to reference product.

Key words: Metoprolol, Bilayer tablet, Immediate release, Sustained release.

الخلاصة

الميتوبرولول هو حاصر أدرينالييني ب١ يستخدم في علاج أمراض القلب. تم تصييغ حبوب الميتوبرولول (١٠٠مغ) كنظام دوائي فموي متغير التحرر بإستخدام مبدأ نظام ثنائي الطبقة، الطبقة الأولى تحوي (٣٠مغ) وتكون مباشرة التحرر وال (٧٠مغ) الاخرى في قالب بطيئ التحرر. الطبقة مباشرة التحرر تتكون من كل من اللاكتوز أوالسليلوز مجهري التبلور كمخففات مع صوديوم نشاألكلايكولت أو صوديوم الكروسكارملوس كمفككات. تبين النتائج بإن الطبقة التي تحوي على السليلوز مجهري التبلور مع ٢% من صوديوم نشاألكلايكولت تعطي وقت تفكك مشابه لحبة الميتوبرولول التقليدية ولذلك أستخدمت في التحضيرات اللاحقة للحبوب ثنائية الطبقة. حُضرت الطبقة بطيئة التحرر بإستخدام ثلاثة بوليمرات هي الاثيل سليلوز ،الهايدروكسي بروبيل مثيل سليلوز و الهايدروكسي اثيل سليلوز كمثبطات تحرر. وجد إن خليط من الاثيل سليلوز و الهايدروكسي بروبيل مثيل سليلوز بنسبة ١:٢ في الصيغة ١١ هو أفضل صيغة بسبب الشكل الجيد للتحرر وهيكلية الحبة وأبعادها كان محافظ عليهم خلال فترة الإختبار، لكن إعتمادا" على عامل التشابه، الصيغة ١٥ (التي تحوي الاثيل سليلوز و الهايدروكسي بروبيل مثيل سليلوز بنسبة ١:٢ مع البولي فنيل بايروليدون كمادة رابطة) كانت أفضل صيغة وأظهرت اعلى عامل تشابه وهو ٧٢.٣ مقارنة بالمنتج المرجعي.

Introduction

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and have traditionally prepared by either compression, or molding methods. Recently, punching of laminated sheets, electronic deposition methods, and three-dimensional printing methods have been used to formulate tablets [(1)]. Modified-release tablets are coated or uncoated tablets that contain special excipients or they are prepared by special procedures, or both, designed to modify the rate, place or time of release of the active substance(s) [(2)]. Layered tablets, type of modified release, are prepared by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control to form two- or three- layered tablets, depending on the number of separate fills. Each layer may contain a different medicinal agent, separated for reasons of chemical or physical incompatibility, staged drug release, or simply for unique appearance of the layered tablet [(3)]. Some layers may be formulated to exert certain functions. Rahmanz Z. et al, designed a bilayer floating tablet of captopril in which one layer responsible for floating of the tablet for prolongation the gastric residence time with a controlled release mechanism[(4)]. The bioavailability of propranolol was enhanced by formulating a bilayer and multilayer buccal mucoadhesive tablet in which one layer adhere to the buccal mucosa so localized the drug in the oral cavity and avoid hepatic first pass metabolism [(5)].

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Received : 1 /8 /2009
Accepted : 28/12/2009

The bioavailabilty of rosiglitazone was improved by developing a bilayer and floating-bioadhesive drug delivery system exhibiting a unique combination of floatation and bioadhesion to prolong residence of rosiglitazone in the stomach (It is highly soluble in 0.1 mol/l HCl) so improve its bioavailability [6].Bilayer tablet is suitable for sequential release of two drugs in combination, with one layer of drug for immediate release while the second layer designed to release drug in an extended release manner. Bhavesh S. et al developed bilayer tablet for treatment of migraine consisting from Ibuprofen in the sustained release layer and metoclopramide (to enhance the absorption of non-steroidal anti-inflammatory drug) in the immediate release layer [7].The most important application of the bilayer is a quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time. This type of system is used primarily when a maximum response needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. When a single constant rate for drug release does not entirely satisfy the therapeutic objective, the quick/slow delivery system may be an interesting alternative. This biphasic release system can be achieved by the application of an immediate release layer to the conventional layered matrix tablet [8].Suitable candidate drugs for this type of administration include nonsteroidal anti-inflammatory drugs (NSAIDs) and antihypertensive, antihistaminic, and anti-allergic agents[9]. Metoprolol (MT) is a cardioselective $\beta_1$blocker exert equilibrium-competitive antagonism of the actions of catecholamines and other adrenomimetics at β-receptors, used in treatment of hypertension, angina pectoris, myocardial infarction, cardiac arrhythmias and heart failure [10]. Peak plasma concentrations are achieved within 1.5 to 2 hours after a single oral dose, but because of the drug's short half-life (3 to 4 hours), the therapeutic plasma concentration can be maintained only if the metoprolol is administered frequently [11]. These characteristics make metoprolol a suitable candidate for administration by a quick/slow delivery system. The purpose of this study is to design a quick/slow delivery dosage form as biphasic bilayer tablet in which one layer containing superdisintegrant like sodium starch glycolate or sodium croscarmellose responsible for immediate release of the drug and the other is matrix layer of retardant polymer like Ethylcellulose (EC), Hydroxypropyl methylcellulose (HPMC) and hydroxyethylcellulose (HEC) responsible for sustained action.

Materials and Methods

Materials

Metoprolol tartrate, hydroxypropyl methylcellulose and colloidal silicon dioxide (CabOSil) from Sigma, Germany. Metoprolol tartrate 50mg tablet: UK limited, England. Metoprolol tartrate 100mg sustained release: Ratiopharm, Germany. Ethylcellulose from Acros organics, United States. Hydroxyethylcellulose from Merck, Germany. Lactose from Riedel-DeHaen, Germany. Microcrystalline cellulose (Avicel PH 102) and croscarmellose from Hekma Drug Industry, Jordan. Starch and talc from AFCO, India. Polyvinylpyrrolidone, sodium starch glycolate (Explotab) and magnesium stearate from BDH laboratory, England.

Methods

Preparation of Immediate Release (IR) Granules

Different formulas (table 1) were prepared using wet granulation method to achieve most acceptable pharmacopial requirements and consider as comparable test with the reference one (Metoprolol tartrate UK limited 50 mg) tablet.After weighing the drug and the excipients enough to prepare 40 tablets in dried form, and then blend the ingredients using mortar and pestle, the powders were mixed with binding solution (10% alcoholic starch paste) gradually until proper ball test consistency was resulted.The wet mass was screened through sieve (10 mesh) and dried in pre warmed oven at 60 ºC for one hour. The dried granules then reduced in size by screening them through 12 mesh size sieve. A known weight of granules equivalent to the stated dose was mixed with calculated amount of magnesium stearate and talc powder for five minutes.

Table 1: Different formulas of metoprolol granules as immediate release (IR) layer

Ingredient (mg)	IR1	IR2	IR3	IR4	IR5	IR6
Metoprolol tartrate	30	30	30	30	30	30
Microcrystalline cellulose (MCC)	103		100	100		
Lactose		103			100	100
Sodium starch glycolate			3		3	
Croscarmellose				3		3
10% alcoholic starch paste	15	15	15	15	15	15
Mg stearate	1	1	1	1	1	1
Talc	1	1	1	1	1	1
Total wt	150	150	150	150	150	150

Preparation of Sustained Release (SR) granules

Different formulas (table 2) were prepared using wet granulation method like immediate release granule to achieve most acceptable pharmacopial requirements. After weighing the drug, polymer(s) and diluent enough to prepare 40 tablets in dried form, and then blend the ingredients using mortar and pestle, the powders were mixed with binding solution gradually until proper ball test consistency was resulted. The wet mass was screened through sieve (10 mesh) and dried in pre warmed oven at 60 ºC for one hour. The dried granules then reduced in size by screening them through 12 mesh size sieve. A known weight of granules equivalent to the stated dose was mixed with calculated amount of magnesium stearate, CabOSil and talc powder for five minutes.

Table 2 : Different formulas of metoprolol granules as sustained release layer

Variable	formulas	Metoprolol tartrate	EC	HPMC	HEC	Lactose	microcrystalline cellulose	10% alcoholic starch paste	Polyvinyl pyrrolidone	Mg Stearate	CabOSil	Talc	Total Layer Wt mg
Effect of EC	F1	70	70			172		35		1	1	1	350
	F2	70	140			102		35		1	1	1	350
	F3	70	210			32		35		1	1	1	350
Effect of HPMC	F4	70		70		172		35		1	1	1	350
	F5	70		140		102		35		1	1	1	350
	F6	70		210		32		35		1	1	1	350
Effect of HEC	F7	70			70	172		35		1	1	1	350
	F8	70			140	102		35		1	1	1	350
	F9	70			210	32		35		1	1	1	350
Effect of EC- HPMC	F10	70	70	70		102		35		1	1	1	350
	F11	70	140	70		32		35		1	1	1	350
Effect of EC- HEC	F12	70	70		70	102		35		1	1	1	350
	F13	70	140		70	32		35		1	1	1	350
Diluent type	F14	70	140	70			32	35		1	1	1	350
Binder type	F15	70	140	70		32			35	1	1	1	350

Preparation of Metoprolol Bilayer Tablet

The quantities of material required to produce the tablets were individually weighed. The SR layer was manually poured into the 10 mm die and was gently precompressed so that a flat surface was created. Then the other IR layer was poured into the die to create the second layer. The layered granules were then compressed to a specified maximum compression.

Evaluation of Bilayer Tablet

Disintegration Test

The different formulas of IR layer were compressed alone at the same compression forced and their disintegration times were compared with the reference conventional tablet (Metoprolol 50 mg).The disintegration time was determined in 0.1N HCl (pH 1.2) [(2)].

Friability Test

This test was done for 20 tablets, starting by weighing them and then operating the friabilator at 25 rpm for 4 minutes, re-weighing the tablets to determine the loss in their weight [12].

Tensile Strength

The tensile strength of five tablets of each prepared formula was determined from diametrical compression tests, which were performed using a universal hardness tester to measure the maximal diametrical crushing force (F) accurately. Together with the measured diameter (d) and thickness (t) of the tablets (by micrometer), the tensile strength (σ_t) is then calculated according to the following equation [13]:

$$\sigma t = \frac{2F}{\prod dt}$$

Uniformity of Dosage Units

The content uniformity was performed for the prepared metoprolol bilayer tablet by taking five tablets and assayed individually. The requirement for this test is met if the amount of ingredient in each of the five tablets lies within the range of 90-110% of the label claim [14].

Dissolution behavior

A suitable dissolution tests were carried out to demonstrate the appropriate release of metoprolol, the dissolution studies were carried out using the USP basket method at 37 ºC ± 0.5 ºC and rotation speed 100 rpm as follows [14]:-

One tablet of each prepared formula was running out in a dissolution jar containing 900ml of 0.1 N HCl (pH 1.2) for two hours, then in 500ml of phosphate buffer (pH 6.8) for the rest of the experiment. Samples of 5ml were withdrawn at specific time intervals (first at 5, 10 and 15 min then at 1,2,3,4,5,6,7,8,9,10,11 and 12 hr), the volume of samples were replaced with the same buffer solution. Samples were filtered and diluted, analyzed using UV spectrophotometer at 223 nm, the procedure was triplicated for each run test. Some variables that affect the dissolution behavior had been studied like retardant polymer type, polymer concentration, polymer – polymer ratio, type of diluent, type of binder and pH of dissolution media (1.2, 4.6 and 6.8).

Swelling and Erosion Study

The swelling and erosion studies were performed for optimized formulation. Briefly, weighed tablets with watch glass [**H1**] and placed in dissolution vessel, containing 0.1 M hydrochloric acid for first 2 hr followed by 6.8 pH phosphate buffer for 4 hr using paddle method at stirring speed of 100 rpm. At selected time interval (1 to 6 hr) the tablets were withdrawn. The watch glass and tablets were blotted dry to remove water and weighed [**H3**]. The axial and radial swelling was measured using micrometer. The wetted tablets were dried in an oven at 110 °C for 24 hr, cooled and dried in a dessicator and finally weighed as dry weight [**H2**] [15]:

The percent absorption was calculated as

A%=100[H3-H2]/H2

The percent erosion was calculated as

E%=100[H1-H2]/H1

Fourier Transform Infrared Studies (FT-IR)

The FT-IR spectra of metoprolol tartrate, physical mixtures and granules of immediate release and sustained release layers were obtained after making potassium bromide discs in the range of 4000 cm^{-1} to 500 cm^{-1} to detect drug–excipients interaction, if any [16].

Statistical Analysis

The results of the experiments are given as a mean of triplicate samples ± standard deviation and were analyzed according to the one way analysis of variance (ANOVA) at the level of ($P < 0.05$).

Results and Discussion

Evaluation of Bilayer Tablet

Disintegration Test

All the disintegration times of the prepared formulas are shown in table (3) are within the pharmacopial requirements but the IR3 is the closest one to the standard metoprolol tartrate 50 mg conventional tablet so it was used for the further bilayer formulation.

Table (3) the disintegration time of the prepared immediate release (IR) layer

Formulas	Disintegration time (min)
IR1	16±2
IR2	5±2
IR3	(11±1.5)
IR4	3±1
IR5	3.5±0.5
IR6	2.5±0.5
Standard tablet (Metoprolol tartrate 50mg tablet)	(10±1)

Friability Test and Tensile Strength

As shown in table (4), all the prepared formula had acceptable weight loss (not more than 1%) and high tensile strength this is mainly due to the composition of each layer. Microcrystalline cellulose used as diluent in the immediate release layer, is well known to

deform in a predominantly plastic manner which is a direct result of the presence of slip planes or dislocations and is thought to be an important factor affecting the compressibility of microcrystalline cellulose [17] and result in the consolidation of granules and increased intraparticulate bonding during compaction in addition to the homogenous distribution of bonds in the compact [18]**.** On the other hand, all the sustained release layers containing a considerable amount of the retarding polymer (20% to 60% of tablet weight) which improve the compressibility of the matrix and this elevated with increase the polymer concentration [19]. The formulas (F7, F8 and F9) have lower strength than that of other formulas this may be attributed to the better capability of the granulating solvent to dissolve the polymeric support of EC (and not to HEC), thus improving the strength properties of tablets [20].

Table (4) Physical properties of the prepared bilayered tablet

Formulas	Friability (%)	Tensile Strength kg /cm^2	Metoprolol content (%)
F1	0.45	13.1	99±4.5
F2	0.38	13.3	93±2.9
F3	0.25	15.6	97±5.9
F4	0.51	10.4	99±4.8
F5	0.44	12.9	98±4.2
F6	0.35	14.3	95±2.1
F7	0.90	5.9	98±4.9
F8	0.79	6.9	95±4.4
F9	0.51	7.6	93±2.2
F10	0.37	16.0	95±1.9
F11	0.25	16.4	98±4.2
F12	0.57	12.8	92±1.2
F13	0.50	13.5	96±5
F14	0.20	15.0	93±4.9
F15	0.15	17.4	92±3.5

Uniformity of Dosage Units

Table (4) shows that, all the prepared formulas complied with the United State pharmacopial specification which is 90-110% of metporolol content in each individual tablet[14].

Variables Affecting the Dissolution Profile of Metoprolol Bilayer Tablets

The Effect of Retarding Polymer Type

The release of metoprolol from formulas F2, F5 and F8 which contain (1:2) drug: polymer ratio for EC, HPMC and HEC respectively is shown in figure (1). A significant difference ($P < 0.05$) was found among the cumulative amount of metoprolol released (after the first hour) with time depending on the nature of each polymer. EC is hydrophobic polymer and the drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network as drug release continues, the interconnecting clusters increase the pore network through which interior drug clusters can diffuse causing eventually rapture of the matrix system and rapid release [21]. HPMC and HEC are hydrophilic polymers on first contact of theirs matrix system with aqueous fluid rapid uptake of water occurs, chains gradually uncoil and extend but never form into linear coils, as the water content increases, the polymer becomes hydrated and the layer takes on the full characteristics of a gel. This is followed by retardation of water uptake by the rest of the tablet due to the formation of this gel layer. The major difference in the release profile of these two polymers due to the difference in the rate of hydration resulted from type of substitution on the cellulosic backbone [22].

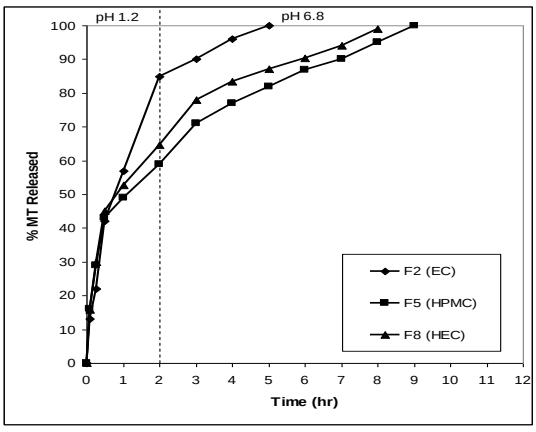

Figure 1: The effect of polymer type at (1:2) drug: polymer ratio on the cumulative release of MT at 37 ºC.

The Effect of Retarding Polymer Concentration

The effect of polymer concentration on metoprolol release from the bilayer tablets was studied for each type of polymers and the result illustrated in the figure (2). Formulas F1, F2 and F3 were prepared utilizing EC at ratio

of 1, 2 and 3 (in respect to the metoprolol) respectively. The same ratios were used for HPMC in formulas F4, F5 and F6, and for HEC in formulas F7, F8 and F9 respectively. It appears that there is a significant difference ($P < 0.05$) in the release of metoprolol from matrices of EC (F 1-3), HPMC (F 4-6) and HEC (F 7-9) when the polymer concentration was increased. In case of EC the results can be attributed to the decrease in the porosity with a concomitant increase in the tortuosity of matrix [19]. The most important factor affecting the rate of release from hydrophilic matrices is the drug**:**polymer ratio. The increase in polymer concentration causes an increase in the viscosity of the gel and formation of a gel layer with a longer diffusional path leading to a decrease in the drug release [23].

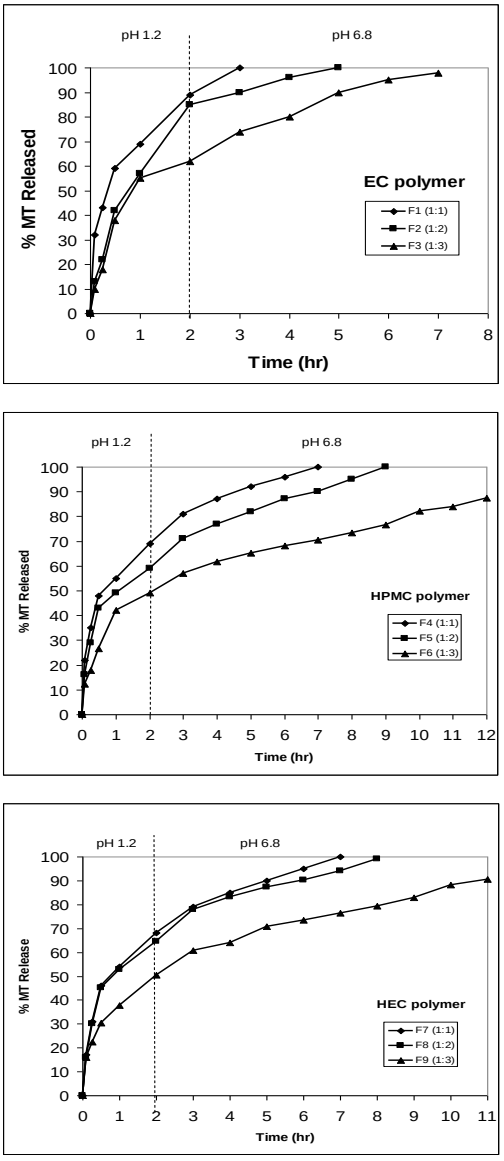

Figure 2: The effect of varying drug:plymer ratio on the cumulative release of MT at 37ºC.

The Effect of Polymer-Polymer Ratio

Four formulas (F10, F11, F12 and F13) were prepared by mixing hydrophobic EC with HPMC and HEC (both hydrophilic polymer) in different ratios 1:1 and 2:1 and the result shown in figure (3).As shown in the figure (2) EC alone was not able to sustained the release of metoprolol beyond 6hr even with 60% of the polymer used (as in F3) in spite of excellent granular and tablet properties this is mainly due to high solubility of the metoprolol that lead to rapid ingress of water and loss the integrity of the matrix [24]. The use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it becomes essential to include hydrophobic polymers in the matrix system [25]. So the mixing of hydrophobic with hydrophilic polymer to improve the retardant ability resulting in good release profile and the tablet integrity and dimensions were conserved for the period of the test.

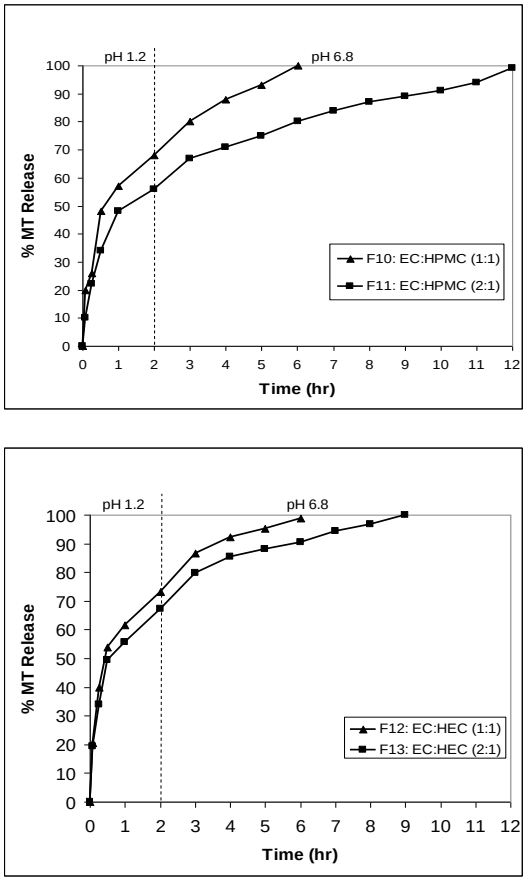

Figure 3: The effect of EC: Hydrophilic polymer ratio on the on the cumulative release of MT at 37 ºC.

The Effect of Diluent Type

To study the effect of diluent, F11 which contain lactose as a diluent compared with the F14 which contain microcrystalline cellulose as in figure (4). Although both lactose and microcrystalline cellulose consider as hydrophilic filler, there was retardation in the release when changing from lactose to microcrystalline cellulose (from 84% to 75% at 8hr). This may be due to the high solubility of lactose so that it will act as channeling agent, permitting a rapid ingress of dissolution medium into the matrix tablets, thus facilitating drug release [26]. While the presence of a swelling, insoluble filler like microcrystalline cellulose changes the release profile due to a change in the rate of swelling at the tablet surface [27].

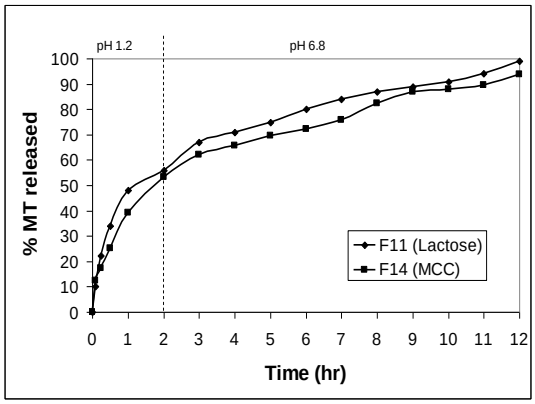

Figure 4: The effect of diluent type on the cumulative release of MT from formulas F11 (Lactose) and F14 (MCC) at 37 ºC.

The Effect of Binder Type

To study the effect of binder, F11 which contain starch as a binder compared with the F15 which contain polyvinylpyrrolidone (PVP) as in figure (5). It was seen that slight retardation in the release of metoprolol from matrix when the starch was replaced by PVP (from 84% to 77% at 8hr). It was hypothesized that this may have been resulted from a change in the properties of the 'pseudo-gel layer' surrounding the tablet, which controls the drug release rate through intimate mixing during hydration of the dosage form and through the formation of strong hydrogen bonds between PVP and HPMC [28].

The Effect of the pH of the Dissolution Media

Three tablets of F11 were running out separately in dissolution jars containing 900ml of pH 1.2, 4.6 and 6.8 the procedure was triplicated for each run test and the result of the drug released compared with that obtained normally (2 hr at pH 1.2 then at 6.8) as in figure (6). There was no significance differences (P> 0.05) among the release of metoprolol at different pH media this mainly due to two reasons. First, the metoprolol is highly soluble drug and its solubility dose not affected by the pH [29]. Second, the mechanism of the drug release is by swelling the polymer to form barrier gel that resist the diffusion and the HPMC swelling property not affected by the pH of the media [22].

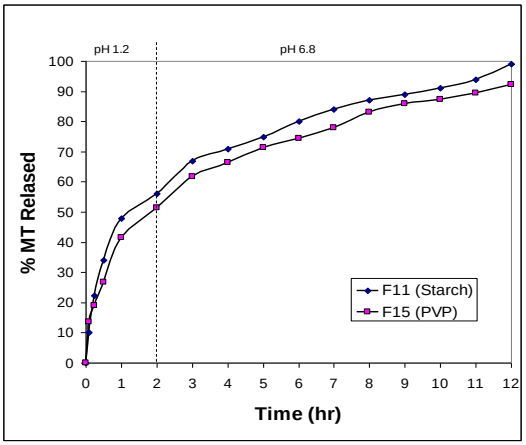

Figure 5: The effect of binder type on the cumulative release of MT from formulas F11 (Starch) and F15 (PVP) at 37 ºC.

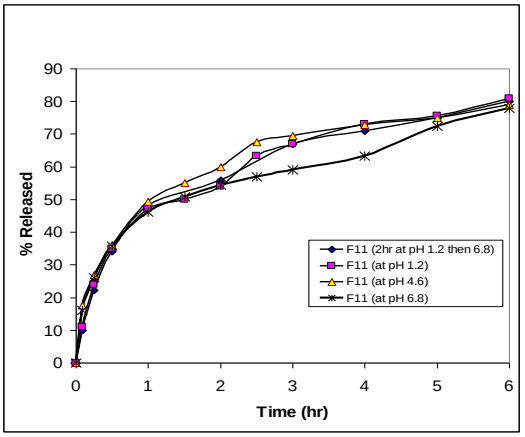

Figure 6: The effect of pH variation on the total amount of metoprolol release at 37 ºC.

Selection of the Best Formula

To select the most promised formula in this study, reference product equivalent to 100 mg of metoprolol as a sustained release tablet (Metoprolol Ratiopharm® 100 sustained release) was utilized as a standard one, this was carried out using similarity factor (f_2) introduced by Moore and Flanner as shown in equation (3). A difference not exceeding 10% at any sampling time point between reference and test products may be acceptable and f_2 value of 50-100 indicates similarity in the dissolution profiles [30]:

$$f_2 = 50 \times \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}\left|R_t - T_t\right|^2\right]^{-0.5} \times 100\right\} \quad \text{..... (3)}$$

Where n is the number of dissolution time points, R_t and T_t are the reference and test dissolution values at time t. F15 (which contain EC:HPMC in ratio of 2:1 and PVP as a binder) showed higher (f_2) among all other formulas and equals to 72.3 as shown in figure(7).

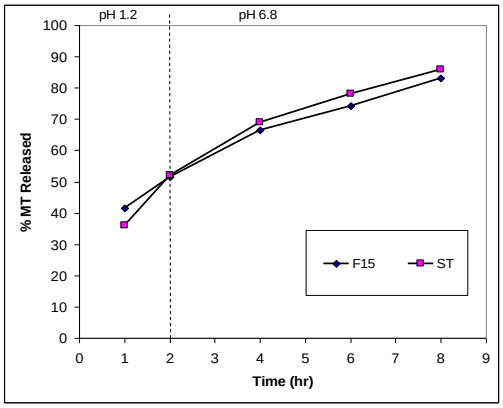

Figure 7: The dissolution profile of selected formula F15 versus reference standard (ST) with (f ¬2¬) =72.3 at 37 ºC.

Swelling and Erosion

Swelling and erosion had been studied to the best formula F15 and the result shown in figure (8) revealed that the tablets were swollen and retained their physical integrity till the end. Although there is an increase in both percentage water absorbed and percentage erosion of the tablet, but the percentage water absorbed was more dominant than erosion indicating that the release was biphasic mechanism mainly by diffusion than erosion[31].

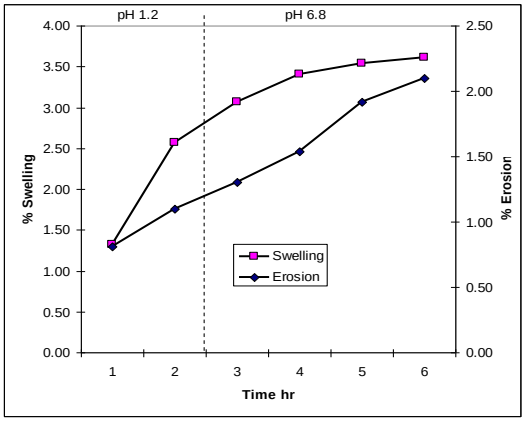

Figure 8: Swelling-eroding behavior of optimized selected formula F15.

FT-IR Studies

The FT-IR spectra of metoprolol tartrate, physical mixtures and granules of immediate release and sustained release layers are shown in figures (9) and (10). The O-H stretching vibration peak of metoprolol is seen in 3458 cm -1 and the C-N peak is seen at 2872 cm -1, N-H bending vibration at 1590 cm -1, at 1112 cm -1 the C-O stretching bond, at 1458 cm -1 the C=C, and at 1244 cm -1 the C-O stretching bond are obvious (32). Similar peaks are observed in the corresponding physical mixture and granules. Furthermore, the broadening of O-H stretching vibration peak mainly due to hydrogen bonding of the drug with the polymers and other excipients, also the absence of significant shifts in the wave numbers of the IR peaks of the granules compared with physical mixture indicates lack the possibility of interaction between metoprolol tartrate and excipients used in this bilayer tablets [16].

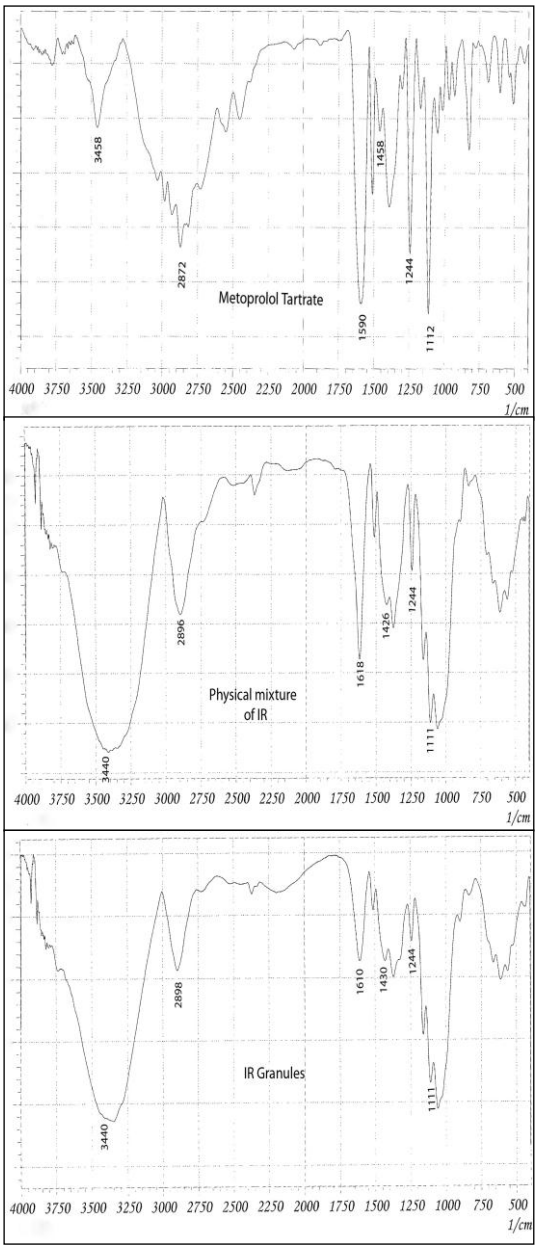

Figure 9: FT-IR spectra of Metoprolol, physical mixture and granules of the IR layer.

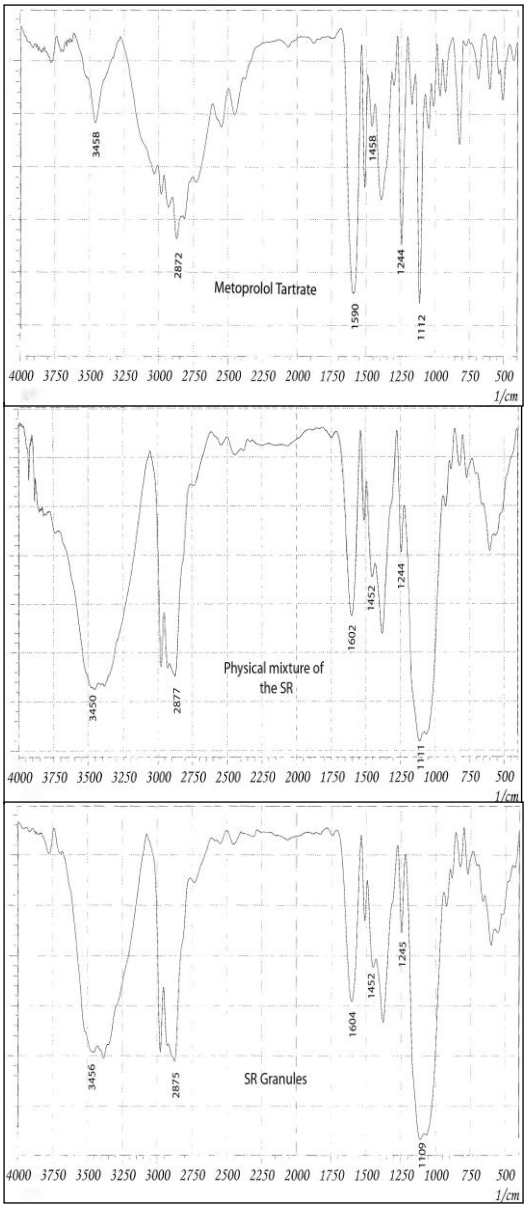

Figure 10: FT-IR spectra of Metoprolol, physical mixture and granules of the SR layer.

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