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Research Article

FORMULATION AND DEVELOPMENT OF IMMEDIATE RELEASE TABLET OF ANTI-HYPERTENSIVE DRUG

Ravi Kumar , Pushpendra Singh, Kailash Pathak and Nishi Prakash jain

RKDF College Pharmacy, Bhopal, MadhyaPradesh, India

Abstract

In the present fast dissolving tablets of Nebivolol HCl are designed by novel co processing to disintegrate rapidly. The co-processed superdisintegrants were prepared by solvent evaporation method with blend of crospovidone and fenugreek seed mucilage. Fast dissolving tablets (FDT) were prepared by direct compression method. These tablets were evaluated for weight variation, hardness, thickness, disintegration time, water absorption ratio, friability and dissolution. It was found that the total maximum amount of drug from the optimized batch CPF5 was released in first 4 minutes of the dissolution study. The tablets disintegrated within 50 sec under experimental in vitro laboratory conditions. It can be concluded from the present work that co-processed superdisintegrants of crospovidone and fenugreek seed mucilage are superior to physical mixture and used in Nebivolol HCl fast dissolving tablets formulation

Keywords: Nebivolol HCl, superdisintegrants, novel co processing, crospovidone and fenugreek seed mucilage.

Introduction :

The development of an appropriate dosage form for older people, children, bed ridden patients, mentally retarded, uncooperative, nauseated patients been widely desired as it become difficult for these patients to swallow conventional tablets (Kremzar L. et al, 1998) Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, non invasive method and ease of administration, leading to high level of patient compliance (Kremzar L et al, 1998, Hanawa T, 1995). To the make the best use of oral cavity we are going for ODTs production to ensure maximum absorption via mucous membrane.

A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates quickly in the oral cavity upon the contact with saliva, resulting in solution or suspension of the administered medicine.

Corresponding Author

E.mail: shailgpharma@gmail.com

FDT dosage forms, also commonly known as fast melt, quick melt, orally disintegrating tablets, and orodispersible systems, have the unique property of disintegrating the tablet in the mouth in seconds.

Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual. Co-processing excipients leads to the formulation of excipient granules with superior properties compared with physical mixtures of components or individual components. The concept of formulating fast dissolving tablets (FDT) of metoclopramide hydrochloride (anti-emetic) using co-processed superdisintegrants which increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets by simple and cost effective (at low concentration of superdisintegrants) direct compression technique.[1-6]

Materials and Methods[6-13]

Procurement of drug and excipients:

The drug, excipients, chemicals/ reagents and equipments used for various experiments are enlisted as follows:

Nebivolol HCl was gifted by ZCL chemicals Ltd. Mumbai, Maharashtra, India. Fenugreek seed mucilage and Crospovidone were purchased from Yarrow chemicals Mumbai, Maharashtra and are of AR grade.

Preparation of Co-processed Superdisintegrants

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and Fenugreek seed mucilage (in the ratio of 1:1, 1:2 & 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through # 44-mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 minutes. The dried granules were sifted through # 44-mesh sieve and stored in airtight container till further use.

Fast dissolving tablets of Nebivolol HClwere prepared by direct compression. All the ingredients (except granular directly compressible excipients) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order. Powder blend was evaluated for bulk density, tapped density, Carr's index and Hauser's ratio.Compressed into tablets of 150mg using 8mm round flat punches on 10-station rotary tablet machine (Clit).

Results and Discussion

Evaluation of Formulated fast dissolving Tablet:

Hardness:. Hardness is amount of strength of tablet to withstand mechanical shocks of handling in manufacture, packaging and shipping and tablet should be able to withstand reasonable abuse when in the hand of consumer . Hardness of
tablet was evaluated by Monsanto hardness tester or Pfizer tester. Hardness was measured in kg/cm^2 and for tablet it is above 4-6 kg/cm^2

Friability: This test is applicable to compressed tablets and is intended to determine the physical strength of tablets. It was evaluated by Roche Friabilator with 100 revolution rotating 25 per minute for 4 min by using 6 tablets. According to USP tablet should have limit < 1%. for acceptance

Following formula was used to calculate the friability.
%F=1- (loss in weight/initial weight)100

Weight variation:

Weight variation was calculated as per method describe in USP.20 tablets was weighed individually and the average wias calculated.The requirements are met if the weight of not more then 2 of tablets differ by more then percentage listed in the tablet and no tablets differ by in weight by more then double that percentage.

Twice folded tissue paper was placed in a Petri dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. Water absorption ratio (R) was then determined according to the following equation:

$$R = 100 \times (w_a - w_b)/ w_b$$

Where w_b and w_a were tablet weights before and after water absorption, respectively

Disintegration test

Disintegration test was measured using disintegration test apparatus. One tablet was placed in each of the six tubes of disintegration test apparatus. I.P. method was followed without using disc. The time required for complete disintegration of tablet in each tube was determined using stop watch.

Content of Active Ingredients:

Prepared tablets were accurately weighed and finely powdered by pestle in a mortar. A weighed portion of each powder equivalent to dose (250mg) of the prepared tablet was transferred in to a volumetric flask and the drug was dissolved in the solvent. The contents of the flask were sonicated for 10 min and diluted with 0.1 N HCl as the solvent. The samples were analyzed spectrophotometrically at 276 nm.

Thickness variation

Ten tablets from each formulation were taken randomly and their thickness was measured with a micrometer screw gauge.

In-vitro Dissolution studies of tablet using dissolution apparatus:

In vitro dissolution studies of the promising fast dissolving tablets of Nebivolol HCl, control and commercial conventional tablet formulations were performed according to USP XXIII Type-II dissolution apparatus (Electrolab, model TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5ºC as dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals (2, 4, 6, 8, 10, 15&30 min) and replaced immediately with equal volume of fresh medium. The samples were filtered through 0.22 mm membrane filter disc and analyzed for drug content by measuring the absorbance at 282 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The release studies were performed in replicates of three.

Evaluation of Formulated fast dissolving Tablet:

Fast dissolving tablets of Nebivolol HCl were prepared using co-processed superdisintegrants and physical mixture of superdisintegrants. Directly compressible mannitol (Pearlitol SD 200) was used as a diluents to enhance mouth feel. A total of six formulations (F2 to F7) and control formulation F1 (without superdisintegrant) were designed. As the blends were free flowing (angle of repose <30^0 and Carr's index <15% , tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specification i.e., below 7.5%. Drug content was found to be in the range of 99 to 101%, which is within acceptable limits. Hardness of the tablets was found to be in the range of 2.96-3.13 kg/cm^2. Friability below 1% was an indication of good mechanical resistance of the tablets. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 44-85% and 30-106 sec respectively. Among all the designed formulations, formulation, F5 was found to be promising and displayed an in vitro dispersion time of 22 sec, which facilitates their faster dispersion in the mouth.

Overall, the formulation F5 containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and Fenugreek seed mucilage) was found to be promising

and has shown an in vitro dispersion time of 22 sec, wetting time of 30 sec and water absorption ratio of 86% when compared to the formulation F2 containing 4% w/w of Physical mixture of superdisintegrant (1:1 mixture of crospovidone and fenugreek seed mucilage) which shows 36sec, 38 sec, 76% and control formulation (F1) which shows 99 sec, 106 sec *and 46% values respectively for the above parameters* .

In-vitro Dissolution studies of tablet using dissolution apparatus:

In vitro dissolution studies on the promising formulation F5, control (F1) and commercial conventional formulations (CCF) were carried out in pH 6.8 phosphate buffer, and the various dissolution parameter values viz., percent drug dissolved in 5 min, 10 min and 15 min , $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ are shown in Table and dissolution profile depicted in fig.. This data reveals that overall, the formulation F5 has shown nearly two and a half fold faster drug release ($t_{50\%}$ 2.41 min) when compared to the commercial conventional tablet formulation of Nebivolol HCl($t_{50\%}$ 6 min)

Conclusion

Summary in the present research work an attempt has been made to optimize, formulate and characterize fast dissolving tablet (s) of Nebivolol HCl. Co-processed superdisitegrants consisting of crospovidone and fenugreek seed mucilage exhibited good flow and compression characteristics.

Nebivolol HCl tablets containing co-processed superdisintegrants exhibited quick disintegration and improved drug dissolution. This formulation is more cost effective than aerosol inhalation pumps available. It was found that the total maximum amount of drug from the optimized batch F5 was released in first 4 minutes of the dissolution study. The tablets disintegrated within 50 sec under experimental in vitro laboratory conditions. It can be concluded from the present work that co-processed superdisintegrants of crospovidone and fenugreek seed mucilage are superior to physical mixture and used in Nebivolol HClfast dissolving tablets formulation.

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Table No.2. Percentage weight variation of tablet (I.P)

S. No	Average weight of individual tablet	Limits (%)
1	≤ 130	10
2	130-324	7.5
3	≥ 324	5

Table-1: Formula for different batches of Nebivolol HCl tablets .

Ingredients	F1	F2	F3	F4	F5	F6	F7
Nebivolol HCl	5	5	5	5	5	5	5
Mannitol	115	85	85	85	85	85	85
Aspartame	10	10	10	10	10	10	10
Superdisintegrants (CP+FSM/CS)	-	30	30	30	30	30	30
Aerosil	45	45	45	45	45	45	45
Pre-gelatinised Starch	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Menthol	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Vanillin	1	1	1	1	1	1	1
Total	150	150	150	150	150	150	150

Where, **F2,F3,F4 -** Physical Mixture of crospovidone(CP) and Fenugreek seed mucilagein(FSM) different Ratios (1:1, 1:2, 1:3), **F5,F6,F7-** Co-processed Superdisintegrants of crospovidone and croscarmellose sodium (CPS) in different Ratios (1:1,1:2, 1:3), **F1-** Control formulation (without superdisintegrants), **CP –** Crospovidone, **FSM–** Fenugreek seed mucilage , **CPS**-croscarmellose sodium

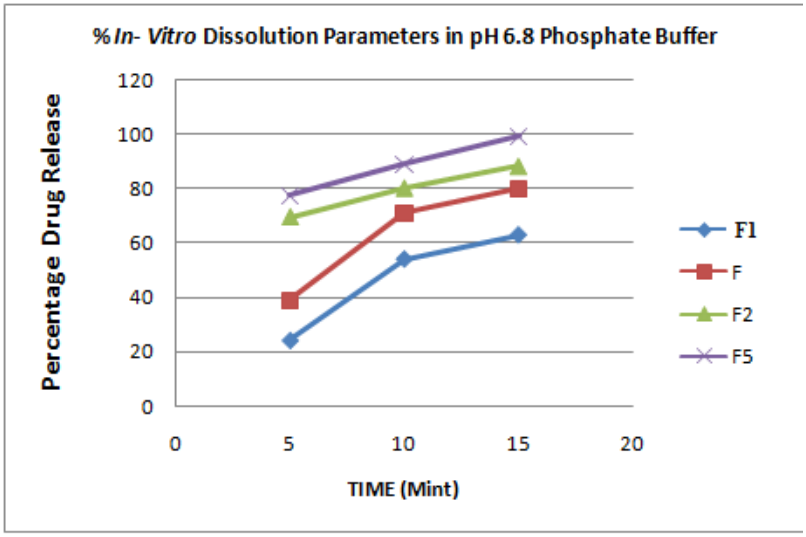

Figure 1 Dissolution rate profiles of optimized formulation in pH 6.8 phosphate buffer

Table 3 Evaluation of Nebivolol HCl FDT Formulations

Parameters	Formulation Code						
	F1	F2	F3	F4	F5	F6	F7
Hardness (kg/cm^2)* ±SD	2.96±0.05	2.9±0.1	2.83±1.4	3.26±0.05	3.13±0.04	3.23±0.05	3.25±0.03
Thickness* (mm)	2.23±0.02	2.17±0.02	2.26±0.05	3.0±0.01	2.11±0.02	2.21±0.01	2.12±0.01
In vitro Dispersion time (s)* ±SD	98±2	36.31±1.52	41.13±0.77	41.36±2.52	22±2	31.33±3.41	39±2.0
Wetting time (s)* ±SDs	106±4.93	39.66±1.52	42±1	45.33±1.5	31±0.5	34.33±1.52	41.56±1.15
Water Absorption ratio (%)* ±SD	46±1	76.33±1.15	71.66±1.52	64±1	86±1	78±2.08	71±2.14
Percent Drug Content (%)* ±SD	99.21±1.52	99.28±1.01	100±1.57	100±2.02	99.97±0.07	101±1.19	98.45±2
Weight Variation(%)	146-159 mg (IP limits ± 7.5%)						

Table 4 Percentage Drug Release *Study -IN Vitro* Dissolution Parameters in pH 6.8 Phosphate Buffer

Time(mint)	F	F1	F2	F5
5	24.34%	39%	69.56%	77.56%
10	54.23%	71.07%	80.34%	89.34%
15	63.12%	80.05%	88.43%	99.45%

Table 5 *IN Vitro* Dissolution Parameters in pH 6.8 Phosphate Buffer

Formulation code	Parameter		
	t50%	t70%	t90%
F 1	9.32 min	13.10 min	>30 min
F	6.65 min	9.5 min	29 min
F2	4.01 min	5.21 min	16 min
F5	2.32 min	3.48 min	9.48 min

Where, F1 is control formulation, F5 is promising fast dissolving tablet formulation, F2 is formulation containing physical mixture of superdisintegrants in 1:1 ratio, F is conventional commercial tablet formulation, $Time_5$ is percent drug