

## Effect of Different Diluent and Binder Types on the Preparation of Bisoprolol Fumarate as Tablet Dosage Form

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### Abstract

Hypertension is one of the main causes of heart disease; beta- blockers play a crucial role in the management of patients with essential hypertension. Bisoprolol is one of the widely used drugs for the treatment of hypertension. Bisoprolol tablets were prepared by two methods (direct and wet) using different proportion and types of diluents, different binder types and forms, then evaluated for, weight variation, hardness, friability, disintegration time and dissolution rate. The results were compared with a reference Bisoprolol tablet.

Both methods of preparation wet and direct compression method gave good results, which are consistent with the requirements of British Pharmacopeia and United States Pharmacopeia. It was found that the type of diluent (mannitol and lactose), binder type (polyvinyl pyrrolidone and acacia) and the presence of starch as a disintegrant affect the hardness, disintegration and the dissolution rate of the tablet. While liquid binder (polyvinyl pyrrolidone solution) gave longer disintegration time (12 min) with higher hardness compared with the powdered binder (polyvinyl pyrrolidone powder) that gave (5 min).

The results indicate that formula F1 which consists of [Mannitol (65mg)/ Avicel 102 (26 mg), starch and magnesium stearate] showed the best results as it has lower disintegration time (2.7 min), faster dissolution rate (100% release within 20 min) and prepared by a low cost method (direct method).

**Key words:** Bisoprolol, diluent, binder, direct compression, wet granulation.

### تأثير مختلف أنواع الممددات و العوامل الرابطة على تحضير مضغوطات البيزوبرولول فيوماريت

هبة أنطوان فتوح<sup>1\*</sup> و علاء عبد الحسين عبد الرسول<sup>\*\*</sup>

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### الخلاصة

ارتفاع ضغط الدم هو احد اسباب امراض القلب . ادوية معوقات البيتا تلعب دور حاسم في علاج المرضى المصابين بارتفاع ضغط الدم الاساسي. يعتبر البيزوبرولول واحدا " من اكثر الادوية الشائعة لعلاج ضغط الدم . الهدف من هذه الدراسة هو تحضير حبوب البيزوبرولول بطريقتين مختلفتين باستعمال انواع ونسب مختلفة من المخفف و اشكال مختلفة من اللواصق وتقييم التراكيب من حيث اختلاف الوزن ، الصلابة ، الهشاشة ، وقت التفكك والذوبانية ومقارنة النتائج مع حبوب البيزوبرولول المتوفرة تجاريا". كلا طريقتي التحضير (الطريقة الرطبة و الكبس المباشر ) اعطت نتائج جيدة و التي هي متوافقة مع متطلبات المصادر الرسمية . و قد وجد ان نوعية المخفف (المانيتول و اللاكتوز ) واللاصق (البوليفينيل بايروليدون و الاكيشيا ) كان لها تأثير على صلابة، وقت تفكك الحبة وبالتالي ذوبانيتها كذلك نوعية المفكك ( من حيث وجود النشا ام لا ) كان لها تأثير على تفكك الحبة.

الحبوب المحضرة بالمادة اللاصقة السائلة ( البوليفينيل بايروليدون السائلة ) اعطت وقت تفكك اطول ( 12 دقيقة ) مع صلابة اعلى من الحبوب المحضرة بالروابط الجافة ( البوليفينيل بايروليدون باودر ) في ( 5 دقائق ). النتائج اوضحت ان تركيبة رقم 1 و المؤلفة من (المانيتول و المايكروكريستالين سليولوز و النشا و المغنيسيوم ستيريت ) اعطت احسن النتائج حيث كان لها وقت قصير للتفكك ( 2.7 دقائق ) وسرعة عالية في الذوبان ( 100% خلال 20 دقيقة ) وكانت محضرة بالطريقة التي تعطي اقل التكاليف.

الكلمات المفتاحية : البيزوبرولول، المخفف، اللواصق، الكبس المباشر، الطريقة الرطبة لتحضير الحبيبات .

### Introduction

Oral route is the most common route of drug administration. The most popular way of delivering a drug for oral use are tablets<sup>(1)</sup>. Tablets can be defined as solid preparations each containing a single dose of one or more active ingredients and usually obtained

by compressing uniform volume of particles<sup>(2)</sup>. Tablets are convenient for the patients and are usually easy to handle and identify<sup>(1,3)</sup>. Tablets are commonly manufactured by one of the following manufacturing processes:

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Direct compression, Wet granulation, Dry granulation methods<sup>(4)</sup>.

Substances included in the manufacturing process other than the active ingredient called excipients e.g: diluents, disintegrants, binders, lubricants, flavoring agents and etc.<sup>(5)</sup>, they are added to perform different functions, they may be used to enhance stability (antioxidants), modify drug release (disintegrants), provide essential manufacturing technology functions (binders, lubricants), enhance patient acceptance (flavoring agents)<sup>(6)</sup>.

Treatment of hypertension both decreases morbidity and prolongs life expectancy.  $\beta$ -blockers are one of the drugs used to treat hypertensive patients<sup>(7)</sup>.

Bisoprolol is one of cardioselective beta blockers used in the management of hypertension, the usual dose of bisoprolol is 5 to 10 mg as a single daily dose tablet<sup>(8)</sup>, it is 2- propanoic acid 1-(4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy)-3-[(1-methylethylamino)as fumarate<sup>(9)</sup>. Bisoprolol has white crystals, very soluble in water, freely soluble in alcohol, its melting point about 100°C, its Pka is 9.5<sup>(10)</sup>.

The goal of this study is to prepare Bisoprolol tablet having faster disintegration time, faster dissolution rate and cheapest way of preparation than that of the reference one.

## Materials and Methods

### Materials

Bisoprolol (Merk), Mannitol (Scharlau, Spain), Avicel 102 (Microcrystalline cellulose 102) (Awamedica drug industry, Iraq), Polyvinyl

pyrrolidone (Sigma, Germany), Acacia, Magnesium stearate (Riedal-De-Haen Ag Seelze, Germany), Single tablet compression machine (Erweka), Electrical melting point apparatus (UK), Sensitive Balance (Germany), Disintegration tester (Erweka), Hardness tester (Pharma), Friability tester (Pharma), Dissolution apparatus (Pharma) and Oven (Rostfrei).

### Methods

Bisoprolol tablet was prepared using different formulas by two different methods (direct compression and wet granulation) then evaluating the prepared Bisoprolol tablets and compared with the reference Bisoprolol tablet (Merk) to find the best formula and method to prepare tablet comply with the Pharmacopeial properties.

### Preparation of calibration curve of bisoprolol

The calibration curve of bisoprolol in distilled water was constructed by preparing series of diluted solutions of the drug from a stock solution (100  $\mu\text{g}/\text{ml}$ ). The absorbance was measured at its  $\lambda_{\text{max}}$  (225 nm) then plotted against the concentration<sup>(11)</sup>.

### Preparation of Bisoprolol tablet dosage form

Table (1) shows the composition of different formulas used to prepare Bisoprolol tablets. Formulas F1, F2, F5 and F7 were prepared by direct compression through mixing all the ingredients together for 15 minutes except magnesium stearate (lubricant), then the lubricant was added and mixed for 2 minutes, the mixture then was compressed into tablets<sup>(12)</sup>.

Table 1: Different formulas of Bisoprolol tablet

Formulas	Ingredients (mg)	Bisoprolol	Mannitol	lactose	Starch	Avicel PH 102	PVP	Acacia	Magnesium stearate	Total weight (mg)
F1		5	65		3	26			1	100
F2		5	26		3	65			1	100
F3		5	Q.S to 100 mg		3		3% soln q.s		1	100
F4		5	Q.S to 100 mg		3			20% mucilage q.s	1	100
F5		5	76			15	3		1	100
F6		5	Q.S to 100 mg			15	3% soln q.s		1	100
F7		5		65	3	26			1	100

On the other hand F3, F4 and F6 formulas, were prepared using wet granulation method by weighing and mixing the ingredients except the lubricant and the binder, then a damp mass was prepared by adding a liquid binder to the powder mixture to facilitate adhesion of the powder particles. The wet mass was screened into granules, after drying the lubricant was added, mixed and the whole formula was compressed into tablets<sup>(13)</sup>.

#### **Flowability measurement of prepared bisoprolol formulas granules mixtures by determination of angle of repose**

The angle of repose ( $\theta$ ) is a relatively simple technique for estimating the flow properties of a powder. It can easily determined by allowing a powder to flow through a funnel and fall freely onto a surface. The height and diameter of the resulting cone are measured and the angle of repose was calculated by the following equation<sup>(13)</sup>:

$$\tan(\theta) = h/r$$

Where h and r are the height and radius of powder cone respectively.

#### **Evaluation of physical properties of Bisoprolol prepared tablets**

This was assessed under standard laboratory lighting, each of ten tablets per formula were examined for color, odor, capping and lamination, texture and appearance<sup>(14)</sup>.

#### **Weight variation test**

The United States Pharmacopeia (USP) weight variation test for all prepared formulas and the reference Bisoprolol tablet was studied by weighing twenty tablets individually, calculating the average weight and comparing each individual tablet weight with the average. The tablets meet the USP requirements if no more than two tablets are out of the percentage limit (10%) and if no tablet differs by more than two times the percentage limit (20%)<sup>(3)</sup>.

#### **Hardness test**

Tablet should be sufficiently hard to resist breaking during normal handling and soft enough to disintegrate properly after swallowing<sup>(13)</sup>. This test was done using hardness tester by which the hardness of three tablets of all prepared formulas and the reference Bisoprolol tablet was determined and expressed in Kg, then the mean readings was calculated<sup>(12)</sup>.

#### **Friability test**

This test was done for the prepared formulas and the reference Bisoprolol tablet, by taking twenty tablets from each formula removing the

dust from them by using soft brush. Tablet samples were weighed and placed in the friabilator, after the given number of rotations (100 rotations/ 4 min.), dust was removed again, the tablets were weighed and compared with the initial weight, the value is expressed as a percentage, a maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable. The percentage of friability was determined by using the following equation<sup>(15,16)</sup>:

$$\text{Friability\%} = \frac{(\text{initial weight} - \text{final weight}) \times 100}{\text{initial weight}}$$

#### **Disintegration test**

The tablet units were placed in a basket type USP disintegration apparatus. Distilled water at  $37^{\circ}\text{C} \pm 0.5$  used as a disintegration medium. The time required for complete disintegration of six tablets was recorded<sup>(10)</sup>. This test was done for all prepared formulas and the reference Bisoprolol tablet.

#### **Effect of diluent**

The effect of diluent proportion in F1 [Mannitol (65)/ Avicel 102 (26)] with F2 [Mannitol (26)/ Avicel (65)] and diluent type in F1 (Mannitol as major diluent) with F7 (Lactose as major diluent) on the hardness and disintegration of tablet was studied.

#### **Effect of binder type**

The effect of binder type polyvinyl pyrrolidone (PVP) and acacia on the hardness and disintegration of the tablet was studied using formulas F3 and F4, respectively.

#### **Effect of method of preparation**

By fixing the ingredients used and changing the method of preparation from direct compression using F5 to wet granulation using F6, the effect of method on the hardness and disintegration time of the tablet was studied.

#### **Effect of type of excipient**

This factor was studied by utilizing of starch as a disintegrant in F1, F2 (containing starch with same % but with different diluent proportion) and F5 (without starch), using the same method of preparation.

#### **Dissolution test**

The dissolution study for the selected formulas (F1, F3 and F5) and a reference Bisoprolol tablet was performed using a USP paddle II at 75 rpm rotation speed at  $37^{\circ}\text{C} \pm 0.5$ . The dissolution medium was 900 ml distilled water; 5 ml sample was withdrawn at different

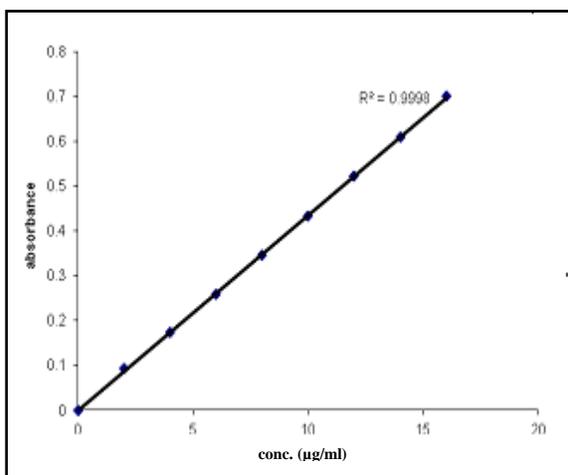
time intervals and replaced by equal volume of dissolution medium. The samples were filtered and the absorbance of the samples was measured spectrophotometrically at the drug  $\lambda_{\max}$  225 nm<sup>(17)</sup>.

#### Stability study within one month

The effect of different temperatures on the degradation of Bisoprolol tablet was studied by storing samples of Bisoprolol tablet F1 under 40, 50 and 60°C for one month; samples were taken at certain time intervals to determine percent drug remaining versus time.

### Results and Discussion

The calibration curve of bisoprolol was plotted using the absorbance versus the concentration of serial dilutions of the drug; a straight line was obtained as shown in figure (1).



**Figure 1: Calibration curve of Bisoprolol in distilled water**

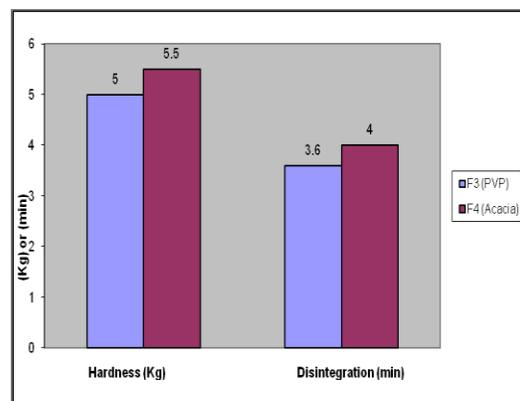
Table (2) shows that all formulas have angle of repose within (25°-30°) which considered to be a good flowability, that means the use of different type of excipients did not make large change in flowability of the formulas. This good flowability for formulas prepared by direct compression method F1, F2, F5 and F7 was due to the presence of Avicel 102 that has good flow property and improve the flowability of the whole formula because it is in granule form<sup>3</sup>, while for the formulas that prepared by wet granulation method their good flowability was due to conversion of powder mixture to more flowable granules form during preparation steps by wet granulation method<sup>3</sup>. Formulas F3 and F6 gave good flow behavior due to the using of PVP in liquid form as a binder which is consistent with the results found that wet granulation with

povidone results in hard granulates with excellent flow properties<sup>(18)</sup>.

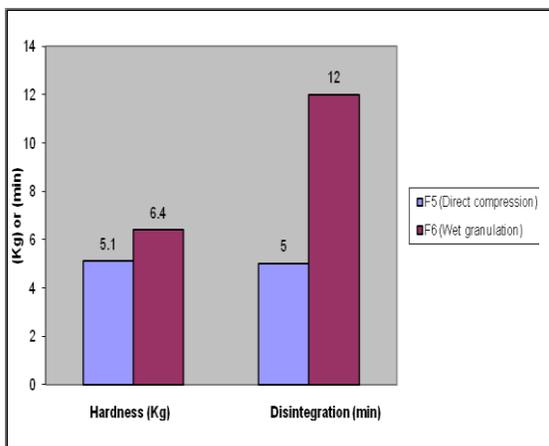
**Table 2: Angle of repose of the prepared powder and granule mixtures**

Formulas	Angle of repose (θ)
F1	27.56
F2	26.69
F3	28.43
F4	28.26
F5	29.72
F6	28.52
F7	29.61

All formulas showed no change in color and odor and no capping and lamination occur. The effect of different binders was studied using F3 which contains PVP liquid binder and F4 which contains acacia mucilage binder both prepared by wet granulation method, their results showed that the presence of acacia in F4 gives higher disintegration time (4 min) compared with F3 (3.6 min), this result is consistent with acacia which can produce tablets with a prolonged disintegration time<sup>19</sup>, nevertheless both fulfill the official B.P requirements. The results are shown in figure (2). Figure (3) shows the effect of type of method of preparation on the hardness and disintegration time of the tablet for F5 which was prepared by direct compression method and F6 which was prepared by wet granulation method.

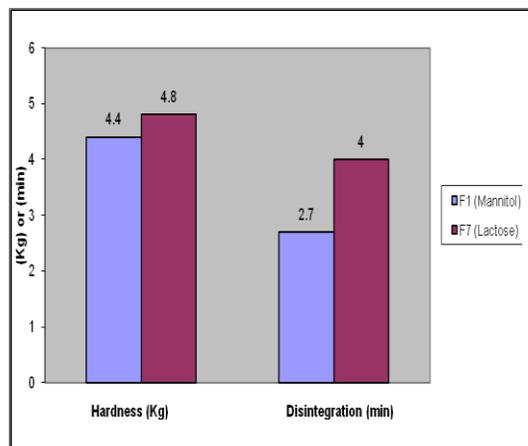


**Figure 2: Effect of different binder on the hardness and disintegration time of formulas F3 (PVP) and F4 (Acacia) Bisoprolol tablets.**



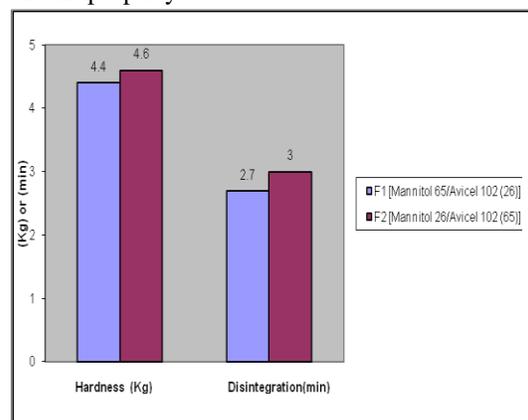
**Figure 3: Effect of method of preparation on the hardness and disintegration time of formulas F5 (Direct method) and F6 (Wet method) of Bisoprolol tablets .**

The results revealed that formula F6 had longer disintegration time (12 min) than formula F5 (5 min), the reason behind the difference in the time of disintegration of them is due to the way of introducing the binder in the formula either as powder or liquid form, the liquid binder have higher binding tendency which gives harder granules compared to powdered binder. This is in agreement with the reported where binders are much more effective when they are added as solutions in the preparation of granulations than when they are added dry to a direct compression formula<sup>3</sup>. This will affect the disintegration time, that's why F6 took more time for the tablet to disintegrate which in turn is consistent with that, the bond promoting properties of binder may, however, counteract rapid disintegration<sup>20</sup>. However both F5 and F6 are within the required range. The effect of diluent type on the hardness and disintegration time was studied depending on the comparison between formulas F1 (Mannitol as major diluent) and F7 (Lactose as major diluent), as seen from their results F7 which used lactose is harder (4.8 Kg) and has longer disintegration time (4 min) than F1 which contains mannitol (4.4 Kg hardness and 2.7 min disintegration time), this result agrees with the reported one about the effect of lactose on the disintegration of tablets when used as a major component as it hinders the development of disintegration force and tends to dissolve rather than disintegrate<sup>21</sup>. These results are shown in figure (4).



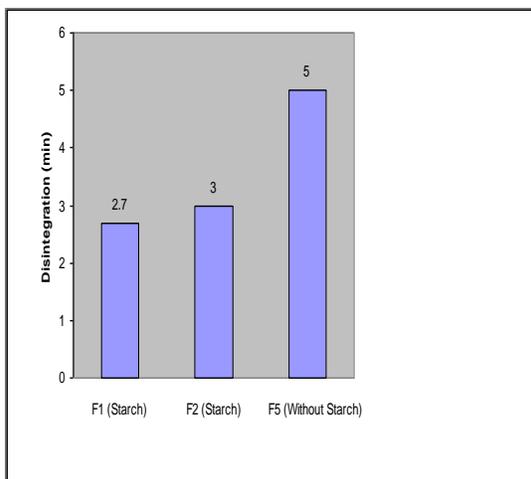
**Figure 4: Effect of different type of diluent on the hardness and disintegration time of formulas F1 (Mannitol) and F7 (Lactose) Bisoprolol tablets .**

The effect of diluent proportion on the hardness and disintegration time was studied using F1 and F2 where both formulas prepared by the same method of preparation under same conditions but with different diluent proportion [Mannitol (65)/Avicel 102 (26)] and [Mannitol (26)/ Avicel 102 (65)] respectively. As seen from figure (5), the different proportion of the diluent gave around the same results of hardness (4.4 Kg and 4.6 Kg respectively) and lower disintegration time( 2.7 and 3 min respectively), this is because of using combination of soluble hydrophilic diluent (Mannitol) with Avicel 102 that has the property of disintegration in addition to the diluent property<sup>3</sup>.



**Figure 5: The effect of diluent proportion on hardness and disintegration time of formulas F1 (Mannitol 65 mg/ Avicel (102) 26 mg) and F2 (Mannitol 26 mg/ Avicel (102) 65 mg) Bisoprolol tablets.**

While comparing the results of F5 (without starch) with those of F1 and F2 (containing starch with different diluent proportion) which are all prepared by direct compression method showing that F5 has longer disintegration time (5 min) than F1 (2.7 min) and F2 (3 min), this result is consistent with both capsules and tablets which are disintegrated rapidly due to the presence of starch disintegrant in the formulations<sup>22</sup>, as shown in figure (6).



**Figure 6: Effect of excipient type on disintegration time of formula F1 (Starch), F2 (Starch) and F5 (without Starch) Bisoprolol tablets .**

The weight variation test showed that all values are within the limited ranges allowed by USP, this indicates a good process of preparation and uniform distribution of the powder within the prepared tablets.

The hardness and friability tests results of all prepared formulas and the reference Bisoprolol tablet were determined and illustrated in table (3); it was found that all are within the acceptable limits (4.4-6.4Kg)<sup>13</sup>.

On the other hand the friability data give indication on the mechanical resistance to loss fine particles from their surfaces<sup>23</sup>. For all prepared formulas and the reference Bisoprolol tablet the friability percentage was (0.3-0.4%) as shown in table (3), being in the acceptable range recommended by official references which should be less than 1%, indicating that the tablet surfaces are strong enough to withstand mechanical shock and attrition during storage and transportation<sup>7</sup>.

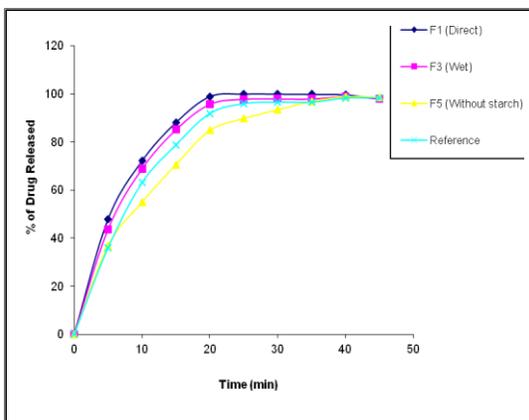
**Table 3: The hardness, friability and disintegration results of the prepared bisoprolol tablets**

Formulas No.	Hardness mean (Kg)	Friability %	Disintegration time (min)
F1	4.4	0.32	2.7
F2	4.6	0.37	3.0
F3	5.0	0.35	3.6
F4	5.5	0.4	4.0
F5	5.1	0.4	5.0
F6	6.4	0.3	12.0
F7	4.8	0.35	4.0
The reference	5.5	0.36	6.0

In this study all prepared formulas and reference Bisoprolol tablet having disintegration time range (2.7-12 min) which fulfills the official requirements (within 15 min) for tablet disintegration<sup>4</sup>. The reason behind the lower disintegration time for formulas F1-F4 and F7 (2.7-4 min) which contain starch as a disintegrant comparing with formulas F5 and F6 (5-12 min) which formulated without starch, was the presence of starch as a disintegrant in them<sup>22</sup>, and they have lower disintegration time (2.7-4 min) compared with the reference bisoprolol tablet (6 min) as seen from table (3).

Formulas (F1, F3 and F5) having the faster disintegration from all groups used and/or using the cheapest excipients so they were selected to study their dissolution and comparing their results with the reference bisoprolol tablet using USP paddle apparatus at speed of 75 rpm in 900 ml of distilled water at 37°C. The results are illustrated in figure (7). It appears that F1 has faster and higher % of drug release (100% within 20 min) as compared with F3 (99% within 30 min), F5(99% within 40 min) and the reference bisoprolol tablet(99% within 40 min), this is due to the presence of hydrophilic soluble diluent (mannitol) which undergoes faster dissolution in addition the disintegration time of F1 is lower than the other (2.7 min), as it is generally known that decreasing the disintegration time leads to increase in the dissolution rate<sup>24</sup> because faster disintegration of tablets delivers a fine suspension of drug particles resulting in higher surface area and faster dissolution<sup>25</sup>. As a result the dissolution properties of tablets are affected by the type of excipient. On the other hand,

stability study of Bisoprolol in the prepared tablet F1 did not undergo any degradation and stay stable with 100% of drug remaining under different temperatures (40, 50 and 60 °C) within one month indicating a stable preparation for F1.



**Figure 7: Effect of method of preparation and presence of starch on the cumulative release of Bisoprolol fumarate in a comparison with concor as a reference in distilled water at 37 °C temperature.**

## Conclusion

Both direct compression and wet granulation method gave tablets with good evaluation results as compared with the reference Bisoprolol tablet.

The type of the diluent, binder type and the presence of starch affect the hardness, disintegration and the dissolution rate of the tablet.

Formula F1 can be chosen to prepare bisoprolol as tablet dosage form as it prepared by easier, simplified and economical method of tablet manufacturing with better results of disintegration (2.7 min) and dissolution rate (100% release within 20 min).

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