International Journal of Pharmacy and Biological Sciences
ISSN: 2321-3272 (Print), ISSN: 2230-7605 (Online)
IJPBS | Volume 8 | Issue 1 | JAN-MAR| 2018 | 197-208
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved| ज्ञान-विज्ञान विमुक्तये
|UGC Approved Journal |

DESIGN, DEVELOPMENT AND EVALUATION OF SUBLINGUAL POROUS TABLET

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ABSTRACT

The objectives of present investigation were to check drug-excipient compatibility. To enhance solubility of BCS II drug. Toformulate and study Invitro release behavior of optimized formulation. Nebivolol is used as an active ingredient, different super disintegrant like Ac-di sol, sodium starch Glycollate, Crosspovidone, subliming agent i.e. Camphor, Mannitol as diluents. Methods used for preparation inclusion complex of drug with β-cyclodextrin by physical mixing, kneading method and co-grinding method. Sublingual porous tablet prepared by direct compression using camphor for sublimation, Phase solubility showed Ap type curve, Hence the complex stechiometriy was assumed to be higher ordered complex. The drug release of prepared complex by Co-grinding method was found within 2 min. The results of multiple linear regression analysis revealed that for obtaining rapidly disintegrating sublingual porous tablets should be prepared by using optimum concentration of camphor and higher percentage of Crosspovidone. Drug release of F_1 batch was found to be 99.39 % in 5 minutes. From results it was concluded that prepared sublingual porous tablets of Nebivolol containing higher percentage of crospovidone and camphor showed minimum disintegration time 18.3±1.64 sec. The maximum drug release was found to be 99.39±1.64% at 5 min. Prepared formulation was stable at room temperature over period of one month.

KEY WORDS

Nebivolol, β-cyclodextrin, co-grinding method, Sublingual porous tablet.

INTRODUCTION

Oral drug administration is one of the most suitable and widely accepted by the patients for the delivery of most therapeutically active drugs. Various dosage forms like tablets, capsules and liquid preparations have been administered by oral route. But, due to some unsuitable physiological conditions of the gastro-intestinal tract like relatively poor absorption, presence of various digestive enzymes of the gastro-intestinal lumen and epithelium, and first pass metabolism by hepatic enzymes, the administration of some drugs is affected. Also, it limits many drugs to reach into the therapeutic level. Hence, to minimize the problems associated with drug- absorption through gastro-intestinal membrane, there is need to develop sublingual drug delivery systems that will enhance the therapeutic drug level, avoids first-pass and gut-wall metabolism, increases the bioavailability of active medicament or improve convenience of dosing. Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the

tongue and floor of the mouth. For these formulations small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. They are popular as NDDS because they are easy to administer and lead to better patient compliance. Bioavailability of some drugs enhance due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drug that pass down into the stomach. Advantages of this delivery include-

Oral mucosa is highly vascularised and having thin membrane and large veins allows the rapid absorption and increases the bioavailability. Thickness of sublingual epithelium is 100-200 µm which is less as compared to buccal thickness. So, the absorption of drugs is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva. It is also suitable for the drugs which are susceptible to acid hydrolysis in stomach or drugs which are extensively metabolized in liver. Low dosage gives high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects [1-5]. Also, administration without water, anywhere, anytime, accuracy of dosage form, ideal for pediatric and geriatric patient, rapid onset of action, increased bioavailability and good stability make this tablet popular as a dosage form of choice in the current market.

Nebivolol is long acting, cardioselective β-blocker currently licensed for the treatment of hypertension. Hypertension is defined as a sustained increase in blood pressure 140/90 mm Hg. actually, in both fatal and non-fatal CVS disease in adult lowest with systolic BP < 120 mm Hg and diastolic BP < 80 mm Hg. At every level of diastolic pressure, risk is greater with higher level of systolic BP. At very high B.P. (210/120 mm Hg) a subset of patient develops fulminant atriopathy characterized by endothelial injury and marked proliferation of cells in the intimal leading to intimal thickening and ultimately to arteriolar occlusion. This pathological basis of the syndrome of immediately life threating hypertension, which is associated with rapidly progressive microvascular occlusive diseases in the kidney (with renal failures) Brain (hypertensive encephalopathy) CHF and pulmonary edema. These patients typically require in hospital management on an emergency basis for prompt lowering of B.P. since the purpose of treating hypertension is to decreases CVS risk, other dietary and pathological interventions may be required [6-7].

The present investigation is deals with preparation of sublingual porous tablet of Nebivolol by using sublimation method with objective to enhance the solubility of BCS class II drug i.e. Nebivolol by preparing inclusion complex with β-cyclodextrin as a complexing agent. A 3^2-full factorial design was applied to investigate the combined effect of two formulation variables: amount of crospovidone, and amount of subliming agent on Invitro disintegration time as dependable variable. Crosspovidone (5%w/w) used as superdisintegrants and camphor (20%w/w) was used as subliming agent along with directly compressible mannitol to enhance mouth feel.

MATERIALS AND METHODS

Materials

Nebivolol was obtained as gift sample from Glenmarc pharmaceuticals (Goa, India), β-cyclodextrin, ac-di sol, sodium starch glycollate, crospovidone, camphor, talc, magnesium stearate, sodium saccharine were purchased from research-Loba chem. industries (Mumbai, India), All other chemicals used were ofanalytical grade.

Methods

Drug excipient compatibility study

FTIR Spectroscopy of Drug-Excipients Compatibility Study

Fourier Transform Infrared spectra were obtained by using an FTIR spectrometer Affinity-1 (Shimadzu). The Samples (Nebivolol, crospovidone, Nebivolol + Crosspovidone, formulation) were previously ground and mixed thoroughly with KBr in mortar pestle in the ratio of 1:100. Forty-five scan were obtained at a resolution of 4 cm^{-1} from 4500 cm^{-1} to 400 cm^{-1}.

Phase solubility study [7-9]

Phase solubility studies carried out according to the method reported by Higuchi and Connors. An excess amount of Nebivolol was added to aqueous solution of β-cyclodextrin having concentration 0.02 M. and prepared 0.001 to 0.02 M concentration of solution. The contents were stirred for 24 hr by constant stirring on rotary shaker. Further supernant liquid filtered and analyzed using UV Spectrophotometer at 280 nm. Plotted a graph of molar concentration of β-cyclodextrin verses concentration of Nebivolol. Stability constant was calculated according to equation –

Kc = slope/Intercept (1-slope) ---------- (Eq.1)

Preparation of complex of Nebivolol with β-cyclodextrin

Inclusion complex of Nebivolol at five mass ratios (1:1, 1:2, 1:3, 1:4 and 1:5) were denoted as PM_1 to PM_5, KM_1 to KM_5, CG_1 to CG_5, respectively, were prepared by following methods:

Physical mixing

Drug and β-cyclodextrin ingredients in different molar ratio were mixed with the help of spatula for 15 min and finally sieved through # 120.

Kneading method

Drug and β-cyclodextrin in different molar ratio were kneaded in mortar by adding small quantity of Water: methanol for 30 min. to form a homogeneous paste. Prepared paste were dried in oven at 45-50^{0}C for 24 hr. finally dried complex were pulverized and sieved through #120.

Co-grinding method

Stechiometric amount of drug andβ-Cyclodextrin was taken in dry mortar pestle. Simply grinding of two components was carried out for 30 min. Samples were collected after 30 min. sieved through #120.

Characterization of Nebivolol-β-Cyclodextrin Complex [10-15]

FTIR study

FTIR study were performed of pure drug and complex prepared by using co-grinding method (1:2 molar ratio). Fourier Transform Infrared spectra were obtained by using an FTIR spectrometer Affinity-1 (Shimadzu 1601). The Nebivolol, Complex was previously ground and mixed thoroughly with KBr in mortar pestle in the ratio of 1:100. Forty-five scan were obtained at a resolution of 4 cm^{-1} from 4500 cm^{-1} to 400 cm^{-1}.

Differential Scanning Colorimetric Study

Thermal analysis of pure Nebivolol and β-Cyclodextrin were carried out using DSC unit (SDT Q600 V20.9 Build 20). Samples were placed in aluminum pans and heated at a scanning rate of 10°C/min from 30 to 200°C.

X-ray Diffraction (XRD) Study

XRD study were performed at room temperature with an X-ray diffractometer (D2 PHASER) The diffraction pattern was measured with a voltage of 30 kV and a current of 100 mA over a 2h range of 3–160°/min using step size of 0.005^0 2Θ at scan speed of 1 s/step.

Drug content of Complex

Accurately weighed complex equivalent to 3 mg of Nebivolol prepared by co-grinding method were dissolved in 100 ml of methanol. To get concentration of 30 µg/ml. The absorbance of stock solution was measured at 280 nm using UV Spectrophotometer (Shimadzu 1601) and calculated the concentration with the help of regression line equation.

***In vitro* Dissolution Testing**

In vitro dissolution study of complex prepared by different method was performed by using USP apparatus II. Complex contents equivalent to 5mg of Nebivolol. Dissolution test was carried out using 900 ml of phosphate Buffer of pH 6.8 at 37±0.5^{0}c and 50 rpm. 5ml Sample of solution withdrawn from the media at 2, 4, 6…30 min interval by replacing sample with fresh phosphate buffer of pH6.8 of same quantity. Absorbance of these solutions was measured at 280 nm. Cumulative percent drug released was calculated.

Preparation of Nebivolol sublingual porous tablet

Accurately weighed amount of complex equivalent to 5 mg of Nebivolol and all additives were homogeneously blended using geometric dilutions and passed through sieve #80. Amount of crospovidone and amount of camphor was added according to factorial designs which were shown in Table 1. Tablets were directly compressed by KBr Press equipped with a 6 mm flat-faced punch and die set. These prepared tablets were subjected to sublimation at 60^{0}C for 12hrs.

Ingredients (mg) / tab.	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Nebivolol CG (1:2) (equi. to 5 mg Nebivolol)	15	15	15	15	15	15	15	15	15
Crospovidone	5	5	5	2.5	2.5	2.5	1.25	1.25	1.25
Camphor	20	15	10	20	15	10	20	15	10
Mannitol	52	57	62	54.5	59.5	64.5	55.75	60.55	60.75
Talc	4	4	4	4	4	4	4	4	4
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Sodium Saccharin	1	1	1	1	1	1	1	1	1
Vanilla	1	1	1	1	1	1	1	1	1
Total	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Table 1: Composition of Sublingual Tablets Preparation of Nebivolol by 3^2 factorial design

Evaluation of Sublingual Porous Tablets

Weight Variation

Weight variation was conducted by selecting 20 tablets at random. Weighed each tablet on electronic balance (Shimadzu AUX 220) and calculated the average weight of tablet. It is the individual variation of tablet weight from the average weight of 20 tablets.

Thickness

The thickness of the tablets measured using a vernier caliper. Three tablets from each batch of formulation were used and the average values and standard deviation were calculated.

Hardness

The hardness of the tablet measured using a Monsanto hardness tester in kg/cm2and average value and standard deviation was calculated.

Friability

For friability10 tablets from each batch were examined using Roche friabilator and the equipment was run for 4 min at 25 revolutions per minute. The tablets were removed from friabilator, dedusted the tablet and reweighed. The percent friability was calculated.

Drug Content

Twenty tablets from each batch were powdered and accurately weighed (10 mg) and dissolved in methanol; solution was diluted with methanol in 100 ml volumetric flask to get final stock solution of concentration 100µg/ml. prepare final solution having concentration 2, 4 and 6µg/ml. Take absorbance of each concentration at 280 nm using UV Spectrophotometer and calculated the drug content with the help of regression line equation.

Wetting Time

The tablets were placed at the center of two layers of absorbent paper fitted into the petridish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch.

Disintegration Time: Dependent Variable

Optimization Data Analysis and Model Validation

The response parameter, disintegration time of the tablets was determined in disintegration test apparatus (IP/BP/USP) standard, Dolphin) with distilled water as a disintegrating medium at a temperature 37°±2°C. All the responses observed for nine formulations of every design were fitted into models using Design-Expert® software.

***In-vitro* drug dissolution study**

Dissolution study was conducted for all the formulations using USP test apparatus 2 (DSK Instrument). Dissolution test was carried out using 900 ml of phosphate buffer (pH 6.8), at 37°C ± 0.5°C for 30 min at 50 rpm. A sample (5 ml) of the solution was withdrawn from dissolution apparatus at 1, 3, 5, 7, 10, 15, 20, 25; 30 min. and withdrawn volume of sample replaced with fresh dissolution media and analyzed the samples by UV Spectrophotometry at 280 nm. The percentage drug release was calculated using an equation obtain from calibration curve. Dissolution of marketed formulations done using 900 ml of 0.1 N HCl and phosphate buffer (pH 6.8), at 37°C ± 0.5°C for 30 min at 50 rpm.

Morphological examination of the prepared porous tablets

The morphological characteristics of the tablets after sublimation of the contained sublimable material were examined using an optical microscope.

Stability Studies

Stability study was performed on optimized batch F_1 to determine the change in weight variation, hardness, friability, drug content and disintegration time of tablets on storage at room temperature for one month. Every week the sample was withdrawn and to evaluated for physical characteristics.

RESULTS AND DISCUSSION

In this study, an attempt was made to develop a sublingual porous tablet for Nebivolol, a 3^2-factorial design was used in the present study, in this design two factors are evaluated, each of 3 levels and experimental trials are performed at all 9 possible combinations. The amount of superdisintegrant (crospovidone) X_1andamount of subliming agent (camphor) X_2selected as independent variable and disintegration time were selected as dependent variables. Nebivolol sublingual porous tablets were prepared by sublimation method using camphor as subliming agent along with directly compressible mannitol which was used to enhance mouth feel.

IR spectroscopic studies indicated that the drug is compatible with all the excipients. Phase solubility

diagram for complex is shown in figure 2. It was observed that there is an increase in linearity resulting in A_P type of phase solubility. Consecutive complexation is assumed where the 1:2 complexes is formed when one additional cyclodextrin molecule forms a complex with an existing 1:1 complex. It means the complex is first order with respect to the substrate but second or higher order with respect to the ligand. Hence the complex stechiometriy was assumed to be higher ordered complex

In phase solubility studies it was observed that as there was increase in concentration of β-cyclodextrin there was increases in solubility of Nebivolol, hence from above observation stechiometriy assumed that 1:1 1:2, 1:3, 1:4, 1:5 molar ratio.The drug content in each complex was determined by the UV spectroscopy method. The drug content was found to be in the range of 100.01±1.21 to 102.9±1.24% in Co-grinding method for molar ratio 1:1 to 1:5 respectively.

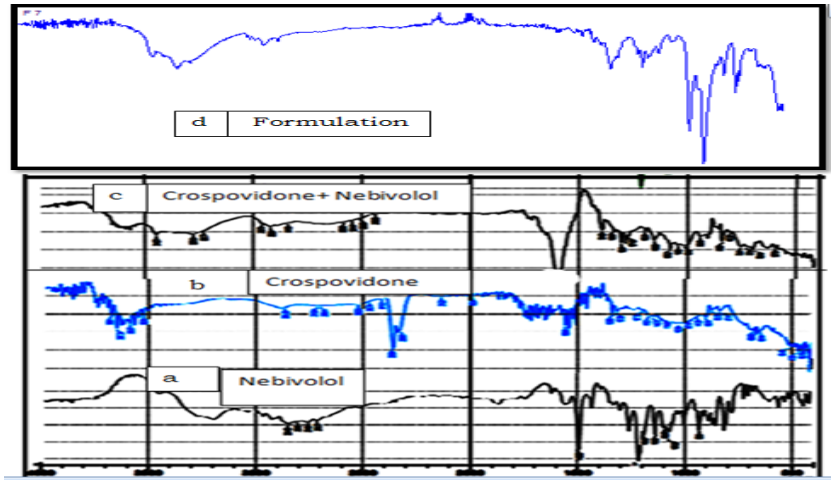

Figure 1: FTIR Spectra of (a) Nebivolol (b) crospovidone (c) Nebivolol + crospovidone (d) formulation

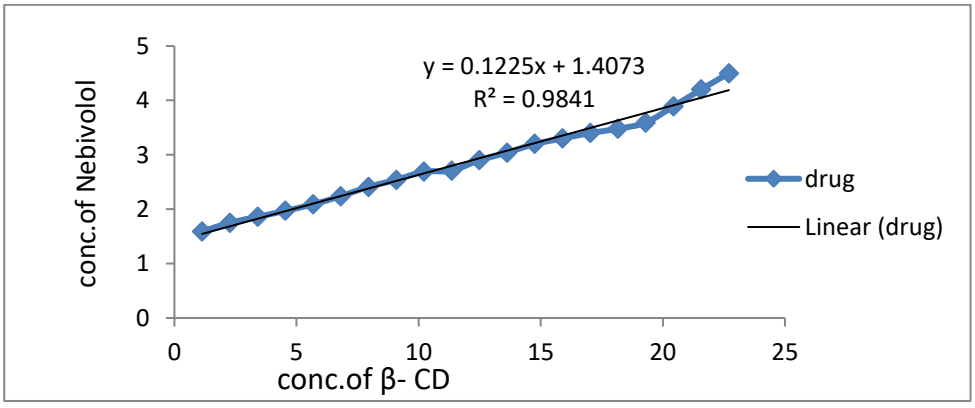

Figure 2: Phase solubility study

Characterization of Complex of Nebivolol

FTIR study [16-17]

FTIR spectra of co-grinding complex were compared with spectra of pure Nebivolol showed in the figure 3. FTIR spectra of complex showed a slight shifting of peak with increases and decreases in peak intensity than those of drug indicating chemical interaction between drug and β-cyclodextrin during co-grinding.Peak at 3536.81 cm^- due to –NH streching, at 1188.90 cm^- due to -C-O streching, 1225 cm^- due to CN streching, and 1095 cm^- due to C-F streching in complex indicating inclusion of Nebivolol in β-cyclodextrin cavity. Also, there is disappearance of peak at 3206.08 cm^- of drug into complex due to drug interaction with β-cyclodextrin. Peak at 1547.5 cm^- in complex are shifted towards left side at 2359 cm^- position it may be due to drug non-covalent interaction of drug and β-cyclodextrin.

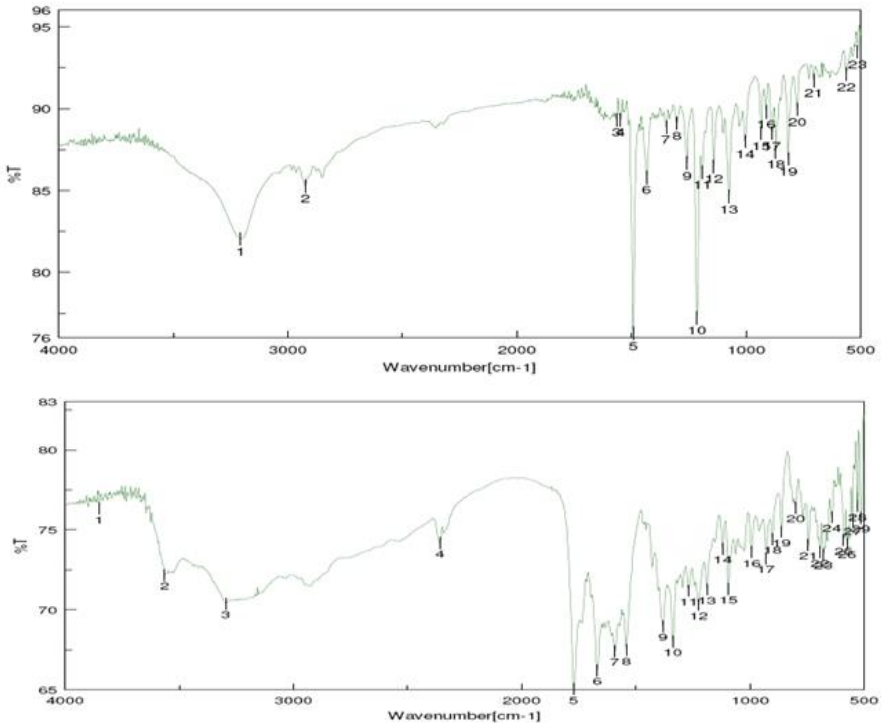

Figure 3: FTIR Spectra of (a) Nebivolol (b) Complex

Differential Scanning Colorimetric Study [18-19]

In DSC Studies curve of pure Nebivolol exhibited endothermic response corresponding to the melting of drug. Onset of melting was observed at 227°C. Figure 4 (c) showed decreases in energy change of melting endotherm, which confirms a considerable extent of reduction in crystallinity of the drug. However, the melting peak of β–Cyclodextrin in complex was observed at slightly lower temperature (255°C) than that of pure β–Cyclodextrin (260^{0}C). This result can be explained on the basis of major interaction between the drug and cyclodextrin. It is speculated that Nebivolol molecularly dispersed in β–Cyclodextrin during co-grinding so decreases in melting endotherm and consequently increase in solubility of Nebivolol. Figure 4 (b) showed decrease in energy change of melting endotherm, which confirms a considerable extent of reduction in crystallinity of the drug due to formation of inclusion complex with β-cyclodextrin and may be dissolution properties of the excipient.

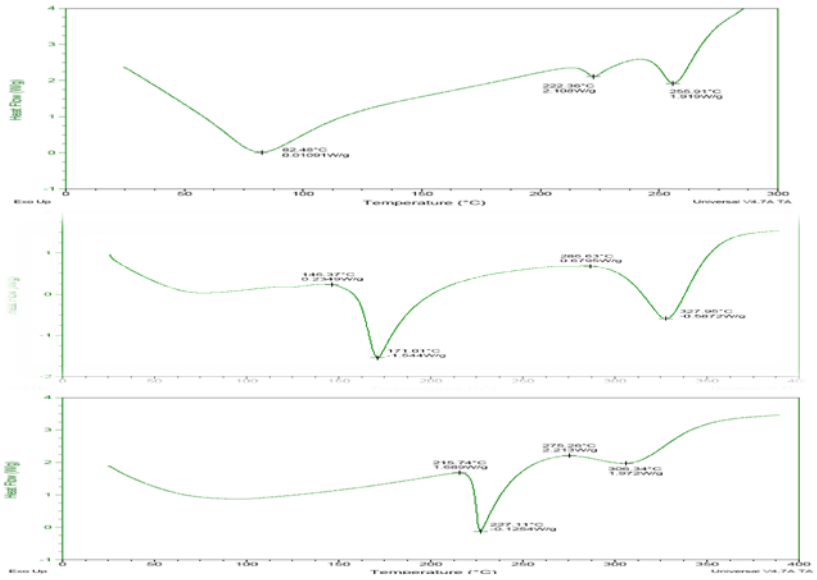

Figure 4: DSC study of (a) Nebivolol (b) Complex (c) formulation

X-Ray Diffraction (XRD) Study [20]

In XRD studiesmany diffraction peaks with high intensity were observed in the diffraction patterns of Nebivolol and β–Cyclodextrin due to its crystalline nature. The crystalline peaks located at 18.45º, 24.88º, 29.60º, 41.56º, 42.49º (2θ) corresponding to Nebivolol crystals were observed and β–Cyclodextrin showed intensity peaks at 12.590, 19.580, 20.780 (2θ) value. In the complex prepared by co-grinding method diffraction peaks low intense peaks as compared to Nebivolol and β–cyclodextrin which is located at 10.120, 13.180, 16.910, 24.670, 28.480 (2θ). XRD patterns of formulation showed less intensity peaks at 14.050, 19.750, 24.610, 28.750, 32.530 (2θ) values. XRD data confirm that a structural modification occurred in molecular state of Nebivolol. The physical characteristic of Nebivolol is crystalline, but that of formulation peaks is less crystalline as compared to drug. The diffused peaks in theformulation shows entrapped drug molecule that were molecularly dispersed in the β-cyclodextrin and consequently increase in solubility.

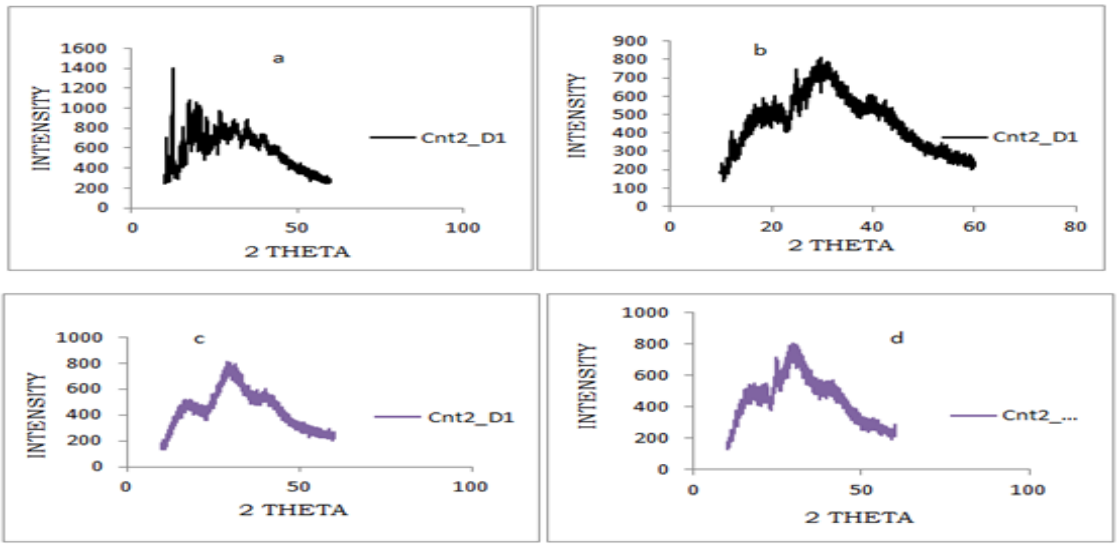

Figure 5: XRD Study of (a) Pure β-cyclodextrin (b) Pure Nebivolol (c) Complex (d) formulation

Dissolution Studies of Nebivolol Complex [21]

Figure 6 shows the dissolution profile of Nebivolol complex prepared by different methods in different molar ratio. As shown, 6 min after starting the experiment, more than 50% of drug was dissolved in the medium. Fast dissolution of the drug from the complexes can be depends on manufacturing method of complex, which can be one of the most important parameters for the preparation of Nebivolol complex with β-cyclodextrin. It shows the 40.15% drug release within 6 min; while complexes show better results.

From dissolution profile of complexes by using co-grinding method it was found that the 1:2 proportion shows 99.02% drug release within 6 min. it may be due to shear stress applied during co-grinding leads to formation of inclusion complex with β-cyclodextrin means it forms or it interplays atomic, thermodynamic and solvent forces that account for the interchanging physico-chemical properties of Nebivolol.

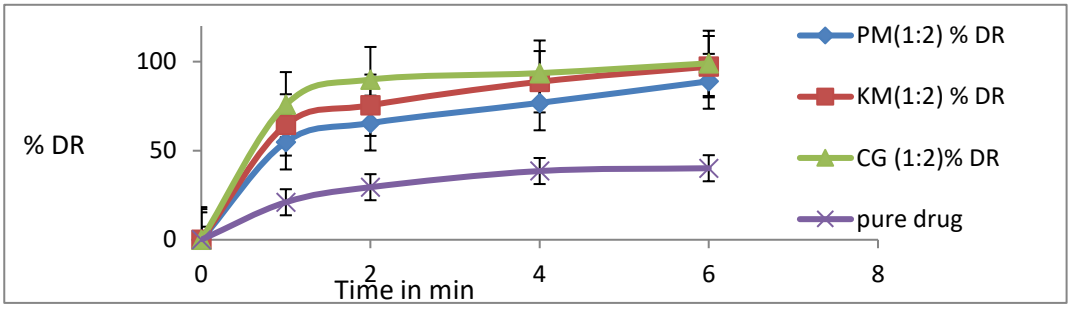

Figure 6: Dissolution profile of complex prepared by different method in 1:2 molar ratio with pure drug

As the material was free flowing (angle of repose < 31.44°, Carr's index 17.02±0.01), weight variation of tablets obtained up to 6.9% with acceptable variation as per IP specification (7.5%), drug content was found to be in the range of 99.96±1.96 to 103.15±1.61%which is within acceptable limits(as per IP the drug content limit is not less than 90% and not more than 110%) hardness of tablet was found to be in the range of 3.2±0.03 to 4.1±0.01 kg/cm^2.The friability values below 1% were showed good mechanical resistance of the tablet and displayed an Invitro disintegration time of 18 second facilitating faster disintegration in the mouth.

In order to investigate the factors systematically, a factorial design was employed in the present investigation. Formulation optimization has been done by 3^2 factorial design, preparing 9 batches of formulations (F_1 to F_9). The polynomial equation was derived Invitro dispersion time, by applying ANOVA at 0.05 level using Design Expert® software (version 8.0.1, Stat-Ease Inc, Minneapolis, MN). Formulation F1 containing 5% crospovidone and 20% w/w camphor was found to be promising with an Invitro dispersion time of 18 sec. i.e. minimum as compared to other formulations [22]

The polynomial equation generated by this experimental design is as follows:

$$\mathbf{Y= \beta_0+\beta_1X_1+\beta_2X_2+\beta_{12}X_1X_2+\beta_{11}X_1^2+\beta_{22}X_2^2} \text{ ---------- (Eq. 8)}$$

Where Y is the dependent variable; β_0 is the intercept; β_1, β_2, β_{12}, β_{11} and β_{22} are the regression coefficients; and X_1, X_2 are the independent formulation variables.

Analysis of variance Table 6 of the responses indicates that response surface models developed for disintegration time were significant.

Code	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Disintegration Time (Sec)	18 ±1.64	22 ±1.08	38 ±1.15	30 ±1.32	27 ±1.10	58 ±1.15	55 ±1.0	57 ±1.52	49 ±1.15

(All values are expressed as a Mean ± SD, n=3)

Table 2: Data of Dependent Variable: Disintegration Time

RESULTS					
R^2 =	0.942803				
F =	9.88999				
Significant	(F-critical = 9.01 @ alpha = 0.05, 1-tailed, DF = 5/3)				
CONSTANT	β_1	β_2	β_{11}	β_{22}	β_{12}
32.6833	-13.5708	-8.8333	4.7625	3.9750	-1.5750
Signif.	**Signif.**	**Signif.**	Insignif.	Insignif.	Insignif.
t-Table = 1.59 @ alpha = 0.05, 1-tailed, DF = 3					

Table 3: Analysis of Variance (ANOVA) of Dependent Variable

Mathematical Modelling

Mathematical relationship generated using multiple linear regression analysis for the studied response variable is expressed as equation

$Y=32.683-13.57X_1-8.833X_2 1.5750X_1X_2+4.7625X_1^2+3.975 X_2^2$--------(Eq. 2)

The polynomial equations (Eq.2) comprise the coefficients for intercept, first-order main effects, interaction terms, and higher order effects. The negative sign for coefficient of X_1 and X_2 reveal that amount of crospovidone and amount of subliming agent effect on the values of disintegration time. The sign and magnitude of the main effects signify the relative influence of each factor on the response. The values obtained for main effects of each factor in equations reveal that amount crospovidone and amount of camphor shows effect on the values of disintegration time. Result of model reveals that on increasing concentration of both crospovidone and camphor, decreases in disintegration time is observed; both coefficient β_1 and β2 bear negative sign. When higher percentage of camphor is used, higher porosity is expected in the tablets expected in the tablets; it is obvious that in the presence of higher concentration of superdisintegrants, wicking is facilitated [23].

The response plot Figure 7 indicated the disintegration time was tended to decrease with increasing amount of crospovidone and camphor. From the response surface plot it was observed that, shaded region indicated that range in response variable means as the concentration of crospovidone and camphor increases, the disintegration time was decreased.

The rapid and desired disintegration of Nebivolol tablets is due to the presence and good proportion of crospovidone and camphor. Due to porosity it has good wicking and absorbing capacities. Porous tablets disintegrated rapidly due to the rapid passage of water into the tablets resulting in the instantaneous rupture of the hydrogen bonds. Thus it is concluded that by adapting systemic formulation approach an optimum point can be reached in shortest time within minimum effort. Subliming technique would be an effective approach compared with use of more expensive adjuvants in the formulation of fast disintegrating with improved drug dissolution, patient compliance, convenience and acceptability[23] .

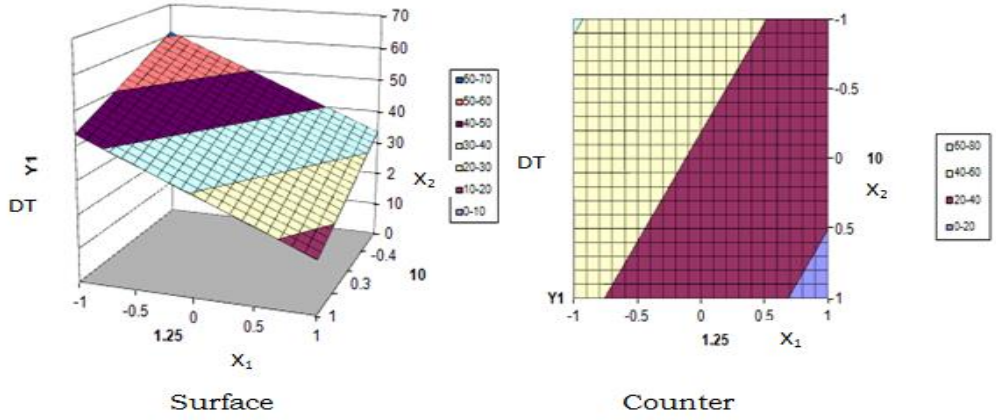

Figure 7: Response Surface and Counter Plot for Disintegration Time for Nebivolol Sublingual Porous Tablets

***In vitro* Drug Dissolution Study**

Dissolution study of sublingual porous tablets as shown in figure 8. Within 5 min, 50% of drug was dissolved in the medium. Fast dissolution of the drug from the formulations depends on manufacturing method, which can be one of the most important parameters for the fast dissolution of Nebivolol. As it is known, the Nebivolol sublingual porous tablets prepared by sublimation method to enhance porosity, due to porosity when tablets come in contact with saliva it facilitates wicking action leads to faster water uptake into tablets exhibits comparatively faster dissolution. When it was compared the dissolution profile of marketed conventional Nebivolol tablet at the end of 30 minutes, it was observed that marketed conventional tablet shows faster dissolution in o.1 N HCl i.e. 103.5% drug release in 10 min. and poor dissolution in phosphate buffer of pH 6.8 i.e. 42.68% in 10 min. But Nebivolol when administered orally it undergoes first pass hepatic metabolism.

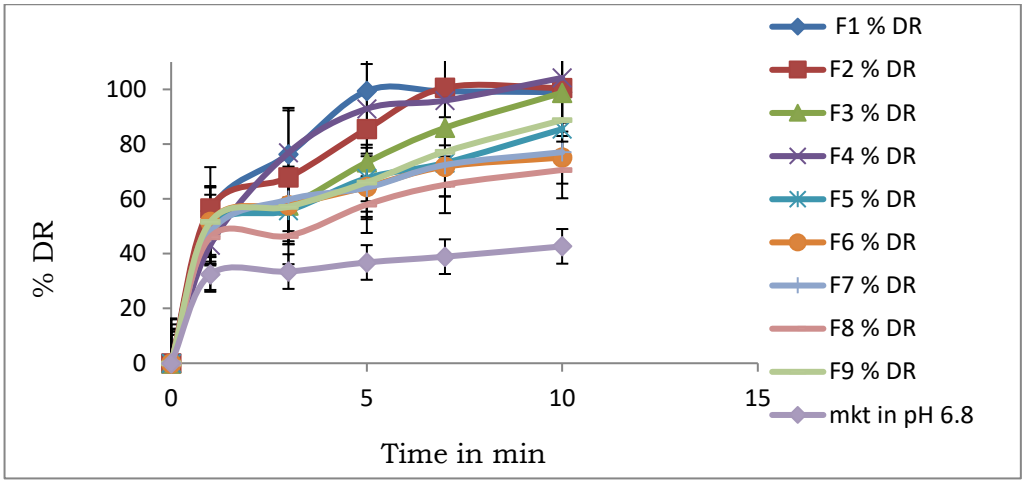

Figure 8: Dissolution profile of sublingual porous tablet formulations compared with marketed formulation

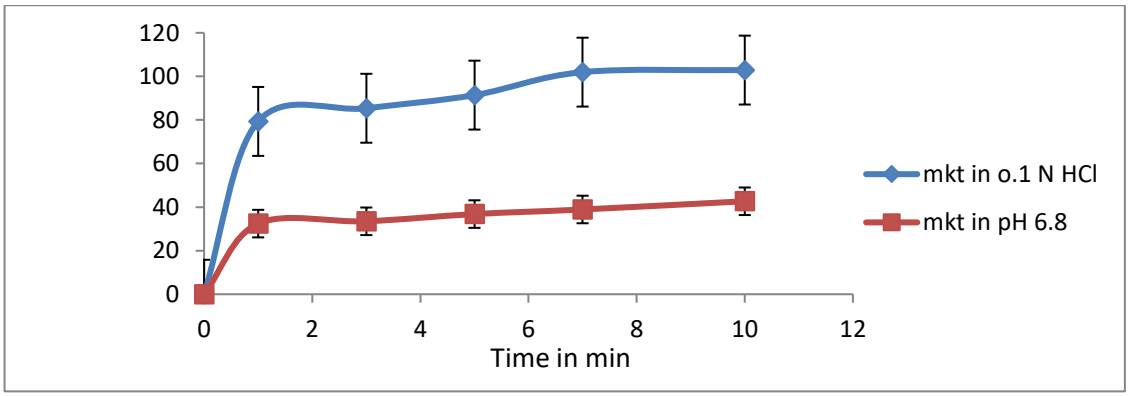

Figure 9: Dissolution Profile of marketed conventional Nebivolol tablet formulation

Morphological examination of the prepared porous tablets

The morphology of the tablets was examined using an optical microscope and selected photographs are illustrated in figures 10 (a, b). It is evident that the sublimation of camphor caused a remarkable change in the outer surface of the tablets manifested as pores and cavities.

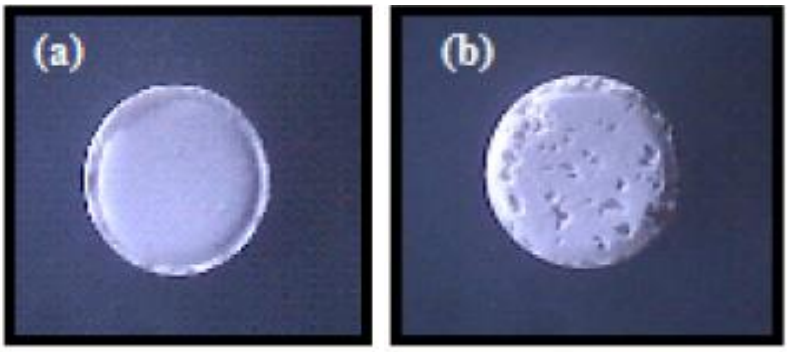

Figure 10: Photographs of (a) directly compressed Nebivolol Tablet containing 20% of camphor before sublimation. (b) Tablet containing 20% of camphor after sublimation.

Stability Studies [24]

In Stability studies ofF_1 formulation indicated that there are no significant no significant changes in weight variation, hardness, friability and disintegration time at the end of 30 days (table 7).

Physical Parameters	0 Days	7 Days	15 Days	30 Days
Weight Variation(mg)^a	84.56±1.45	84.9±1.40	84.14±1.44	84.5±1.45
Hardness(kg/cm^2)^a	3.40±0.01	3.50±0.01	3.49±0.01	3.45±0.01
Friability (%)	0.55	0.55	0.54	0.52
Disintegration Time(sec)^a	19.3±1.15	19.3±1.12	19.5±1.16	20.08±1.15

(All values expressed as a Mean ±SD, n=3)

Table 4: Data of Stability Study for Optimized Batch F_1

CONCLUSION

Co-grinding method employed shows better enhancement of solubility. Formulated sublingual porous tablet of Nebivolol shows better result for DT i.e. within 1 min. and dissolution study found to be for F1 batch 99.59 % within 5 min. Nebivolol is BCS class II drug. Conventional Nebivolol tablets available in market are not suitable where quick onset of action is required, to overcome these problems; there is a need to develop a rapidly disintegrating sublingual porous tablet. Administered without water anywhere, anytime and absorbed directly into systemic circulation through sublingual mucosa. No such sublingual tablet of Nebivolol is available in the market. The formulated sublingual porous tablet of Nebivolol used for the emergency treatment of hypertension.

ACKNOWLEDGEMENT

Author is thankful to SSCOP Ghogaon, Gov. COP Karad for providing necessary facilities and help also thankful to Mr. A.S. Shete sir for providing his kind guidance.

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