



Development of Sublingual tablets of Bisoprolol Hemifumarate / Hydroxypropyl - β -Cyclodextrin Complex for Potential treatment of Angina Pectoris.

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Abstract

Fast-disintegrating tablet drug delivery is gaining an importance for drug delivery technology especially for geriatric and pediatric patient because of swallowing difficulties. In certain diseases such as hypertension and angina pectoris therapy, taking a fast pharmacological response is of important criteria. Thus, the aim of the present work was to prepare a novel fast disintegrating Bisoprolol Hemifumarate (BH) tablet formulation for sublingual administration based on the use of 2-hydroxypropyl- β -cyclodextrin (HP- β CD) which forms an inclusion complex with (BH) to improve the permeability of the drug to sublingual membrane, in addition to mask the taste of the drug through the inclusion complex. Attempts have been made to prepare fast disintegrating tablets of (BH) using superdisintegrants like croscarmellose sodium and crospovidone in concentration of (5%). Eight different formulae (B1-B8) with variable tablet excipients were prepared by direct compression method using different mucoadhesive polymers such as chitosan and polyethylene glycol 6000 at different concentration (3% and 6%) for reduction the flushing action of saliva and to provide enough contact time for drug to be absorbed. The tablets were evaluated for the weight variation, hardness, friability, wetting time, disintegration time and dissolution study. The formulae B2 and B7 possessed the lowest disintegration time due to the presence of the high concentration of chitosan, which has some disintegration action, thus were subjected to a pharmacokinetic study using human volunteers. The bioavailability of B2 was significantly higher than that of the reference (Concor®) ($p > 0.05$). Thus, the present investigations suggest that (BH) sublingual tablets allowed the rapid tablet disintegration, improved bioavailability and effective in emergency treatment of anginal pain and hypertension.

Keywords: Sublingual tablets, Bisoprolol Hemifumarate, 2-hydroxypropyl- β -cyclodextrin, inclusion complex, Bioavailability.

Introduction

In recent years, sublingual oral drug formulations have been developed to overcome the problems related to swallowing difficulties and produces faster onset of action than orally ingested tablets [1]. For these formulae, small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity; the medication then is absorbed partially or entirely into systemic circulation from blood vessels in the sublingual mucosa [2]. Bisoprolol hemifumarate is a highly beta1-selective beta-adrenoceptor antagonist that blocks catecholamine stimulation of β 1-adrenergic receptors in the heart and vascular smooth muscle that result in a reduction of heart rate, cardiac output and depresses plasma renin levels[3]. This effect may used to reduce workload on the heart and hence oxygen demands, so that the drug is indicated for treatment of angina pectoris, arrhythmias and

hypertension[4]. BH is dose dependently absorbed after oral administration with low molecular weight and good water solubility, so it is suitable candidate for sublingual dosage form. Cyclodextrins are frequently used to enhance the bioavailability by increasing the drug availability at the surface of biological barrier [5]. Cyclodextrins have also beneficial in reducing gastric irritation [6] and masking unpleasant tastes or odors [7]. On the European market, the sublingual tablets with nicotine complexed with β -CD (Nicorette Microtab) are available, which offer fast absorption, without unpleasant taste and local mucosa irritation[8]. Various techniques can be used to formulate rapidly disintegrating tablets; direct compression is one of these techniques which requires incorporation of highly water soluble excipients to achieve fast tablet disintegration[9]. The purpose of this study was to produce sublingual tablets of (BH) for treatment of hypertensive patients and, those who are suffering from angina pectoris, especially for elderly in addition, of enhancing the



permeability of the drug through complexation with HP- β -CD. In-vivo study was done using six male volunteers to compare the pharmacokinetics of the prepared formulae with the reference (Concor® tablets).

Materials and Methods

Materials

Bisoprolol hemifumarate (Merck-Barcelona, Spain); 2-Hydroxy propyl- β -cyclodextrin (chemical Co., Milwaukee, WI, USA); Polyethylene glycols 6000 (Morgan pharmaceutical Co., Egypt); Chitosan high molecular weight (Sigma, St.Louis, USA); Aerosil 200: Colloidal silicon dioxide (Degussa-Huls Ltd., Frankfurt, Germany); Crospovidone : Cross linked polyvinyl pyrrolidone (Fluka, Germany); Crosscarmellose sodium (FMC corporation, Philadelphia ,USA); Magnesium stearate, (Prolabo, France); Granular mannitol (Sigma, St.Louis, USA).

Preparation of solid complex

(BH) and HP- β -CD were weighed accurately at a 1:1 molar ratio and mixed by trituration in a mortar to prepare the physical mixture, while the inclusion complex was prepared by kneading method [10]. The required amounts of (BH) and HP- β -CD were accurately weighed and transferred to a mortar then triturated with minimum volume of ethanol-water (50:50, v/v) solution. The slurry obtained was kneaded for 30 minutes and then dried under vacuum at room temperature in presence of calcium chloride as a dehydrating agent.

Physicochemical characterization of BH- HP- β -CD binary solid systems

Differential scanning calorimetry (DSC)

DSC analysis was performed using DSC (Model DT-60, Shimadzu). Samples (3–4 mg) were heated in open aluminum pans at a rate of 10 C/min in a 0–400 C temperature range under a nitrogen steam. The instrument was calibrated using indium (melting point, 156.61 C; enthalpy of fusion, 28.71 J g⁻¹). DSC studies were performed for (BH) powder, HP- β -CD polymer, the physical mixture (1:1) and the prepared inclusion complex.

Fourier transform-infrared (FT-IR) spectroscopy

The FTIR spectra were recorded using a Bruker FTIR spectrophotometer according to the KBr disc technique. The FTIR measurements were performed in the scanning range of 4000 - 400 cm⁻¹ at ambient temperature.

Formulation of Bisoprolol hemifumarate sublingual tablets

Preparation of tablet

Sublingual tablets of (BH) was prepared according to table no.1. All the excipients except magnesium stearate and Aerosil 200 were mixed uniformly followed by addition of magnesium stearate and aerosil. Tablets were compressed with single flat-faced punch (8mm), Erweka type, GmbH, Germany. The total weight of the formula was maintained at 100mg.

Evaluation of tablets

All the tablets were evaluated for different parameters; uniformity of weight, diameter and thickness, hardness, friability, disintegration time, wetting time, drug content and in vitro dissolution study.

Uniformity of weight: Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated

Hardness: For each formula, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability: Twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4min. after revolution the tablets were dusted and weighed.

Disintegration test: the tablets were inserted in each of the six cells of the USP disintegration tester apparatus(Hanson Research ,USA) ; In this experiment simulated saliva fluid (SSF) pH=6.75 kept at 37 ± 0.5 C was used as disintegration medium at constant frequency of 30±2 cycles/min. Disintegration time was that at which all tablets were de-aggregated leaving no residue on the basket [11, 12]

Wetting time: A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. This experiment mimics the action of saliva in contact with the tablet [13].

Table no. 1: Formulation of fast disintegrating Sublingual tablet of Bisoprolol hemifumarate

Formulation	B1	B2	B3	B4	B5	B6	B7	B8
Bisoprolol hemifumarate	5	5	5	5	5	5	5	5
HP- β -CD	21	21	21	21	21	21	21	21
Chitosan	3	6	-	-	-	-	6	3
PEG6000	-	-	3	6	3	6	-	-
Crospovidone	-	-	-	-	5	5	5	5
Crosscarmellose sodium	5	5	5	5	-	-	-	-

* All formulae contained, 0.5mg Magnesium stearate, 1mg Aerosil 200 , 0.5mg Mint flavor

* All formulae contained 21 mg of HP- CD to achieve (1:1) molar ratio of the complex

* Total tablet weight to 100 mg (using granular mannitol as diluent and serve as sweetener)

Determination of tablets content uniformity

Each tablet was crushed and dissolved in 10 ml methanol. The solution was filtered, diluted and the drug content was analyzed spectrophotometrically (Shimadzu, UV-1601) at 223nm.

Dissolution Test: It was made by using USP Dissolution Tester and Apparatus II (rotating paddle) with simulated saliva fluid (SSF) pH=6.75 kept at 37 ± 0.5 C .

In vivo studies

The study was carried out to compare the pharmacokinetics of (BH) from formulae B2 and B7 to the reference (Concor® tablets) following administration of a single dose of BH (5mg) using randomized, single dose, three-way crossover open-label study randomized crossover design (table no. 2).

Subject Population: Six healthy Egyptian male volunteers (median age 28 years, median weight: 75 kg, median height: 180 cm) participated in this study. The volunteers underwent physical examination and complete hematological and biochemical examinations. None of the volunteers had any history of drug or alcohol abuse, nor did they have any acute or chronic gastrointestinal cardiac, vascular, hepatic or renal disease. No concurrent medication was allowed during the course of the study, and each subject read, understood and signed an informed written consent. All subjects were informed about the risks and objectives of the study.

Sample Collection: The drug was administered sublingual after overnight fasting and washout period of 1 week. Blood samples (5 mL) were collected into heparinized tubes at different time intervals: 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 h. The blood samples were withdrawn into tubes washed with diluted heparin to guard against coagulation of blood. The blood samples were then centrifuged at 3000 rpm for 10 minutes and the clear plasma was then collected in polyethylene capped tubes and stored at -20 C till assayed.

Table no. 2: Randomization plan of Bisoprolol Hemifumarate sublingual formulae (B2 and B7) viz. the conventional market (Concor® 5mg tablets, Amoun-Egypt)

Volunteer Number	Phase I	Phase II	Phase III
1	B2	B7	Reference
2	B7	B2	Reference
3	Reference	B2	B7
4	B2	Reference	B7
5	B7	Reference	B2
6	Reference	B7	B2

Chromatographic conditions

A modified HPLC method of analysis of Braza et al [14] for determination of (BH) in plasma was adopted. The HPLC apparatus consisted of: Isocratic pump LC-10 AS and a UV/VIS detector SPD-10A connected to a C-R6A Integrator (Shimadzu, Koyoto, Japan). The analytical column was Ponapak C18 HPLC column, 4.6 250 I.D mm, particle size 125 μ A (Waters Associates, Ireland). The mobile phase consisted of acetonitrile and 0.01 M phosphate buffer pH 5.5 at a ratio (30:70) v/v. The components of the mobile phase were mixed and adjust to pH 3 using phosphoric acid then filtered through Millipore filter (0.45 μ m nylon membrane), the mobile phase was delivered at a flow rate of 2.0 ml min⁻¹ and the detection wavelength was 223 nm.

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Pharmacokinetic analysis

Pharmacokinetic parameters from plasma data following administration of the two formulae were estimated using, WinNonlin® (version 1.5, Scientific consulting, Inc., Cary, NC, USA). C_{max} (ng/mL), t_{max} (h) were the observed maximum drug concentration and the time needed to reach this concentration respectively. The area under the curve, $AUC_{(0-24)}$ (ng.h/mL) was calculated then the relative bioavailability ($AUC_{test} / AUC_{standard} \times 100$). The pharmacokinetic parameters were; C_{max} , t_{max} , and AUC_{0-24} .

Statistical analysis

Statistical analysis was expressed as mean \pm Standard deviation (SD) and performed with t test for paired data using SPSS® 7.5 for windows software. The level of statistical significance was chosen as p 0.05.

Results and Discussion

Characterization of the solid complexes

To confirm the existence of inclusion complexation of BH, HP- β CD, DSC and IR analyses were carried out.



Differential Scanning Calorimetry (DSC)

Figure no.1 shows the DSC thermograms of BH, HP- β CD, physical mixtures and the solid inclusion complexes in 1:1 molar ratio. The DSC thermogram of (BH) was a typical of the crystalline substance, exhibiting a sharp endothermic peak at 106.5 C. For HP- β CD, it was observed a peak around 60°C corresponding to water loss and an endothermic peak at 333 C.

It was clear that the sharp endothermic peak of the drug, around 100°C became shorter in the thermograms of the physical mixtures that could be attributed to the reduced purity. On the other hand, the characteristic peak of the drug was totally disappeared in the complex thermogram. Similar results were observed in inclusion complex of Prazosin hydrochloride with HP- β CD [15].

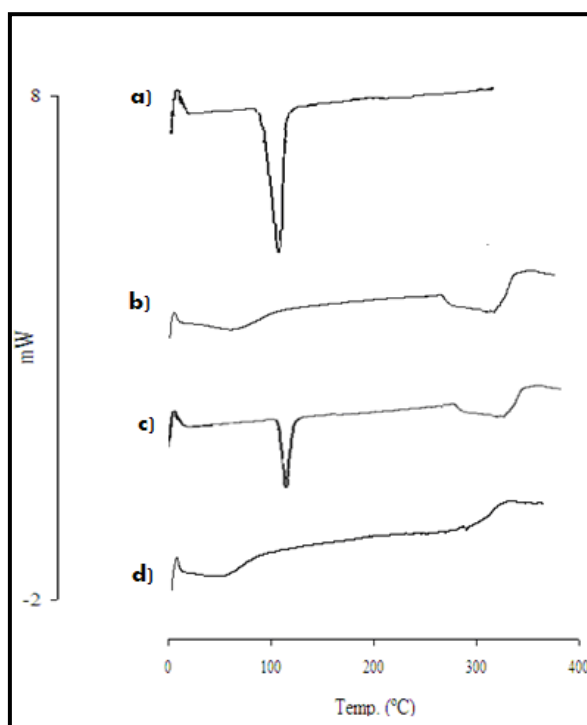


Figure no. 1: DSC thermograms of: a) pure BH , b) Pure HP- β -CD, c) Physical mixture, d) Inclusion complex

Fourier-transform infrared spectroscopy

The IR spectra of BH, (BH/HP- β CD), 1:1 physical mixtures and the inclusion complex, illustrated in figure no. 2. BH shows its characteristic peaks at 2850-2450 cm^{-1} assigned for methyl group, 3200-3600 assigned -NH and -OH stretching, 3030 cm^{-1} assigned to aromatic stretching, 1610 cm^{-1} for carbonyl group and 1574 cm^{-1} for CH-NH- group. For HP- β CD, the spectra illustrate an intense broad absorption bands at 3500-3300 cm^{-1} corresponding to the free -OH stretching vibration [16]. The IR spectrum of the physical mixture shows the superposition of pure components spectra, indicating the absence of interaction

between (BH) and HP- β CD in the physical mixture. On the other hand, the IR spectra of (BH/ HP- β CD) inclusion complex showed considerable differences when compared with those of the physical mixtures. The characteristic peaks of (BH) completely disappeared, this indicate the presence of host-guest interaction[17].

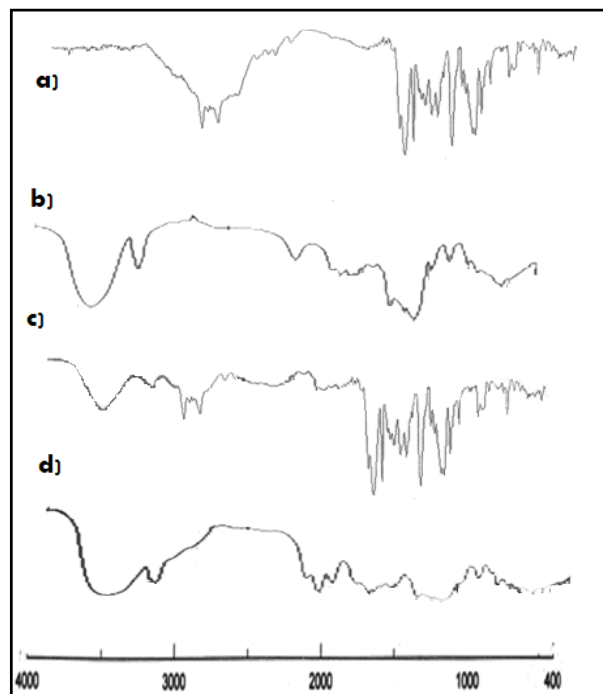


Figure no. 2: FTIR patterns of: a) Pure Bisoprolol hemifumarate, b) Pure HP- β -CD, c) Physical mixture, d) Inclusion complex

Evaluation of the sublingual tablets

The weight uniformity test showed that none of the tablets deviated by more than 5%, indicating that all formulae fulfills the pharmacopoeial limits for weight variation. In addition, the prepared tablets showed a uniformity of diameter and thickness; the values of tablets diameter were in the range of 8.00 to 8.13 mm while the values of the tablets thickness were in the range of 2.00 to 2.07 cm. All formulae of the tablets were evaluated for various physical parameters which were reported in table no. 2.

All the tablets maintained hardness in the range of 2.5 – 4.6 kg/cm^2 . The percent of friability was in the range of 0.41-0.92%. The drug content in different formulae was highly uniform and in the range of 95-102%. Regarding the disintegration time, it was noticed that the formulae contain PEG 6000 result in prolongation of the disintegration time of tablets due to its binding effects[18]. The formulae B2 and B7 possessed the lowest disintegration time and wetting time due to the presence of the high concentration of chitosan (6%), which has some disintegration action so they were selected for in vivo study. Upon carrying out the dissolution test, it was observed that 100% of the drug was released three minutes

after the start of the dissolution run in all formulae. This was due to the water-soluble nature of the drug. Thus, the dissolution tests were not of value to the study.

Table no.3: Characterization of Bisoprolol Hemifumarate Sublingual tablets

Formula Number	Hardness (Kg/cm ²)±S.D	Friability (%)	In-vitro disintegration time(sec.)±S.D	Wetting Time	% of drug content ±S.D.
B1	3.3±0.27	0.795	55.70±8.22	48.94±5.90	95.57±3.19
B2	4.6 ±0.48	0.405	17.19±2.89	24.9±3.58	98.18±2.65
B3	3.8±0.25	0.779	34.86±4.98	39.19±2.78	99.91±2.15
B4	2.8±0.46	0.921	78.12±9.63	69.94±12.68	101.58±1.37
B5	3.7±0.81	0.779	49.27±6.14	40.76±4.25	102.47±0.93
B6	2.90±0.49	0.891	119.39±10.33	81.39±6.31	99.33±1.97
B7	4.2±0.36	0.55	24.25±4.82	21.37±2.86	98.44±1.76
B8	4.3±0.21	0.611	69.35±4.80	71.88±9.26	102.57±3.80

Table no 4: Pharmacokinetic parameters ±S.D of Bisoprolol hemifumarate following the administration of a single oral dose 5mg of selected sublingual tablets B2, B7 and reference (Concor® tablets)

Pharmacokinetic parameter	Formula		
	Concor®	B2	B7
C _{pmax} (ng/ml)	17.862±3.52	20.807±2.48	19.617±4.628
t _{max} (hr)	2±(0.57)	0.95±(0.143)	1.1 ±(0.198)
AUC ₍₀₋₂₄₎ (ng.hr/ml)	270.833±(21.74)	308.315±(17.95)	289.318±(28.37)
T _{1/2} (hr)	10.234±(1.57)	11.076±(0.78)	9.825±(1.28)
Relative bioavailability	-	113.76%	106.794



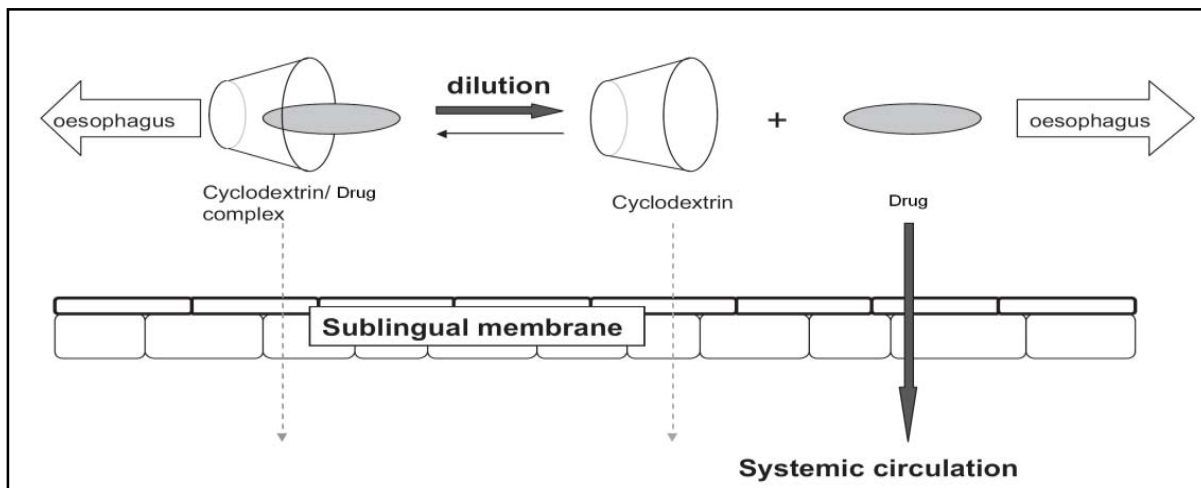


Figure no.3: The equilibrium between cyclodextrin, drug and drug/cyclodextrin inclusion complex [19].

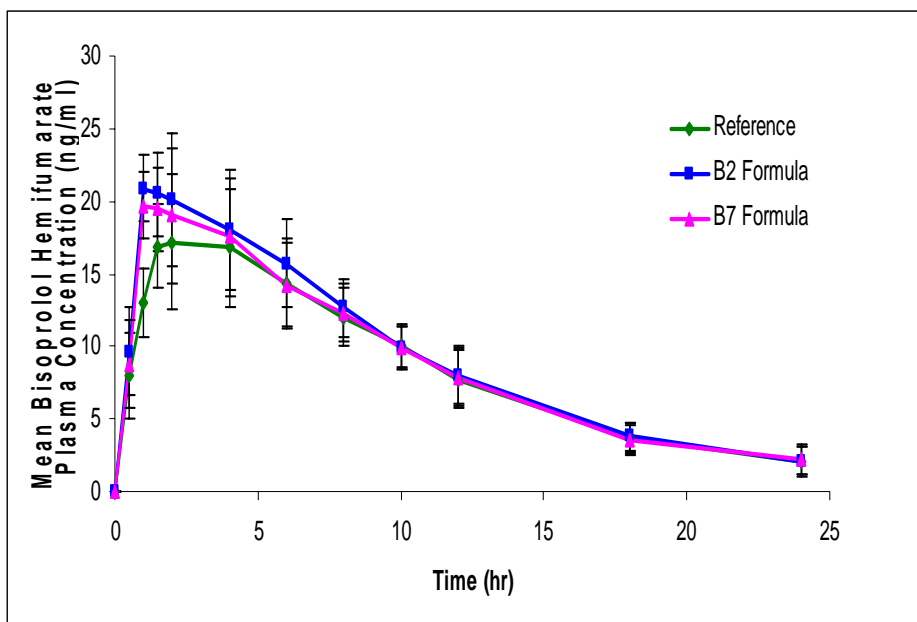


Figure no. 4: Plasma concentration of Bisoprolol Hemifumarate following the administration of Reference (Concor® tablet), B2 and B7 tablets. Data represent the mean values of $n=6 \pm S.D.$

Pharmacokinetics of Bisoprolol Hemifumarate from Sublingual tablets formulations

Figure no.4 illustrates the mean concentrations of the drug following the administration of each formula, whereas table no.3 gives the pharmacokinetic parameters of Concor®, B2 and B7. The mean plasma concentration-time profiles for (BH) 5 mg tablet by sublingual and oral route show a comparable in time of

occurrence of maximum plasma concentration (T_{max}) for (BH) prepared formulae which were faster in sublingual route of administration when compared to oral route. The mean C_{max} estimated from B2 and B7 were 20.807 ± 2.48 ng/mL and 19.617 ± 4.628 ng/mL, respectively, while it was 17.862 ± 3.52 ng/mL for Concor® tablets. The mean AUC_{0-24} which reflects the total amount of drug absorbed over the 24 h time period for Concor® tablets, B2 and B7 was found to be $270.833 \pm (21.74)$ ng

h/mL, 308.315±(17.95)ng h/mL and 289.318±(28.37)ng h/mL respectively, and determined to be statistically significant different ($p < 0.05$) for B2, while it was of non significant difference for B7. The relative bioavailability of B2 and B7 were 113.76% and 106.794% compared to Concor® tablets which taken as reference standard.

The higher C_{max} and faster t_{max} observed in both B2 and B7 than the reference conventional tablet (Concor®, Amoun-Egypt) may be attributed to the rapid disintegration and drug absorption through the epithelium of sublingual membrane and consequently the bioavailability increased [20]. In addition the effect of HP- β CD as incorporated product which have the ability to interact with macromolecules of sublingual membrane more efficiently, causing marked improvement in the drug sublingual absorption

[21, 22] as illustrated in figure no.3. The results of in vivo studies showed that formulation B2 containing 6%Chitosan, and 5% Crospovidone has the maximum C_{max} and AUC and minimum t_{max} values.

Based on the results of the present study, it can be concluded that the formulation of Bisoprolol hemifumarate 5 mg sublingual tablets

Conclusion

containing (BH) complexed with HP- β CD using appropriate excipients seems to be a promising alternative formula to oral administration route of Bisoprolol hemifumarate in acute management of angina pectoris and hypertension.

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