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Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF CARVEDILOL USING CROSPOVIDONE

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ABSTRACT

Objective: The objective of the study was to formulate fast dissolving tablets (FDT) of carvedilol. **Methods:** Wet granulation method was adopted for the development of FDT using super disintegrant crospovidone. Pre compression parameters, post compression parameters, wetting time, in vitro dispersion time, and in vitro dissolution study were evaluated for developed formulation. Compatibility studies of formulations were determined by Fourier Transform Infrared Spectroscopy (FTIR) **Results:** CP4 formulation showed maximum 91.67 % of drug release at the end of 40 minutes among all 4 formulations. Short term stability studies (at 40±2ºC/75±5% RH) were conducted on CP4 formulation showed that there no significant changes in physiochemical parameters, drug content, and in vitro dissolution study. From the FTIR study showed that there were no drug excipient interactions for developed formulation. **Conclusion:** It was observed that dissolution profile of carvedilol is more in CP4 batch as it contains more amount of crospovidone.

Keywords: Carvedilol, FDT, FTIR spectroscopy, crospovidone.

INTRODUCTION

Carvedilol [1] is used for the treatment of various cardiovascular disorders like angina pectoris, congestive heart failure (CHF), cardiac arrhythmia and hypertension. It is a poorly water-soluble drug having problems with variable bioavailability. It was taken as a drug candidate for the formulation of FDT due to its chemical [2] stability and short biological half-life (7-10h). For the consideration of substantial first pas effect and its shorter plasma half-life, it can be chosen an ideal drug candidate for FDT [3].Out of various novel drug delivery system (NDDS) for designing dosage forms like FDT [4, 5] for convenient to be manufactured and administered free of side effects, offering immediate release and enhance bioavailability [6] so as to achieve better patient compliance. Oral drug delivery systems preferably tablets are mostly used dosage forms for being compact offering uniform dose and painless delivery. But older and paediatrics patients suffer in dysphasia because physiological changes [7] associated with those groups. Disease conditions like Parkinsonism, mental disabilities, motion sickness, unconsciousness, and unavailability of water can be observed in group of populations called dysphasia. To avoid such short comings, certain innovative drug delivery system like FDT hasbeen developed. These are novel dosage forms which dissolve in saliva within few seconds when put on the tongue. Fast-dissolving drug delivery system dissolves in the oral cavity [8] without the need of water or chewing. Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient. FDTcan be known as melt-in-mouth tablets, repimelts, porous tablets, orodispersible, quick dissolving or rapid disintegrating tablets [9].The FDT is absorbed from the mouth, pharynx, andoesophagus as saliva passes down into the stomach. The solution containing active ingredients is absorbed through gastrointestinal epithelium to reach the target and produce desired effect [10].In the present study, FDT of carvedilol were designed using wet granulation method using various excipients and crospovidone as natural superdisintegrant.

MATERIALS AND METHODS

Materials

Carvedilol was received as a gift sample from Maxtar Bio-Genetics (Baddi), H.P. Crospovidone and Aerosil were obtained as gifts from Aurobindo labs Pvt Ltd, A.P. Magnesium stearate, talc, micro crystalline cellulose, and potassium dihydrogen-o-phosphate were procured from SD fine chem. Ltd Mumbai. Sodium hydroxide, and methanol were procured from Qualigens fine chemicals Mumbai.

Compatibility study

FTIR study: The FTIR is used to know the identification of functional groups in various chemicals as well as incompatibilities [11] between the drug and excipients. KBr-pellet method is used to prepare pellets. The pellet was kept in the sample holder and scanned from 4000 to 400 cm^{-1} in FTIR spectrophotometer (Bruker, Germany).

Preparation of FDT

The tablets were prepared by wet granulation [12] technique. Accurately weighed quantities of ingredients mentioned in Table-1 were passed through sieve no. 12, and crospovidone was passed through sieve no.20.The blending was performed manually using mortar and pestle by the way of geometric dilution without addition of lubricant and glidant. Aqueous solution was used for moistening of mixture and then passed through sieve no 30 followed by drying for 3-4 h in hot air oven. The dried granules are obtained from hot air oven and sifted through sieve no 12 followed by blending with talc and magnesium stearate. The homogenous mixture were placed into tablet punching machine(10 station rotary tablet machine Clint India) getting tablet weight 150 mg each using deep concave punch.

Table 1: Composition of Carvedilol FDT

Ingredients (mg)	CP1	CP 2	CP3	CP4
Carvedilol	6.25	6.25	6.25	6.25
Crospovidone	0	4	8	12
Micro crystalline cellulose	136	132	128	124
Aerosil	1.5	1.5	1.5	1.5
Sodium saccharin	2	2	2	2
Magnesium stearate	2.25	2.25	2.25	2.25
Talc	2	2	2	2
Total weight(mg)	150	150	150	150

Evaluation of tablets

Pre compression parameters of FDT granules

The prepared granules were evaluated for pre compression parameters [13-17] such as angle of repose, bulk density, tapped density andcompressibility index (Carr's index).Fixed funnel

method was used to determine the angle of repose. The bulk density and tapped density were determined by bulk density apparatus (Sisco, India).The Carr's index can be calculated by the following formula.

$$\%\text{Carr'sindex} = \frac{et-eb}{et} \times 100 \quad \ldots\ldots(1)$$

Where e_t is the tapped density of granules and e_b is thebulk density of granules.

The Hausner's ratio can be calculated by the taking the ratio of tapped density to the ratio of bulk density.

Table 2: Scale of flowability determined by different methods [18]

Flow property	Angle of repose	Compressibility index	Hausner's ratio
Excellent	25-30	≤10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	> 66	> 38	>1.6

Post-compression parameters of FDT

Thickness

The thickness [19] of individual tablets is measured by using vernier calliper.

Hardness

The hardness of prepared tablets was determined by using Monsanto hardness tester [20] and measured in terms of kg/cm^2.

Friability

Roche friabilator is used for the determination of friability [21] of tablets. Ten tablets were initially weighed (W_0) together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed (W).The percentage of friability was calculated using the following equation.

$$\%\text{Friability} = F = \left(1 - \frac{W}{W_0}\right) \times 100 \quad \ldots\ldots (2)$$

Where, W_0 and W are the weight of the tablets before and after the test respectively. The limit for percentage of friability is between 0.5-1%.

Weight Variation

The weight variation [22] test was done by weighing 20 tablets individually (Shimadzu digital balance), calculating the average weight and comparing the individual tablet weights to the average. The tablets meet the USP test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Disintegration test

Six tablets along disc were introduced in each tube of basket of disintegration [23] test apparatus (Lab care instruments). The basket was positioned into a beaker containing 900 ml of distilled water and operated at 37 ± 2^o C. The time of disintegration of the tablet was recorded. The average time and standard deviation were calculated.

Wetting time

The wetting time [24] of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in apetri dish with a 10 cm diameter. Wetting time was measured by placing a tablet on a piece of tissue paper folded twice and was placed in a small petri dish containing 6 ml of simulated saliva pH 6.8, and the time for complete wetting was measured.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petri dish (internal diameter = 6.5cm) containing 5 ml of distilled water. A tablet was placed on the tissue paper. The wetted [25] tablet was weighed. The water absorption ratio(R) was determined according to the following equation,

$$\text{Water absorption ratio} = \frac{Wa-Wb}{Wa} \times 100 \quad \ldots\ldots (3)$$

Where W_a is the weight of the tablets before the test and W_b is the weight of the tablet after water absorption.

Drug content

Ten tablets from each batch of FDT formulations were taken and triturated to form a powder. The powder weight equivalent [26] to one tablet was dissolved in a 100 ml volumetric flask filled with phosphate buffer pH 6.8 using magnetic stirrer for 24 h. The solutionwas filtered through Whatman filter paper No.1 diluted suitably and analyzed by UV-spectrophotometer (Elico164) at λmax 242 nm.

In vitro dissolution study

The dissolution test [27, 28] was performed using 900 ml of phosphate buffer pH 6.8 at 37 ± 0.5^0 C and 50 rpm in USP Type-II dissolution apparatus. In specified time intervals, an aliquot of 5 ml samples of the solution were withdrawn from the dissolution apparatus and with the replacement of fresh fluid to dissolution medium. The samples were filtered through filter paper of 0.45 µm. Absorbance of these solutions were measured at λmax 242 nm using a UV/Visible Spectrophotometer (Elico164).

In vitro dispersion time

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an FDT. In vitro dispersion [29] time was measured by dropping a tablet in a measuring cylinder containing 6 ml of simulated salivary fluid of pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was measured.

Stability studies

The formulation was subjected to accelerated stability [30] studies as per ICH (The International Conference of Harmonization) guidelines. The packed tablets in air tight container were placed in stability chambers (Thermo lab scientific equipment Pvt. Ltd. Mumbai, India) maintained at 40±2ºC/75±5% RH for 3 months. Tablets were periodically removed and evaluated for physical characteristics, drug content, in-vitro drug release etc.

RESULTS AND DISCUSSION

FTIR study

Carvedilol showed characteristic peaks at 3195.59 cm^{-1} (O-H stretching), 2982.52 cm^{-1} (Amine stretching), 1621.03 cm^{-1} (N-H bending vibrations) and 1260.02 (O-H bending and C-O stretching) cm^{-1} and 1027.85 cm^{-1}(alkyl aryl ether bending vibration) and the optimized batch CP4 showed the similar characteristic absorption band without any significant change in the wave number of drug indicating no chemical interaction between drug and excipients.

Pre-compression parameters of FDT formulations

Powder granules for 4 formulations were assessed for rheological properties such as angle of repose, bulk density, tapped density, Carr's index and Hausner's Ratio. All the values obtained for pre compression granules were within pharmacopoeial limits. It is mentioned in Table 3.

Table 3:Pre-Compression Parameters of FDT Granules

Formulation code	Angle of repose (degree)[a]± S.D	Bulk density (g/ml)[a]± S.D	Tapped density (g/ml)[a]± S.D	Carr's Index (%)[a]± S.D	Hausner's Ratio[a]± S.D
CP1	28.27±0.11	0.516±0.08	0.548±0.06	5.83±0.06	1.06±0.04
CP2	27.12±0.12	0.523±0.06	0.559±0.08	6.44±0.06	1.06±0.03
CP3	26.13±0.08	0.518±0.08	0.556±0.06	7.33±0.05	1.07±0.06
CP4	25.32±0.06	0.521±0.06	0.565±0.04	7.78±0.04	1.08±0.06

N.B.- All values are expressed as mean± S.D, [a] n = 3

Post-compression parameters of FDT formulations

The post-compression parameters such as hardness, weight variation, drug content uniformity, friability,and thickness have given below (Table 4).The other parameters such as wetting time, disintegration time and in vitro dispersion time have given below (Table 5). All values are obtained in acceptable ranges of pharmacopoeial limits.

Table4:Post-Compression Parameters Of Fdt Formulations

Formulation code	Hardness (kg/cm^2)[a] ±S.D	Friability (%)[a] ±S.D	Drug content(%)[b] ±S.D	Average wt. of one tablet(mg)[c] ±S.D	Thickness (mm)[a] ±S.D
CP1	3.90±0.08	0.69±0.11	97.25±0.01	150.3±0.16	4.1±0.10
CP2	3.80±0.21	0.52±0.01	97.41±0.02	150.2±0.15	4.2± .11
CP3	3.77±0.32	0.67±0.02	99.03±0.03	149.8±0.14	4 ± 0.14
CP4	3.50±0.35	0.88±0.10	99.45±0.04	150.0 ± 0.11	4 ± 0.13

N.B.- All values are expressed as mean± S.D, [a] n = 3, [b]n = 10, [c]n = 20

Table 5: Post-Compression Parameters of FDT Formulations

Formulation code	Disintegration time(s)[a] ±S.D	In vitro dispersion time(s)[a] ±S.D	Wetting time(sec)[a] ±S.D	Water absorption ratio[a] ±S.D
CP1	32 ± 1.01	38± 1.14	27 ± 1.1	69.23.± .3
CP2	23 ± 1.05	35± 1.12	21 ± 1.02	70.50± 1.8
CP3	19 ± 1.11	29± 1.05	17 ± 1.06	71.51.± .2
CP4	15 ± 1.23	22± 1.02	14 ± 1.07	58.48± 1.6

N.B.- All values are expressed as mean± S.D, [a] n = 3

In vitro dissolution study

In vitro drug release studies were performed in pH 6.8 phosphate buffer, on the above promising formulation (CP4) gives the maximum amount of drug release comparing to other formulations. The percentage cumulative drug release (% CDR) of CP4 was best giving 91.67 % in 40 mins compared to other batches CP1 (75.08 %) in 50 mins, CP2 (82.11 %) in 50 mins and CP3 (83.12 % in 50 mins. It was observed that the drug release was maximum in CP4 because the concentration (8% of total tablet weight) of crospovidone was more compared to other batches. Hence concentration of super disintegrants has a direct effect on drug release of formulated batches. The dissolution profiles of the above formulations are depicted in figure 1.

Short-term stability studies

Short-term stability studies on the above promising formulation (at 40±2°/75±5% RH for 3 months) have shown no significant changes in physical appearance, drug content and in vitro dispersion time.

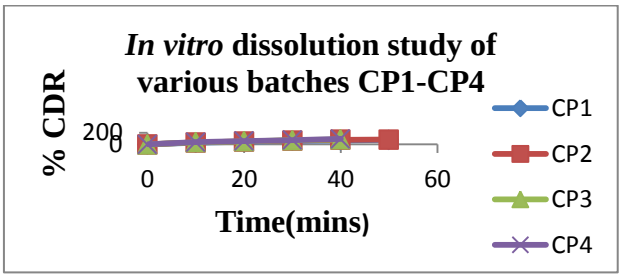

Fig.1: Comparative in vitro dissolution study of carvedilol batches CP1-CP4 (n=3).

CONCLUSION

The study clearly demonstrates that FDT of carvedilol could be successfully prepared by wet granulation method using crospovidone. From the developed formulations the release of carvedilol was best in CP4 formulation Hence the current technology of FDT will surely enhance the patient compliance providing rapid onset of action..

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