

# *Hibiscus sabdariffa* Mucilage as a Disintegrant in Formulating Fast Dissolving Tablets

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**ABSTRACT:** The aim of the present work was to prepare and evaluate fast dissolving tablets of nebivolol with a view to enhance patient compliance and minimize the side effects. In this study, fast dissolving tablets of nebivolol were formulated by direct compression method using mucilages of tapioca seeds (*Manihot esculenta*), basella climb (*Basella alba*), red sorrel (*Hibiscus sabdariffa*) as natural disintegrants and crosspovidone as a synthetic superdisintegrant in different ratios with directly compressible mannitol (Pearlitol SD 200) as a diluent to enhance the mouth feel. The prepared formulations were evaluated for hardness, friability, drug content, *in vitro* dispersion time, wetting time, water absorption ratio, *in vitro* drug release, stability and excipients interaction. Among all the formulations, the formulation (FHD<sub>3</sub>) containing 8% w/w mucilage of *Hibiscus sabdariffa* was the overall best formulation ( $t_{50\%}$  1.7 min) based on *in vitro* drug release studies. Stability studies on the formulations indicated that there are no significant changes in drug content and *in vitro* dispersion time ( $p < 0.05$ ). From the above studies, it can be concluded that fast dissolving tablets of nebivolol can be prepared using different mucilages as natural disintegrants for faster dispersion and disintegration in the mouth.

**Key words:** Fast dissolving tablets, nebivolol, crosspovidone, *Hibiscus sabdariffa*, natural disintegrants

## INTRODUCTION

Recent advances in novel drug delivery system (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. Modified formulation with such approach is the fast dissolving tablets of nebivolol, an anti-hypertensive drug given orally to reduce blood pressure.<sup>1</sup> Many patient express difficulties in swallowing tablet and hard gelatin capsules, leading to non-compliance and ineffective therapy.<sup>2</sup> Other problems experienced in conventional oral dosage forms include patients with mental illness, uncooperative behavior and those suffering from nausea, motion sickness, sudden episodes of allergic

attack and coughing.<sup>3-5</sup> Thus, the concept of formulating fast dissolving tablets of nebivolol evolved, which offers a suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristics with potentially increased bioavailability.

Mucilage is most commonly used as adjuvant in the manufacture of different pharmaceutical dosage form. They possess a variety of pharmaceutical properties, which include binding, disintegrating, suspending, emulsifying and sustaining properties at different proportions in various pharmaceutical dosage forms. The synthetic polymer used as excipients suffer from many disadvantages such as high cost, toxicity, non-biodegradability and environmental pollution during their synthesis.<sup>6-9</sup> Natural mucilage are preferred over semi-synthetic and synthetic materials, due to their non-toxic, low cost, free availability, emollient and non-irritating

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nature.<sup>10,11</sup> *H. sabdariffa* contains proteins, amino acids, flavanoids, organic acids and their derivatives. It also contains vitamins B<sub>1</sub>, C and beta-carotene. It is medicinally used as antihypertensive, laxative, purgative, diuretics and in treatment of nervous diseases. *Manihot esculenta*, *Basella alba* and *Hibiscus sabdariffa* mucilage are easily available having low cost and non toxicity as compared to synthetic disintegrants.

In the present study, the fast dissolving tablets of nebivolol were prepared by direct compression method using natural and synthetic disintegrants to compare the efficiency of different natural and synthetic disintegrants.

## MATERIALS AND METHODS

Nebivolol was a gift sample from Cadila Pharma. Ltd., Gujarat. Crospovidone was obtained from Wockhardt Research Centre, Aurangabad, Maharashtra, India. Micro-crystalline cellulose was gift sample from Alkem Labs Pvt. Ltd., Mumbai, Maharashtra, India. All the other chemicals were of analytical grade.

**Extraction of *Hibiscus sabdariffa* mucilage.** The fresh samples were cleaned using running tap water and dried in a good air draft under shade overnight until constant weight or in oven at 42°C. Then the samples were ground into fine particles. The powder was soaked and stirred in 95% ethanol in water in a ratio of 1:10 (w/v). Then the samples were taken in muslin cloth to separate the crude extract. The crude extract was stored at 4 °C which forms solid mass for further use<sup>12</sup>.

**Extraction of other natural mucilages.** Mucilages from *Manihot esculenta* and *Basella alba* were extracted by following the same method described above.

**Formulations of nebivolol fast dissolving tablets.** Fast dissolving tablets of nebivolol were prepared by direct compression method, using

mucilage of *M. esculenta*, *B. alba* and *H. sabdariffa* as natural disintegrants and crospovidone (CP) as a synthetic superdisintegrant in different ratios and directly compressible mannitol as diluent. All the ingredients were passed through 60 number mesh separately. The drug and mannitol were mixed by small portion of both each time and blending it to get a uniform mixture and kept aside. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed at 7 mm size to get a tablet of 150 mg weight.<sup>13</sup> The tablets were prepared according to the formulae shown in table 1.

**Evaluation of tablets.** The prepared batches of formulation were evaluated for the pre-compression parameters like bulk density, tapped density, angle of repose and Carr's index as shown in table 2 and post compression parameters such as drug content uniformity, weight variation, hardness, friability, thickness, *in vitro* dispersion time, *in vitro* drug release and stability studies (Table 3)<sup>14,15</sup>

**Weight variation.** The weight variation test was done according to the USP where twenty tablets were selected randomly and weighed individually, and the individual weight was compared with average weight for the determination of weight variation.

**Tablet hardness.** The hardness of each batch of tablet was checked by using digital hardness tester. The hardness was measured in terms of kg/cm<sup>2</sup>. Three tablets were chosen randomly and tested for hardness. The average hardness of three determinations was calculated.

**Friability.** Ten tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off and again weighed. Percentage friability was calculated by using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

**Tablet thickness.** Thickness was measured using Vernier calipers. It was determined by checking the thickness of three tablets from each formulation.

**Drug content uniformity.** Ten tablets were weighed and powdered, a quantity of powder equivalent to 5 mg of nebivolol was transferred to a 50 ml volumetric flask and dissolved in 40 ml methanol. The drug was extracted into the methanol by vigorously shaking for 15 minutes. Then the volume was adjusted to 50 ml with methanol and the liquid was filtered. The nebivolol content was determined by UV-spectrophotometry by measuring the absorbance at 281 nm after appropriate dilution with methanol. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

**Wetting time and water absorption ratio.** A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wet tablet was then weighed (see in Table 3).<sup>16</sup>

The water absorption ratio 'R' was determined using following equation:

$$R = 100 \times \frac{W_a - W_b}{W_b}$$

where,

$W_a$  = weight of tablet before water absorption,

$W_b$  = weight of tablet after water absorption.

**In vitro dispersion time.** Tablet was added to 10 ml of pH 6.8 phosphate buffer solution at  $37 \pm 0.5^\circ\text{C}$ . Time required for complete dispersion of a tablet was measured (Table 3)<sup>17</sup>.

**In vitro dissolution study.** *In vitro* dissolution of nebivolol fast dissolving tablets was studied in USP XXII type-II dissolution apparatus (Electrolab USP TDT-06T) employing a paddle stirrer. 900 ml of pH 6.8 phosphate buffer was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution media was previously warmed to  $37 \pm 0.5^\circ\text{C}$  and was maintained throughout the experiment. One tablet was used in each test, 5 ml

of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 281 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium<sup>18</sup>.

**Accelerated stability studies.** Stability studies on the promising formulation (FHD<sub>3</sub>) were carried out by storing 15 tablets in amber coloured screw capped bottle at elevated temperature of  $40 \pm 2^\circ\text{C}$ /75% RH (Stability chamber, Oswald) for 3 months. At an interval of one month, the tablets were visually examined for any physical changes, analysed for percent drug content and *in vitro* dispersion time.

## RESULTS AND DISCUSSION

In the present work fast dissolving tablets of nebivolol were prepared by direct compression method, employing mucilages of Tapioca seeds (*Manihot esculenta*), Basella climb (*Basella alba*) and Red sorrel (*H. sabdariffa*) as natural disintegrants and crosspovidone as a synthetic superdisintegrant in different ratios and mannitol as a diluent. A total of 13 formulations and a control formulation FC<sub>0</sub> (without superdisintegrant) were designed. All the blends were free flowing having angle of repose <  $30^\circ$ , Carr's index < 15%, tapped density < 0.640, bulk density < 0.570 and hausner's ratio < 1.15 indicating all the blends have values within the IP limits (given in Table 2).

Tablets obtained were of uniform weight (due to uniform die fill) with acceptable variation as per IP specification i.e. below  $\pm 7.5\%$ . Drug content, hardness, water absorption ratio and wetting time were found to be in the range of 97.82 to 98.47%, 2.6 to 2.9 kg/cm<sup>2</sup>, 68.11% to 95.45% and 18.14 to 68.74 sec respectively (given in table 3). Friability value of the prepared tablets was found to be less than 1% (an indication of good mechanical resistance of tablets).

Among all the designed formulations, the formulation FHD<sub>3</sub> (containing 8% w/w of *Hibiscus sabdariffa*) was found to be promising. The *in vitro* dispersion time, wetting time and water absorption

**Table 1. Formulations of nebivolol fast dissolving tablets prepared by direct compression method.**

Ingredients	Formulation Code												
	FC <sub>0</sub>	FCP <sub>1</sub>	FCP <sub>2</sub>	FCP <sub>3</sub>	FTS <sub>1</sub>	FTS <sub>2</sub>	FTS <sub>3</sub>	FBA <sub>1</sub>	FBA <sub>2</sub>	FBA <sub>3</sub>	FHD <sub>1</sub>	FHD <sub>2</sub>	FHD <sub>3</sub>
Drug	5	5	5	5	5	5	5	5	5	5	5	5	5
Mucilage of <i>M. esculenta</i>	-	-	-	-	3	6	12	-	-	-	-	-	-
Mucilage of <i>B. alba</i>	-	-	-	-	-	-	-	3	6	12	-	-	-
Mucilage of <i>H. subdariffa</i>	-	-	-	-	-	-	-	-	-	-	3	6	12
Crosspovidone	-	3	6	12	-	-	-	-	-	-	-	-	-
MCC PH102	30	30	30	30	30	30	30	30	30	30	30	30	30
Aspartane	3	3	3	3	3	3	3	3	3	3	3	3	3
Pineapple Flavour	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3
SSF ( )	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol (Pearlitol SD200)	104.5	101.5	98.5	92.5	101.5	98.5	92.5	101.5	98.5	92.5	101.5	98.5	92.5
Total weight	150	150	150	150	150	150	150	150	150	150	150	150	150

FTS- Formulation containing mucilage of *Manihot esculenta* powder, FC<sub>0</sub>- (Control) Formulation without super disintegrant, FCP- Formulation containing crosspovidone, FHD- Formulation containing mucilage of *Hibiscus subdariffa*, FBA- Formulation containing mucilage of *Basella alba*.

**Table 2. Pre-compression parameters of formulations prepared by direct compression method.**

Parameters	Formulation code												
	FC <sub>0</sub>	FTS <sub>1</sub>	FTS <sub>2</sub>	FTS <sub>3</sub>	FBA <sub>1</sub>	FBA <sub>2</sub>	FBA <sub>3</sub>	FHD <sub>1</sub>	FHD <sub>2</sub>	FHD <sub>3</sub>	FCP <sub>1</sub>	FCP <sub>2</sub>	FCP <sub>3</sub>
Bulk density (gm/cc)	0.57	0.50	0.49	0.51	0.50	0.51	0.52	0.50	0.54	0.55	0.52	0.53	0.54
Tapped density (gm/cc)	0.64	0.58	0.52	0.60	0.59	0.56	0.56	0.57	0.59	0.63	0.59	0.58	0.57
Angle of repose (°)	30.10	32.10	28.10	32.52	29.68	31.52	29.68	31.02	30.90	32.50	31.18	32.14	33.04
Carr's index (%)	10.14	10.11	8.11	10.10	9.12	10.11	8.92	10.52	10.19	9.14	11.00	7.76	7.05
Hausner's ratio	1.12	1.16	1.00	1.08	1.01	1.15	1.12	1.13	1.12	1.21	1.13	1.16	1.07

**Table 3. Post-compression parameters of formulations prepared by direct compression method.**

Parameters	FC <sub>0</sub>	FTS <sub>1</sub>	FTS <sub>2</sub>	FTS <sub>3</sub>	FBA <sub>1</sub>	FBA <sub>2</sub>	FBA <sub>3</sub>	FHD <sub>1</sub>	FHD <sub>2</sub>	FHD <sub>3</sub>	FCP <sub>1</sub>	FCP <sub>2</sub>	FCP <sub>3</sub>
Hardness (Kg/cm <sup>2</sup> )	2.6 ±0.070	2.7 ±0.070	2.8 ±0.099	2.7 ±0.070	2.8 ±0.099	2.7 ±0.070	2.7 ±0.070	2.8 ±0.099	2.8 ±0.099	2.9 ±0.070	2.8 ±0.099	2.8 ±0.099	2.6 ±0.070
Thickness (mm)	2.64 ±0.020	2.66 ±0.020	2.70 ±0.010	2.69 ±0.010	2.69 ±0.010	2.71 ±0.020	2.70 ±0.070	2.68 ±0.020	2.67 ±0.010	2.72 ±0.020	2.71 ±0.010	2.72 ±0.080	2.71 ±0.010
Friability (%)	0.62 ±0.010	0.58 ±0.010	0.60 ±0.011	0.59 ±0.010	0.61 ±0.010	0.62 ±0.020	0.59 ±0.014	0.58 ±0.014	0.59 ±0.007	0.60 ±0.026	0.61 ±0.005	0.60 ±0.010	0.59 ±0.010
<i>In vitro</i> dispersion time (sec)	110.23 ±0.9	67.64 ± 1.01	42.6 ±1.990	26.32 ±1.01	57.69 ±0.01	34.86 ±0.58	27.1 ±1.005	55.9 ±0.995	38.3 ±1.006	25.02±0.01	60.2 ±1.995	23.70 ±2.01	16.40 ±1.01
Wetting time (sec)	112.13 ±1.0	68.74 ±1.97	43.79 ±0.97	28.63 ±0.97	59.8 ±1.012	36.1 ±1.040	28.9 ±0.980	57.1 ±0.980	39.86 ±0.01	27.1 ±2.010	61.8 ±1.005	24.81 ±0.99	18.14 ±0.97
Water absorption ratio (%)	56.20 ±0.99	68.1 ±1.009	74.55 ±0.98	81.87 ±1.03	72.1 ±0.100	78.1 ±1.005	83.5 ±1.012	72.0 ±1.090	76.4 ±1.015	84.3 ±1.015s	71.0 ±0.990	84.44 ±0.99	95.4 ±0.980
Percent drug content (%)	97.8 ±0.020	97.8 ±0.034	97.9 ±0.100	97.9 ±0.009	98.16 ±0.60	98.2 ±0.569	98.1 ±0.017	98.28 ±0.42	98.2 ±0.026	98.1 ±0.020	97.8 ±0.087	97.9 ±0.080	98.47 ±0.57

Weight variation (148 -155 mg) within IP limits of ± 7.5%, \*Average of three determinations.

**Table 4. Comparative *in-vitro* dissolution parameters of promising fast dissolving tablet formulations, control and commercial conventional formulation (CCF) in ph 6.8 phosphate buffer.**

Formulation code	Dissolution parameters						
	D <sub>5</sub> (%)	D <sub>10</sub> (%)	D <sub>15</sub> (%)	DE <sub>10min</sub> (%)	t <sub>50%</sub> (min)	t <sub>70%</sub> (min)	t <sub>90%</sub> (min)
FC <sub>0</sub>	21%	41%	52%	20.95%	>30min	>30min	>30min
FTS <sub>3</sub>	67%	88.5%	100.5%	61.93%	1.9min	4.9min	10min
FBA <sub>3</sub>	53%	84.10%	92.5%	59.07%	2.1min	6.6min	13.8min
FHD <sub>3</sub>	72.10%	91.5%	100.1%	66.62%	1.7min	4.7min	9.4min
FCP <sub>3</sub>	79.5%	100%	-	71.82%	1.5min	2.9min	7.1min
CCF	21%	46%	52.5%	22.99%	13min	2.9min	>30min

**Table 5. Stability data of FHD<sub>3</sub> formulation at 40°C/75% RH.**

Sl. No.	Time in days	Physical changes	Percent drug content ±SD*	<i>In-vitro</i> dispersion time*
1.	1 <sup>st</sup> day (initial)	--	98.10 ± 0.0346	25.02 ± 0.019
2.	30 <sup>th</sup> day (1 month)	No changes	98.28 ± 0.0699	25.24 ± 0.142
3.	60 <sup>th</sup> day (2 month)	No changes	98.36 ± 0.0721	25.51 ± 0.026
4.	90 <sup>th</sup> day (3 month)	No changes	98.40 ± 0.173	25.72 ± 0.017

\* Average of three determinations

**Table 6. Statistical analysis for drug content data of FHD<sub>3</sub> formulation.**

Sl. No.	Trials	1 <sup>st</sup> day (A)	90 <sup>th</sup> day (B)	A – B
1.	1	97.75	97.60	0.15
2.	2	98.35	98.10	0.25
3.	3	98.20	98.01	0.19
4.	Mean % drug content	98.10	97.90	0.20
5.	± SD	0.3122	0.266	0.046

t=2.50 (p&lt;0.05)

**Table 7. Kinetic data of promising fast dissolving tablet formulations, control and conventional commercial formulation (CCF) in ph 6.8 buffer.**

Formulation code		Zero-order	First-order
FC <sub>0</sub>	R	0.7886	0.954
	A	28.075	1.956
	B	8.3993	0.0145
FTS <sub>3</sub>	R	0.6753	0.9831
	A	35.81	1.9582
	B	5.474	0.018
FBA <sub>3</sub>	r	0.7162	0.9902
	A	32.908	1.8662
	B	5.5349	0.0661
FHD <sub>3</sub>	r	0.7689	0.6828
	A	29.28	1.6514
	B	5.6382	0.0675
FCP <sub>3</sub>	r	0.9217	0.9634
	A	11.969	1.8386
	B	2.287	0.1016
CCF <sub>3</sub>	r	0.9075	0.9633
	A	10.544	1.7795
	B	2.0564	0.1085

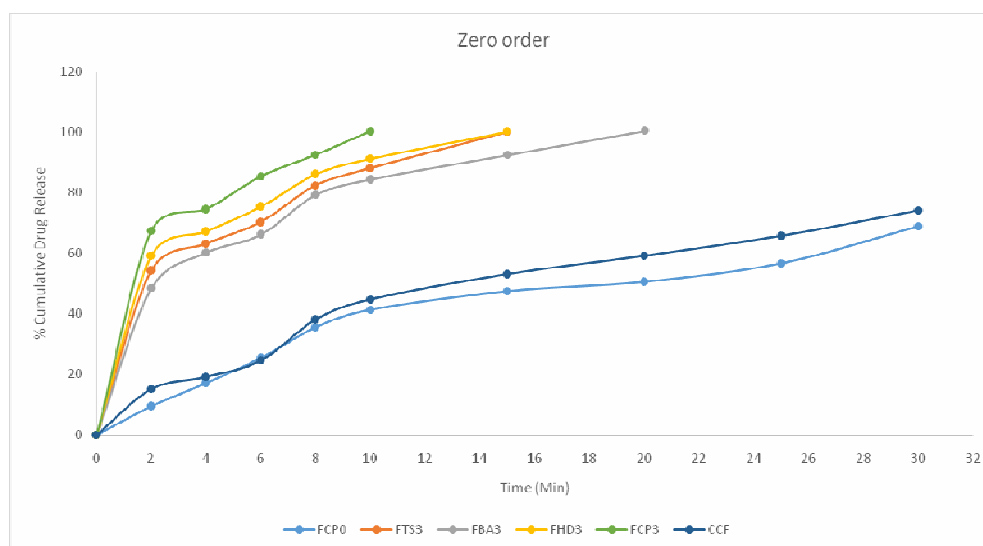


Figure 1. Comparative cumulative % drug release versus time plots (zero-order) of promising fast dissolving tablet formulations, control and conventional commercial formulations (CCF) in pH 6.8 phosphate

ratio of FHD<sub>3</sub> were found to be 25.02 sec, 27.12 sec and 84.35% respectively (Table 3). The experimental data also revealed that the results obtained from the *H. sabdariffa* mucilage are better than those of conventional commercial formulation.

*In vitro* dissolution studies of the control formulation (FC<sub>0</sub>), commercial conventional formulation (CCF) and promising formulations (FHD<sub>3</sub>, FCP<sub>3</sub>) were carried out at pH 6.8 phosphate buffer and the various dissolution parameters, such as percent drug dissolved in 5 min, 10 min and 15 min (D<sub>5</sub>, D<sub>10</sub> and D<sub>15</sub>), dissolution efficiency at 10 min (DE<sub>10</sub>), t<sub>50%</sub>, t<sub>70%</sub> and t<sub>90%</sub> as shown in table 4 and dissolution profile as depicted in figure 1. These data reveal that overall formulation FHD<sub>3</sub>, which showed more than eight fold faster drug release (t<sub>50%</sub> 1.7 min) when compared to CCF (t<sub>50%</sub> 13.0 min) tablet of neбиволол and released nearly more than 18 fold than control formulation.

IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of FHD<sub>3</sub> and FCP<sub>3</sub> showed all the characteristics peaks of neбиволол pure drug, thus conforming that no interaction of drug occurred with the component of the formulations. Stability studies of the FHD<sub>3</sub> formulation presented in table 5 and table 6 indicated

that there is no significant changes in drug content and *in vitro* dispersion time at the end of three months period (p<0.05).

## CONCLUSION

From the present work, it can be concluded that fast dissolving tablets of neбиволол prepared by using mucilage of *H. sabdariffa* showed better drug release and disintegration time as compared to tablets prepared from other natural and synthetic disintegrants.

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