Research Article

Formulation and Evaluation of Fast Dissolving Tablets of Carvedilol using Sodium Starch Glycolate

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ABSTRACT

The objective of the study was to develop fast dissolving tablets (FDT) of carvedilol. Wet granulation technique was used for the preparation of FDT using super disintegrants sodium starch glycolate. The formulated tablets were evaluated for pre compression parameters; post compression parameters, wetting time, in vitro dispersion time, *in vitro* dissolution study. Fourier Transform Infrared Spectroscopy (FTIR) study was used to know compatibility studies of formulations. The tablet formulation batch FD4 was considered as the overall best formulation as it showed in vitro drug release study of 97.08 % at the end of 50 mins. Short term stability studies (at 40±2ºC/75±5% RH) on the best formulation indicated that there no significant changes in drug content. From the FTIR study indicated that there are no drug excipient interactions. It can be concluded that dissolution profile of carvedilol is more in FD4 batch as it contains more amount of sodium starch glycolate.

Keywords: Carvedilol, FDT, FTIR spectroscopy, sodium starch glycolate.

INTRODUCTION

Carvedilol[1] is an alpha and a beta adrenoreceptor-blocking agent used in the treatment of various cardiovascular disorders like angina pectoris, congestive heart failure (CHF), cardiac arrhythmia and hypertension. Carvedilol is a racemic mixture in which nonselective beta-adrenoreceptor blocking activity is present in the S (-) enantiomer and alpha-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol is a poorly water-soluble oral antihypertensive agent, with problems of variable bioavailability and bio-equivalence related to its poor water-solubility.Carvedilol was selected as a drug candidate for the formulation of FDT for the following reasons. It is chemically[2] stable. The biological $t_{1/2}$ is 7 to 10 h. In view of substantial first pas effect and its shorter plasma half life, therefore is an ideal drug candidate for FDT. Solid dosage forms like tablets are the most popular dosage forms[3] existing today because of its convenience of self administration, compactness and easy manufacturing. 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 dysphagia because physiological changes[7] associated with those groups. Generally dysphagia is observed population who are associated with a number of conditions like parkinosonism, mental disabilities, motion sickness, unconsciousness, unavailability of water etc..To avoid such problems certain innovative drug delivery systems like FDT have been developed. These are novel dosage forms which dissolve in saliva within few seconds when put on tongue. A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrants 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. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients. These are also called melt-in-mouth tablets, repimelts, porous tablets, orodispersible, quick dissolving or rapid disintegrating tablets[9]. The FDT are absorbed from the mouth, pharynx and oesophagus 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 sodium starch glycolate as natural superdisintegrants with prime objective arriving of a cost effective product.

MATERIALS AND METHODS

Carvedilol was received as a gift sample from Maxtar Bio-Genics (Baddi)., cherlapally, H.P. sodium starch glycolate 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 allows identification of functional groups in various chemicals as well as incompatibilities between the drug and excipients. In this method individual samples [11] as well as the mixture of drug and excipients were ground mixed thoroughly with potassium bromide (1:100) for 3-5 minutes in a mortar and compressed into disc by applying pressure of 10 kg/cm to form a transparent pellet in hydraulic press. 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 sodium starch glycolate was passed through sieve no.20. All the ingredients lubricant magnesium stearate and talc (glidant) were manually blended homogenous by way of geometric dilution. The mixture was moistened with aqueous solution and granulated with sieve no.20 and placed in hot air oven at 60º C for sufficient 3-4 h. Then dried granules passed through sieve no.12 and blended with mgnesium stearate and talc. The homogenous mixture were placed into tablet punching machine (Rotary tablet machine Clint India) getting tablet weight 150 mg each using deep concave punch.

Table 1: Composition of carvedilol FDT

Ingredients (mg)	FD1	FD2	FD 3	FD 4
Carvedilol	6.25	6.25	6.25	6.25
Sodium starch glycolate	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 and compressibility index (Carr's index).Fixed funnel method was used to determine 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.

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

Where e_t is the tapped density of granules and e_b is bulk 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

Postcompression parameters of FDT

Thickness

The thickness[19] of individual tablets is measured by using vernier caliper which gives the accurate measurement of thickness. It provides information of variation of thickness between tablets. Generally the unit for thickness measurement is mm. The limit of the thickness deviation of each tablet is ±5%.

Hardness

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

Friability

Friability[21] of tablets was performed in a Roche friabilator. 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.

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

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.

$$\text{The weight variation of } n^{th} \text{ tablet} = \frac{\left(\left|\overline{W} - W_n\right|\right)}{\overline{W}} \text{ x } 100\% \quad \text{..... (3)}$$

Where weight of tablets are w_1, w_2, w_3,..w_n..,w_{20}.and average weight of the tablets = $\overline{W}$

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 tablet was recorded. The average time and standard deviation were calculated. Three trails were performed.

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 petridish 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 Petridish containing 6 ml of simulated saliva pH 6.8, and the time for complete wetting was measured. Five tablets from each batch were used.

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 test was done in triplicate. The water absorption ratio(R) was determined according to the following equation,

$$\text{Water absorption ratio} = \frac{Wa - Wb}{Wa} \times 100 \text{..... (4)}$$

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 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. Solution was filtered through Whatman filter paper No.1 diluted suitably and analyzed by UV-spectrophotometer (Elico164) at λmax 242 nm.

***In vitro* dissolution studies**

The release rate of[27-30] FDT were determined using United States Pharmacopeia (USP) dissolution testing apparatus type 2 (paddle method) .The dissolution test was performed using 900 ml of Phosphate buffer pH 6.8, at 37 ± 0.5^0 C and 50 rpm. In specified time intervals an aliquot of 5 ml samples of the solution were withdrawn from the dissolution apparatus and with 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). The drug release was plotted against time to determine the release profile of various batches.

***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[31, 32] 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 purpose of stability[33, 34] study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The formulation was subjected to accelerated stability 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 parameters were found within the pharmacopoeial limits. It is mentioned in Table 3.

Table 3: Pre-compression parameters of FDT formulations

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
FD1	28.56±0.06	0.515±0.08	0.554±0.06	7.57±0.08	1.07±0.06
FD2	26.32±0.07	0.514±0.06	0.559±0.08	8.05±0.06	1.08±0.08
FD3	25.20±0.06	0.517±0.08	0.566±0.12	8.65±0.11	1.09±0.06
FD4	24.11±0.07	0.521±0.12	0.554±0.14	5.95±0.08	1.06±0.08

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

Table 4: 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 1tablet(mg)[c]±S.D	Thickness(mm)[a] ±S.D
FD1	3.94 ± 0.08	0.71 ± 0.11	98.02 ± 0.01	151.12 ± 0.16	4.01 ± 0.10
FD2	3.86 ± 0.21	0.58 ± 0.01	97.41 ± 0.02	151.5 ± 0.15	4.02 ± 0.11
FD3	3.75 ± 0.32	0.69 ± 0.02	99.11 ± 0.03	149.8 ± 0.14	4 ± 0.14
FD4	3.63 ± 0.35	0.78 ± 0.10	99.95 ± 0.04	150.2 ± 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
FD1	34 ± 1.01	48± 1.14	29 ± 1.1	79.11.± 1.3
FD2	33 ± 1.05	45± 1.12	24 ± 1.02	72.50 ± 1.9
FD3	29 ± 1.11	39± 1.05	20 ± 1.06	71.51.± 1.2
FD4	25 ± 1.25	32± 1.02	18 ± 1.07	64.41 ± 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 (FD4) gives maximum amount of drug release comparing to other formulations. The percentage cumulative drug release (% CDR) of FD4 was best giving 97.08 % in 50 mins comparing to other batches FD1 (79.87 %) in 60 mins, FD2 (87.44 %) in 60 mins and FD3 (89.42 in 60 mins. The dissolution profiles of the above formulations are depicted in figure 1.

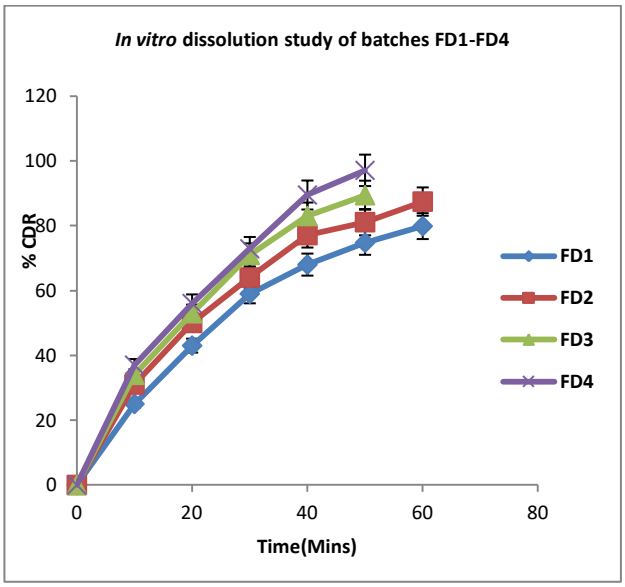

Figure 1: Comparative *in vitro* drug release study of carvedilol batches FD1-FD4 (n=3).

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.

CONCLUSION

The study clearly demonstrates that FDT of carvedilol could be successfully prepared by wet granulation method using sodium starch glycolate. From the developed formulations the release of carvedilol was best in FD4 formulation Hence the current technology of FDT will surely enhance the patient compliance providing rapid onset of action.

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