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Formulation characterization and *in-vitro/in-vivo* evaluation of orodispersible tablets of Nebivolol HCl

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ABSTRACT

Objective of the present research work was to prepare orodispersible tablets of Nebivolol hydrochloride (NEB) for dysphagic patients. Nebivolol, an anti-hypertensive drug, was chosen as a model drug in this study. Oral bioavailability of nebivolol is only 12% due to extensive first pass hepatic metabolism by Cytochrome P450 2D6 enzyme. Orodispersible tablets of NEB were prepared using different super-disintegrating agents such as crospovidone, croscarmellose sodium and sodium starch glycolate at different concentrations. The best formulation was selected based on disintegration and dissolution profile that was further taken for sublimation studies using camphor, menthol and thymol. Drug-excipients interaction studies were carried out by FTIR spectrophotometer with each of the excipients and optimized formulation. The orodispersible tablet formulation containing 10% w/w of menthol showed disintegration time of 11 sec with more than 98% drug release within 14 min. Therefore, this formulation was optimized and considered for further in vivo studies. In vivo studies of orodispersible tablets in rabbits showed significantly better pharmacokinetic profile (AUC, T_{max}, C_{max}) compared to marketed conventional tablets. Therefore, from this study it was concluded that, orodispersible tablets of NEB may prove to be more efficacious in the treatment of hypertension in dysphagic patients.

Keywords: Orodispersible tablets, Super-disintegrants, Sublimation, Pharmacokinetics

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INTRODUCTION

Dysphagia is a biomechanical disorder considered as a clinical syndrome. It is defined as "an inability to swallow, or a sensation that solids or liquids do not pass easily from the mouth to the stomach" [1, 3]. From many reported studies it has been estimated that over six million adults have dysphagia [1]. It can occur in all age groups, but the prevalence increases with increase in age [1, 3]. Other categories that experience problems using conventional dosage forms include are mentally ill, uncooperative and nauseated patients, those with condition of motion sickness, sudden episodes of allergic attack or coughing [2]. Oral conventional formulations such as tablets, capsules and liquids pose difficulty in swallowing, especially in dysphasic patients [3].

Nebivolol HCl (NEB) is an oral, cardio selective third generation β-receptor blocking agent, primarily used to treat hypertension [4]. After oral administration of NEB, the peak plasma concentration reaches within 0.5-2 h. It undergoes extensive first pass hepatic metabolism due to cytochrome P450 2D6 (***CYP2D6***) enzymes and its oral bioavailability is only 12% in extensive metabolizers. Half life also varies extensively from 10.3 h (in extensive metabolizers) to 31.9 h (in poor metabolizers). The recommended daily dose of NEB is 5 mg. Depending on the blood pressure (BP) of the patient, dose may be increased slowly at 2 weeks intervals to maximum of up to 40 mg daily [5].

There is a need for the suitable dosage form which addresses low bioavailability of NEB and eases the administration to dysphagic patients. This study tries to address the same by formulating novel oral drug delivery systems of NEB in the form of orodispersible tablets to increase its pharmacokinetic profile and ease administration to dysphagic patients.

In this study, we formulated orodispersible tablets (ODTs) and compared *in vitro* and *in vivo* drug release profiles with conventional tablets. ODTs containing NEB were prepared using two different approaches namely: super-disintegrants addition and sublimation. In addition, combination of both the approaches was proposed and evaluated to optimize tablet characteristics. The prepared tablets were subjected to both pre and post compression parameters and evaluations including: FTIR, DSC studies, carrs' index, angle of repose, hausner ratio, hardness, friability, disintegration time and dissolution. ODT formulation was optimized based on disintegration time (DT) and dissolution rate. *In vivo* pharmacokinetic studies were done in male NewZealand white rabbits for optimized ODT formulation and compared with conventional marketed tablets.

MATERIALS AND METHODS

Materials

Nebivolol.HCl was obtained as gift sample from Aurobindo Pharma, Hyderabad, India. Crospovidone (CP), croscarmellose sodium (CCS), sodium starch glycolate (SSG), microcrystalline cellulose (MCC) and mannitol were purchased from SD fine chemicals ltd, Mumbai, India. Sodium lauryl sulphate (SLS) and aspartame was purchased from standard reagents, Hyderabad, India. Magnesium stearate, camphor, menthol, thymol were purchased from ESSEL fine chem., Mumbai, India. All other ingredients used were of analytical reagent grade.

Methods

Formulation of orodispersible tablets

Orodispersible tablets of NEB were prepared by direct compression method. The details of formulation composition are shown in Table 1. NEB, equivalent to 10 mg was used in total tablet weight of 200mg. CP, CCS and SSG were used as super-disintegrants, SLS was used as surfactant, mannitol and MCC as diluents, aspartame as sweetening agent and magnesium stearate as lubricant. Drug and all the ingredients were weighed accurately and passed through sieve #60 before mixing. All the ingredients were transferred to mortar and well ground for 15 min [6]. The resulting mixture was compressed in single punch compression machine using 7 mm flat surface punches. Based on the DT and drug release profile, formulation F8 (containing 4% of CCS) was optimized and further chosen for sublimation studies. As shown in Table 2, Camphor, menthol and thymol were used as sublimating agents. Prepared tablets were vacuum dried at 60 ^{O}C for 24 h to facilitate the sublimation [7].

Table No.1 Formulation of orodispersible tablets of Nebivolol using super-disintegrating agents

Ingredients (mg)	Formulation code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Nebivolol.HCl	10	10	10	10	10	10	10	10	10	10	10	10
SLS	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Mannitol	50	50	50	50	50	50	50	50	50	50	50	50
CP	2	4	6	8	-	-	-	-	-	-	-	-
CCS	-	-	-	-	2	4	6	8	-	-	-	-
SSG	-	-	-	-	-	-	-	-	2	4	6	8
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Aspartame	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium.stearate	2	2	2	2	2	2	2	2	2	2	2	2

**Total weight of the tablet was 200 mg. CP = Crospovidone, CCS = Croscaramellose sodium, SSG = Sodium starch glycolate, MCC = Microcrystalline cellulose, SLS-sodium lauryl sulphate.*

Table No.2 Formulation of orodispersible tablets of Nebivolol using sublimating agents

Ingredients (mg)	Formulation code											
	C1	**C2**	**C3**	**C4**	**M1**	**M2**	**M3**	**M4**	**T1**	**T2**	**T3**	**T4**
Nebivolol.HCl	10	10	10	10	10	10	10	10	10	10	10	10
SLS	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Mannitol	50	50	50	50	50	50	50	50	50	50	50	50
CCS	8	8	8	8	8	8	8	8	8	8	8	8
Camphor	5	10	20	30	-	-	-	-	-	-	-	-
Menthol	-	-	-	-	5	10	20	30	-	-	-	-
Thymol	-	-	-	-	-	-	-	-	5	10	20	30
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Aspartame	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium.stearate	2	2	2	2	2	2	2	2	2	2	2	2

**Total weight of the tablet was 200 mg. CCS = Croscaramellose sodium, MCC = Microcrystalline cellulose, SLS = sodium lauryl sulphate.*

Evaluation orodispersible tablets

The ODTs were subjected for physicochemical evaluations as described below. The formulation that was found optimal was further re-formulated by sublimation method and evaluated.

Pre and post compression parameters

Pre-compression parameters (bulk and tapped density, carrs' index, hausner ratio, angle of repose) and post compression parameters (weight variation, hardness, thickness, friability, Moisture uptake) were determined for the tablet blend and compressed tablets respectively as per pharmacopoeial specifications [8, 9, 10].

In vitro disintegration time

Method reported by Kadria et al was followed with some modifications (6). Briefly, tablets were placed in a beaker containing 20 ml distilled water at 37 ± 0.5 °C. Time for complete disintegration of the tablet was measured in triplicate; average values were considered for comparison [6].

Drug release studies

In vitro dissolution of the ODTs was studied using USP XXIV Type II dissolution apparatus (Electrolab, Mumbai, India). A paddle stirrer at 100 rpm and 900 ml of pH 6.8 phosphate buffer maintained at 37 ± 0.5 ^{O}C as dissolution medium was used [11]. Aliquots (5 ml each) were withdrawn at specified time intervals (2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25 and 30 min) and replaced with equal volume of fresh medium to maintain the sink condition. The samples were analyzed for drug content using previously reported HPLC method [12].

FTIR studies

FTIR studies were performed to find any possible drug-excipient interaction by KBr pellet method using Perkin-Elmer spectrophotometer, USA (Model-1615). For this study, pure Nebivolol, Nebivolol with each of super-disintegrants, Nebivolol with each of sublimating agents, Nebivolol with mannitol, MCC, SLS and optimized formulations were studied. Drug and excipients (1:1) were prepared and co-ground with KBr. The resultant mixture was subjected to FTIR studies. Scans were performed from 400-4000 cm^{-1} and an average of 40 scans were taken per sample.

DSC studies

Differential scanning calorimetry (DSC) was performed on pure NEB and optimized ODT formulation. Calorimetric analysis was carried out using DSC 60 (Shimadzu Corporation, Kyoto, Japan) instrument. Briefly, accurately weighted sample was taken in an aluminium pan and crimp sealed. In the DSC chamber, samples were allowed to equilibrate at 25^{O}C. Then, the samples were subjected to heating run over temperature range of 25–300^{O}C at a heating rate of 5^{O}C/min. DSC thermograms were directly obtained from the software supplied with the instrument [13].

Chromatographic conditions

Chromatography was carried on C18 column using a mixture of methanol and water (80:20% v/v) as the mobile phase at a flow rate of 1.0 mL/min using a detection wavelength of 282 nm at temperature 25 ^{O}C. Drug concentration was calculated and expressed as cumulative percent of the drug released [12].

***In vivo* studies**

The *in vivo* studies were performed in male NewZealand white rabbits (n = 12). Animal ethical committee clearance was taken before performing the experiment (CPCSEA/IAEC/EXP/25/50/2013/EXP-02). The rabbits were fasted overnight (12 h) before administration of the formulations. The animals were randomly divided into two groups (A and B) with six animals in each group. Group 'A' rabbits were anaesthetized with intravenous injection of pentobarbital at a dose of 25 mg/kg [18]. Then they were positioned on a table with the lower jaw supported in a horizontal position [9]. The ODT formulation was carefully placed on the tongue of group 'A' rabbits. As a control, marketed tablet (Nebicard, Torrent Pharmaceuticals limited, India) was administered orally by dispersing in 2 ml of water to group 'B' rabbits via oral gavage [9]. The dose of 10 mg/kg body weight was chosen for the study based on previously reported literature [14].

Blood samples for pharmacokinetic analysis were obtained by marginal ear vein puncture at different time intervals (0, 15, 30, 45, 60, 120, 240, 360, 480 min, 12, 24 and 36 h) post dosing. Blood samples were collected in microfuge tubes containing sodium citrate (3.4% w/v) as an anticoagulant. To separate the plasma, sample were centrifuged for 10 min at 3,500 rpm at 4 ^{O}C temperature.

Preparation of plasma samples for HPLC studies

The method previously reported by punna rao et al. for rat plasma was used with minor modifications [14]. The method was partially validated in rabbit plasma before use. Calibration curve was plotted for NEB in rabbit plasma and regression analysis was carried out. Hundred micro liters of clear plasma sample was taken and 300µL of acetonitrile was added with vortexing (1 min) to precipitate the proteins. This was followed by centrifugation at 7826 × g for 20 min at 4^{O}C. From the centrifuged samples, clear supernatant (~150 µL) was collected and transferred to a sample loading vial and injected into the HPLC system. Separation was carried on C8 column using a mobile phase consisting of acetonitrile and potassium di-hydrogen orthophosphate buffer (pH 3.5 ± 0.1) in the ratio of 37:63 v/v at a flow rate of 1.0 mL/min with detection at 282 nm [14]. Pharmacokinetic data were analyzed using PK solver add-in in MS-Excel 2007 [15].

RESULTS AND DISCUSSION

Results and discussion of ODTs

Different super-disintegrants were evaluated in the formulation of NEB ODT. For this, three frequently used super-disintegrants (CP, CCS and SSG) were evaluated at four different concentrations (1, 2, 3 and 4% w/w). The effect of disintegrant type and their respective concentration is shown in Fig. 1. From the figure, it is evident that, there is an inverse linear relation between disintegrant concentration used in the formulation and DT time.

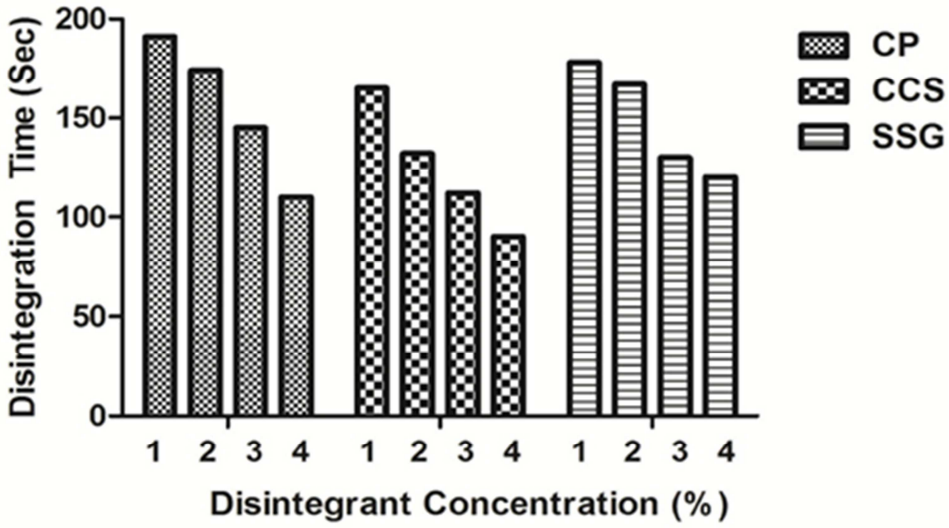

Figure 1: Comparison of disintegration time of formulations prepared using different super-disintegrants by direct compression

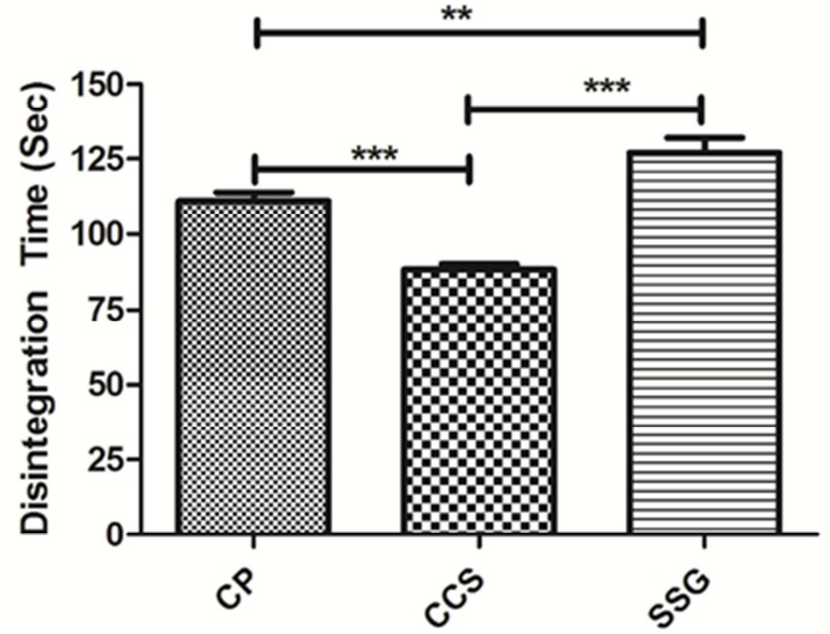

Figure 2: Comparison of disintegration time of formulations containing highest concentration (4% w/w) of super-disintegrants

Based on the data from figure 1, the highest concentrations of each of the disintegrants (4% w/w) were used for comparison. We applied one way ANOVA, followed by Post-hoc test (Bonferroni's test) to test the difference between the groups. The F-value was 90.84 and mean sum of square was 0.9680. This datum is presented in Fig. 2. From the figure, there was a statistically significant difference ($P<0.05$) between different disintegrants of same concentration (4%) on the overall DT of the formulations. The formulations with 4% w/w CCS showed lowest mean DT (90 ± 3 sec, $n = 3$) compared to formulations with CP (110 ± 3 sec, $n = 3$) and SSG (120 ± sec, $n = 3$).

Interestingly, with higher concentration of SSG, the DT of formulation increased. This could be attributed to the mechanism of disintegration of SSG [swell and burst (SSG) versus wicking mechanism (CCS and CP)]. It has been reported that, with increase concentration of SSG, a gel-like matrix is produced that hinders, rather than hastening DT [19]. Therefore, based on the data available, CCS was selected for further optimization to achieve a target DT below 30 sec.

To further reduce the DT time, formulations containing 4 % w/w CCS (F8) was re-formulated by sublimation method. For this method, sublimating agents (camphor, menthol and thymol) were evaluated at four different concentrations (2.5, 5, 10 and 15% w/w) and DT was noted. The formulation containing 10% w/w menthol showed DT of 10 sec. It was observed that, with increasing concentration of sublimating agent, there was a linear decrease in DT (r^2=0.934). This decrease in DT with increasing sublimating agent concentration could be due to formation of a porous structure in the tablet matrix. As the sublimating agent leaves the system and escapes into the atmosphere, it leaves behind a void which increases porosity of the tablet thus decreasing DT. The formulation containing 15 %w/w menthol (M4) showed lowest DT (10 sec) but failed in the friability test (1.42%). Therefore, formulation containing 10% w/w of menthol (M3) was taken for statistical comparison with the formulation containing super-disintegrant (4% w/w of CCS). A comparison of DT between formulations using super-disintegrant (CCS) and menthol (with same concentration of CCS) is shown in figure 3. Unpaired t-test at 95 % confidence interval was used to compare the mean DT between the formulations. From figure 3, there was a statistically significant difference ($P<0.05$) in DT between these two methods. The DT times for formulation with sublimating agent was within the limit of 30 sec [16]. This formulation (M3) also showed 98.82% drug release within 14 min. Therefore, ODT formulation (M3) with sublimating agent (menthol 10 % w/w) was optimized and considered for further *in vivo* studies.

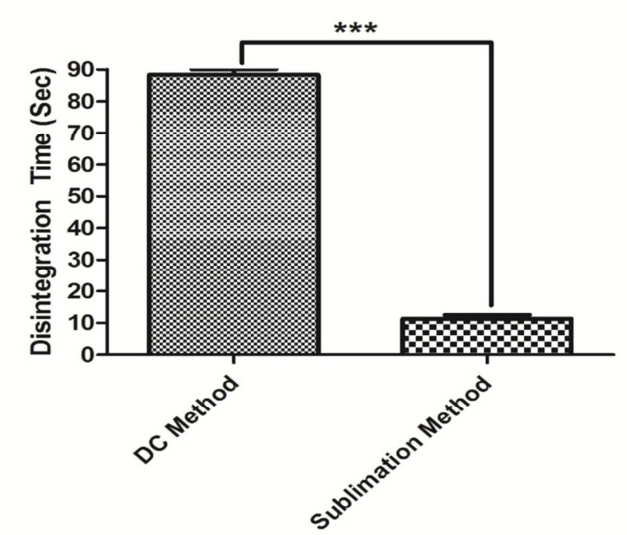

Figure 3: Comparison of disintegration time of formulations prepared using super-disintegrant (ccs 4% w/w) by direct compression and using sublimating agent (menthol 10% w/w)

Pre-compression parameters

Pre-compression parameters were studied for both blends of ODT formulations prepared using super-disintegrants (CP, CCS, SSG) and sublimating agents (camphor, menthol, thymol). Results (Table 3 and 4) show that all formulations had adequate flow properties.

Table No. 3 Pre-compression of formulations prepared using different super-disintegrating agents by direct compression

Formulation code	Bulk density (gm/cc)±SD	Tapped density (gm/cc)±SD	Cars index±SD	Hausner's ratio±SD	Angle of Repose (θ)	Flow property
F1	0.34	0.39	12.75	1.14	31.45^0	Good
F2	0.34	0.38	11.62	1.13	31.35^0	Good
F3	0.32	0.33	2.39	1.02	26.32^0	Excellent
F4	0.32	0.33	3.89	1.04	26.54^0	Excellent
F5	0.43	0.48	11.49	1.12	33.38^0	Good
F6	0.37	0.43	13.56	1.15	33.32^0	Good
F7	0.36	0.42	12.82	1.14	34.53^0	Good
F8	0.33	0.34	4.022	1.04	27.41^0	Excellent
F9	0.34	0.38	11.39	1.12	32.31^0	Good
F10	0.33	0.33	2.071	1.02	28.46^0	Excellent
F11	0.45	0.51	12.40	1.14	33.21^0	Good
F12	0.32	0.33	2.39	1.02	25.49^0	Excellent

n = 3

Table No.4 Pre-compression parameters of formulation prepared using sublimating agents by direct compression.

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index	Hausner ratio	Angle of Repose (θ)	Flow Properties
C1	0.38	0.44	12.44	1.14	28.46^0	Good
C2	0.44	0.49	11.42	1.12	29.46^0	Good
C3	0.33	0.34	4.61	1.04	25.46^0	Excellent
C4	0.32	0.33	1.80	1.01	25.21^0	Excellent
M1	0.32	0.34	4.09	1.04	28.46^0	Excellent
M2	0.34	0.38	12.08	1.13	31.46^0	Good
M3	0.35	0.41	14.55	1.17	32.46^0	Good
M4	0.32	0.33	2.39	1.02	26.46^0	Excellent
T1	0.37	0.42	12.47	1.14	32.36^0	Good
T2	0.35	0.41	14.55	1.17	32.52^0	Good
T3	0.37	0.42	12.47	1.14	34.33^0	Good
T4	0.32	0.33	1.50	1.01	27.12^0	Excellent

n = 3

Post compression properties

Post compression studies were performed for both ODT formulations prepared using super-disintegrants and sublimating agents. From the results (Table 5 and 6), it is evident that DT for ODT reduce significantly (P>0.001), when prepared by sublimation method.

Table No.5 Post-compression properties of ODTS prepared using super-disintegrating agents

Parameters	Formulation code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Weight variation (mg)***	198±2	200±2	200±3	203±3	198±2	197±3	202±2	203±3	198±2	197±3	198±2	202±3
Hardness (kg/cm^2)*	5.8±0.2	5.8±0.3	5.7±0.3	5.6±0.2	5.9±0.3	5.0±0.3	5.1±0.3	5.8±0.2	5.9±0.4	6.2±0.4	6.1±0.3	6.1±0.3
Thickness (cm)	3.35±0.8	3.41±0.10	3.38±0.08	3.38±0.6	3.37±0.05	3.39±0.08	3.36±0.06	3.39±0.08	3.41±0.08	3.4±0.10	3.4±0.06	3.37±0.08
Friability (%)*	0.2±00	0.25±0.1	0.4±0.01	0.24±00	0.26±0.01	0.46±0.02	0.28±0.02	0.29±0.03	0.27±0.02	0.37±0.02	0.29±0.02	0.31±0.02
Disintegration time (sec)**	191±4	174 ±5	145±8	110 ±6	165±5	132±5	112±6	90±5	178±6	167±6	130±8	120±10

*Value are expressed as Mean ± SD, *** n = 20, ** n = 6, * n = 3*

Drug dissolution Studies

In vitro drug release data is presented in Fig. 4 (A-F). From the figure, it is evident that the NEB-ODT formulation (F8) containing 4 % w/w CCS dissolved to an extent of 98.81 % within 18 min. The optimized formulation (M3) containing 10 % w/w of menthol (with 4 % w/w CCS) released 98.82 % of drug within 14 min. The data were fitted into various mathematical equations. The best fit equation was first order equation with 'r^2' value of 0.9886. Analysis using Korsmeyer-Peppas equation gave 'r^2' value of 0.9943. The 'n' value was calculated to be 0.47 indicating non-Fickian mechanism of drug release. Both diffusion and dissolution contributes to the drug release from the ODT formulation.

Table No.6 Post-compression parameters of ODT prepared using sublimating agents after drying

Parameters	Formulation code											
	C1	C2	C3	C4	M1	M2	M3	M4	T1	T2	T3	T4
Weight variation (mg)***	192±2	187±2	180±2	169±3	190±4	189±2	177±3	171±2	190±2	186±3	175±2	167±4
Hardness (kg/cm^2)*	4.6±0.3	4.5±0.3	4.3±0.4	3.8±0.4	4.5±0.3	4.5±0.2	4.4±0.2	3.8±0.3	4.5±0.2	4.2±0.3	3.9±0.4	3.4±0.3
Thickness (cm)	3.33±0.13	3.34±0.09	3.39±0.12	3.37±0.08	3.36±0.09	3.36±0.08	3.38±0.06	3.39±0.06	3.36±0.07	3.39±0.08	3.38±0.12	3.39±0.10
Friability (%)*	0.38±0.08	0.39±0.12	0.55±0.12	0.84±0.02	0.40±0.06	0.39±0.06	0.52±0.04	1.42±0.04	0.52±0.10	0.53±0.10	0.43±0.14	1.1±0.12
Disintegration time (sec)**	52±2	30±4	22±4	17±4	45±2	21±2	11±2	10±2	60±4	45±5	23±4	15±3

*All the values are presented as mean ±SD. *** n = 20, ** n = 6, * n = 3*

FTIR studies

FTIR studies were performed on pure NEB, NEB with each of super-disintegrants, NEB with each of sublimating agents, NEB with mannitol, MCC, SLS and optimized formulations. All characteristic peaks of NEB were present in their original positions, denoting the absence of drug-excipient interaction.

FTIR spectrum of NEB shows characteristic peaks at 3195 cm^{-1} (O-H stretching), 2982, 2921, 2848 cm^{-1} (C-H stretching), and 1621, 1544 cm^{-1}(C=C stretching), 1302cm^{-1} (C-N stretching) and 1139 $^{cm-1}$(C-O stretching). IR spectra are shown in Fig. 5, 6, 7, and 8. From the figure, no shifts in peak positions were observed for pure NEB, in presence of CCS, CP, SSG (Fig. 5), Camphor, Menthol, Thymol (Fig. 6), Mannitol, MCC, SLS (Fig. 7) and optimized formulations F8 and M3 (Fig. 8).

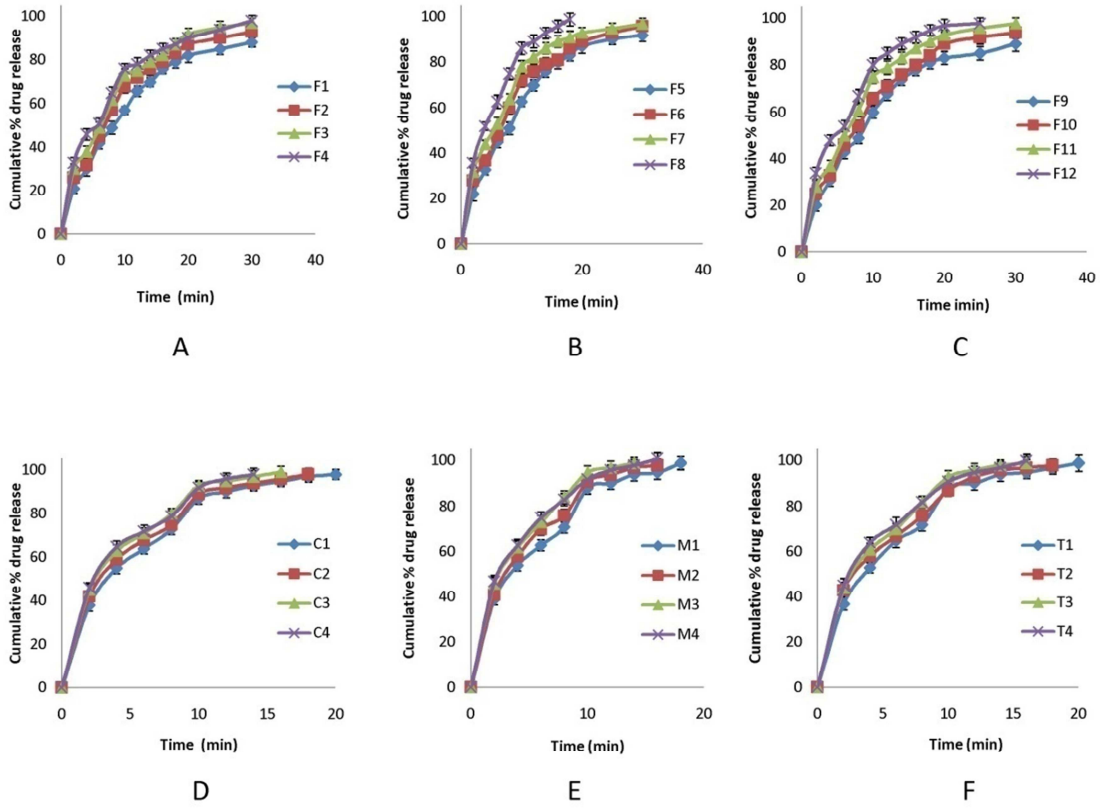

Figure 4: *In vitro* drug release profile in ph 6.8 buffer for neb-odt formulations containing super-disintegrant CP (A); CCS (B); SSG (C) and sublimating agents Camphor (D); Menthol (E); Thymol (F)

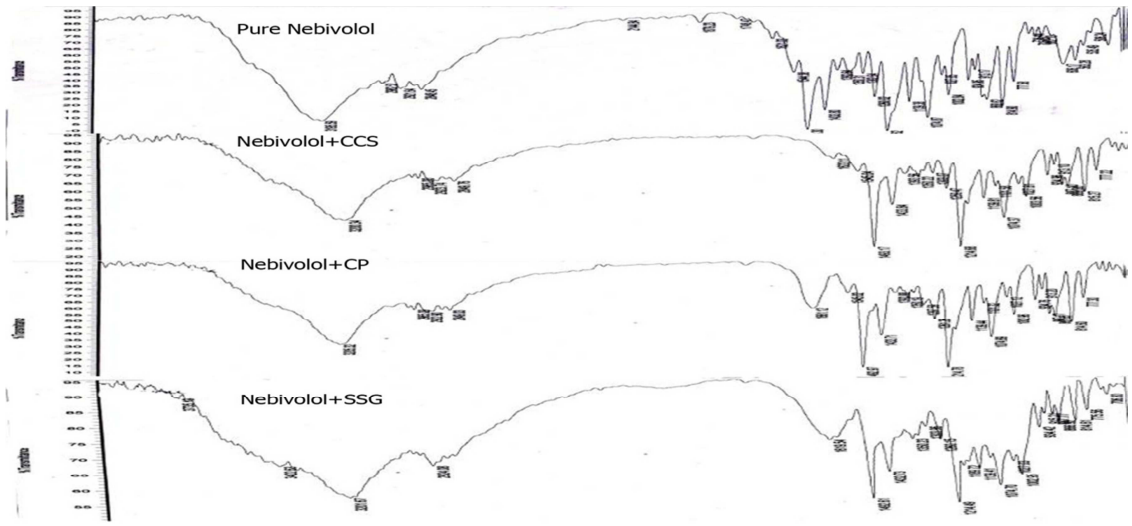

Figure 5: IR-Spectrum of pure NEB; NEB with Croscaramellose Sodium (CCS); NEB with Crospovidone (CP); and NEB with Sodium Starch Glycolate (SSG). Scans were performed from 400-4000cm^{-1}. Average of 40 scans was taken

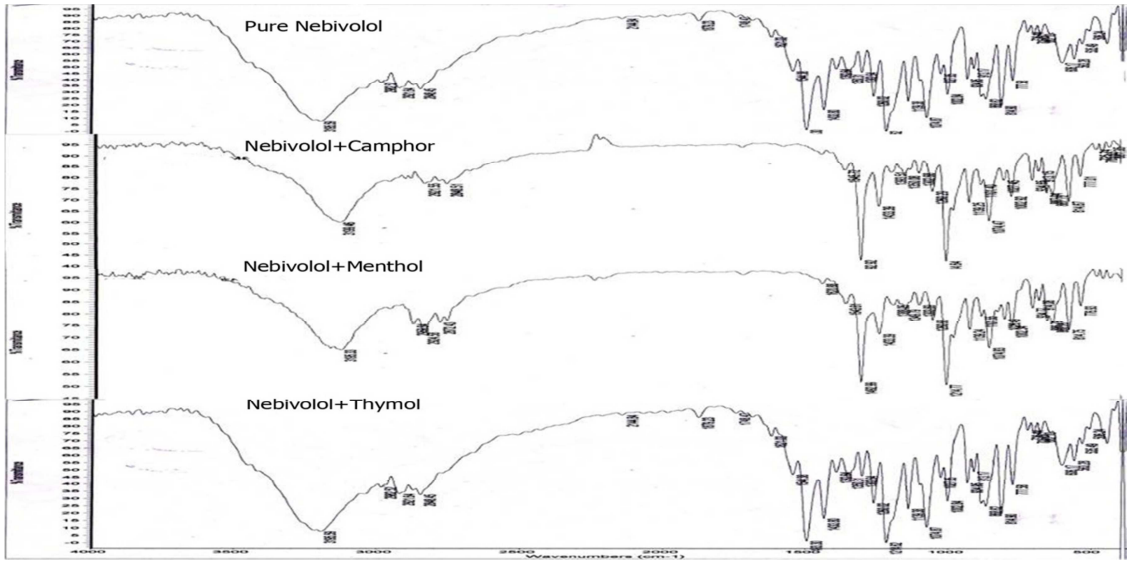

Figure 6: IR-Spectrum of pure NEB; NEB with Camphor; NEB with Menthol; and NEB with Thymol. Scans were performed from 400-4000cm^{-1}. Average of 40 scans was taken

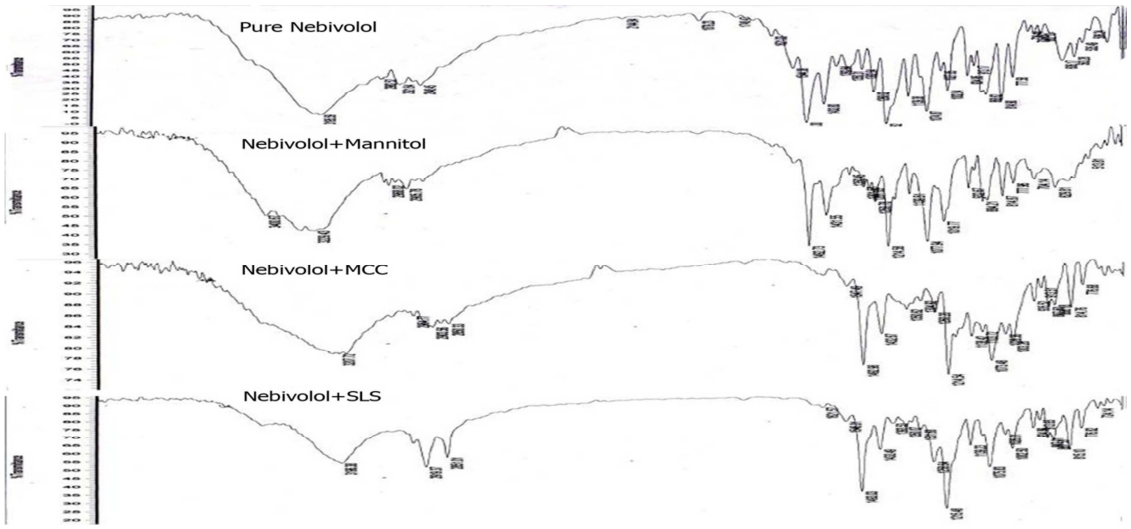

Figure 7: IR-Spectrum of pure NEB; NEB with Mannitol; NEB with Microcrystalline cellulose (MCC); and NEB with Sodium Lauryl Sulphate (SLS). Scans were performed from 400-4000cm^{-1}. Average of 40 scans was taken

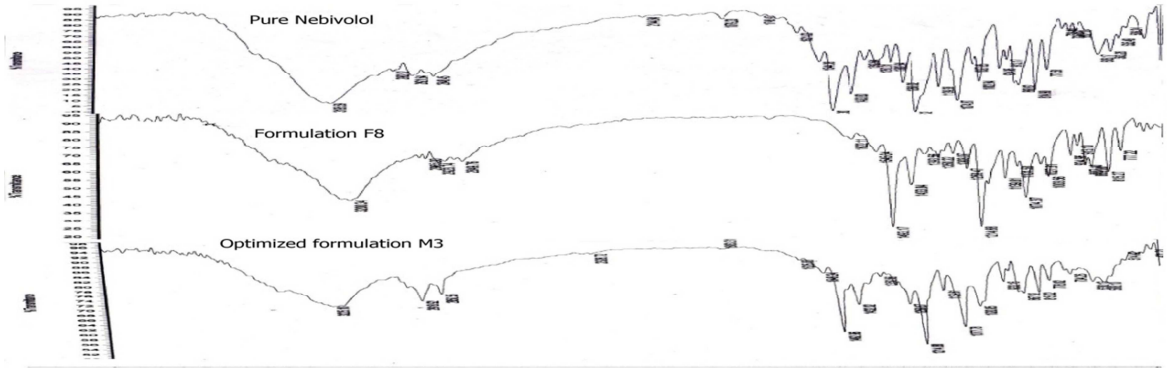

Figure 8: IR-Spectrum of pure NEB; formulation F8 and Optimized ODT formulation (M3). Scans were performed from 400-4000cm^{-1}. Average of 40 scans was taken

DSC Studies

A peak 228 °C in figure 9A, corresponds to melting point of the Nebivolol hydrochloride. A complete disappearance of the drug melting peak was observed in DSC thermogram (Fig. 9B) of optimized ODT formulation that may be attributed to the fusion of drug in the molten mannitol matrix before drug reached its melting point. The one endothermic peak at 167.71^{O}C was of mannitol that was used as diluents in the formulation. Apparently, drug was present in amorphous form within the mannitol matrix.

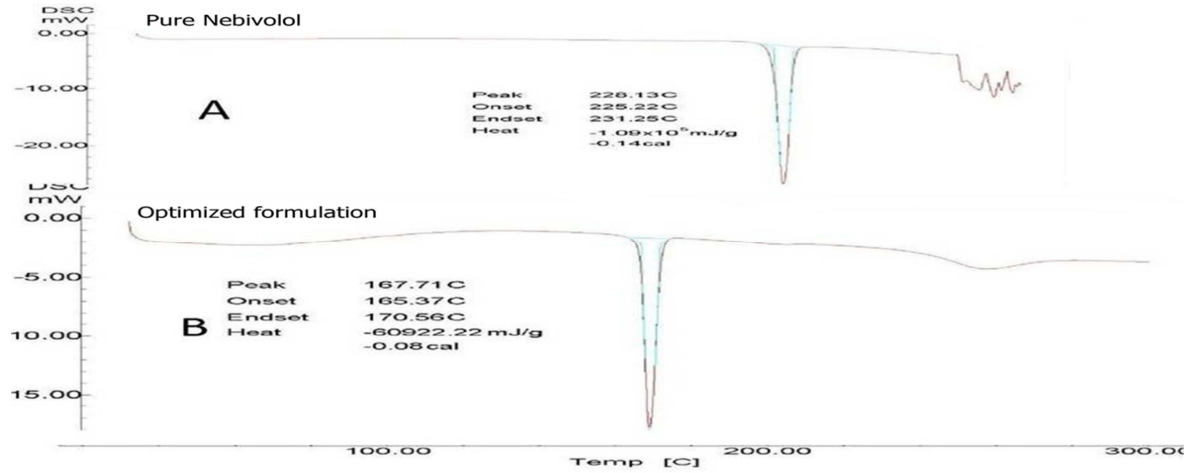

Figure 9: DSC Thermograms of pure Nebivolol (A); Optimized ODT formulation (B)

***In-vivo* Studies**

To evaluate the effectiveness of optimized formulations in the *in vivo* conditions, we performed pharmacokinetic studies in male NewZealand white Rabbits (n = 12). The time vs plasma drug concentration data obtained from pharmacokinetic studies are presented in Fig. 10 below. From the figure, it is evident that, compared to marketed formulations, there was a significant difference (P<0.1) in T_{max} and C_{max} values for ODT formulation. In ODT formulation, earlier T_{max} was achieved (45 min).

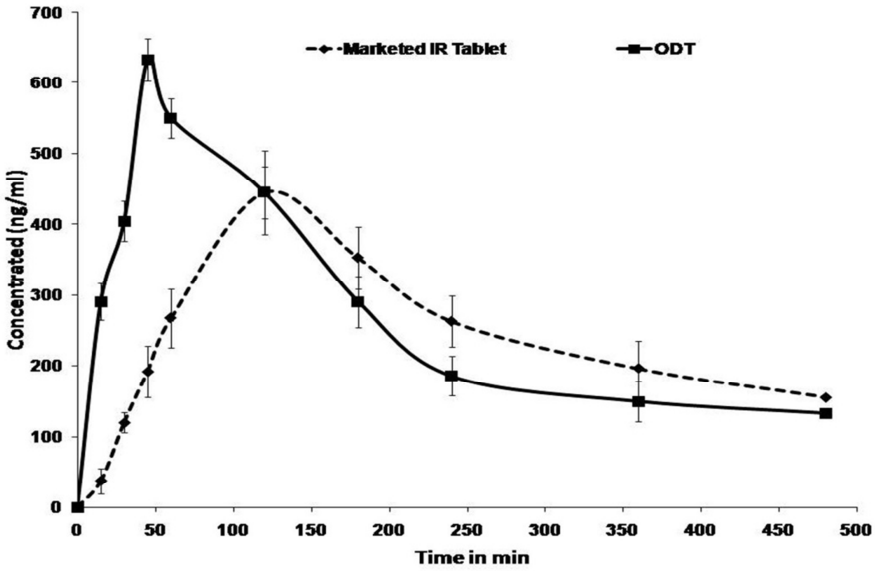

Figure 10: Plasma concentration–time profile of NEB in NewZealand white rabbits followed by oral administration of marketed immediate release tablets and optimized ODT formulation (10mg/kg)

Higher C_{max} was achieved in case of ODT formulation, compared to conventional marketed product. This was attributed to higher rate of dissolution, better solubility and by pass of first pass metabolism [17]. This was further confirmed by comparing AUC_{0-t} of the formulations. As with C_{max} values, the AUC_{0-t} values for ODT were significantly higher (P<0.1) compared with marketed formulation. NEB has oral bioavailability of 12% in humans owing to high first pass metabolism [4]. Design of ODT formulations can bypass first pass effect because some percentage of drug gets absorbed through buccal cavity, thus avoiding first pass effect. Compared to marketed formulation, there was ~93% increase in relative bioavailability (Frel). The pharmacokinetic parameters are summarized in Table 7.

Table No.7 Pharmacokinetic parameters of Nebivolol after oral administration of marketed tablet and ODT formulation to rabbits (10 mg/kg, n = 6)

Parameter	Marketed formulation	ODT formulation
Cmax (ng/ml)	445.15±39.86	632.53±38.44*
Tmax (min)	120±18	45±10*
MRT(0-t) (min)	486.31±54.38	613.50±66.48
AUC(0-t) (µg/ml*min)	119.607±32.54	127.307±28.68*
Frel	-	93±2.5

*Each value represents the mean ±SD (n = 6). * P<0.01 compared to marketed formulation.*

CONCLUSION

In this study, we have made systematic efforts to prepare ODTs of NEB by using various super-disintegrating agents, sublimating agents and synthetic polymers respectively. Optimized orodispersible tablets could significantly reduce the time taken to reach peak plasma concentration (T_{max}) and maximum plasma concentration (C_{max}). These formulations could be effective for treatment of hypertension to dysphagic patients.

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