Role of Cogrinding in Enhancing the *In vitro* Dissolution Characteristics of Carvedilol

P.V. Swamy, H Shilpa, SB Shirsand, SN Gada and MB Kinagi

Department of Pharmaceutical Technology, HKE Society's College of Pharmacy, Sedam Road, Gulbarga-585 105 (Karnataka-India)

ABSTRACT

In the present study, an attempt was made to increase the *in vitro* dissolution rate of carvedilol (antihypertensive) by cogrinding technique using various carriers, namely lactose, corn starch, treated agar, microcrystalline cellulose. The coground mixtures were prepared using the above excipients in four drug-carrier ratios, viz., 1:1, 1:3, 1:4 and 1:9. The prepared coground mixtures were evaluated for drug content, *in vitro* dissolution characteristics, short-term stability and drug-carrier interaction (by FTIR). The coground mixtures MCC_9 and TAG_9 prepared with a drug-carrier ratio of 1:9 using microcrystalline cellulose and treated agar respectively, showed promising results in enhancing the dissolution rate of carvedilol and released nearly 80% of drug within 30 min. Tablets prepared from the above coground mixtures showed two-three times faster dissolution compared to the commercial conventional tablet formulation of carvedilol, when $t_{50\%}$ and $t_{70\%}$ values were considered. Short-term stability studies on these tablet formulations showed no significant changes in the drug content and $t_{70\%}$ values ($p<0.05$). From the present study, it can be concluded that cogrinding technique can be used for enhancing the dissolution rate of poorly water soluble drug carvedilol providing nearly first order drug release.

Key Words: Carvedilol, cogrinding technique, dissolution enhancement, treated agar, microcrystalline cellulose.

INTRODUCTION

During the last decade the trend in drug discovery has produced more and more compounds that exhibit high lipophilicity and poor water solubility. Such physicochemical characteristics lead to problematic biopharmaceutical properties, which in turn diminish the likelihood of success in the clinic [1]. Potential bioavailability problems are prevalent with extremely hydrophobic drugs, whose aqueous solubility is less than 0.1 mg/ml at 37^o C [2]. Enhancement of dissolution rate and oral bioavailability of poorly water soluble drugs still remains one of the challenging aspects for the pharmaceutical technologists [3].

Carvedilol (non-cardioselective ß-blocker) is an antihypertensive used in the management of hypertension, angina pectoris and heart failure [4]. It is a white to off white crystalline powder, practically insoluble in water, gastric and intestinal fluids. Its glass transition temperature (Tg) is relatively low (around 39^o C), hence was selected as the drug candidate for the present study [5]. In the present study, an attempt has been made to increase dissolution rate of carvedilol (CDL) by novel co-grinding method using four excipients, namely, lactose (L), corn-starch (CS), treated agar (TAG) and microcrystalline cellulose (MCC), with a view to improve the dissolution rate and develop a fast release formulation fulfilling the official dissolution requirements, thus enhancing the potential bioavailability of the drug. The incorporation of the drugs into inert lipidic vehicles such as oils, self-emulsifying formulation [6], solid dispersion [7], complexation [8], salt-formation [9], prodrugs [10], co-grinding [11], solvent deposition [12], ordered mixtures [13], roll mixing [14], micronization [15] are some of the alternative reported methods for enhancing the dissolution rate of poorly water soluble drugs with an aim to the development of suitable formulation for oral use.

MATERIALS AND METHODS

Carvedilol BP was received as a gift sample from Unichem India Laboratories, Mumbai and agar-agar was procured from Himedia Lab Pvt Ltd, Mumbai and microcrystalline cellulose from Sd-Fine Chem Ltd, Mumbai. All the other chemicals and solvents used were of analytical reagent grade.

Preparation of Treated Agar:

Treated agar **(TAG)** powders were prepared by taking 10 gm agar powder in distilled water (100 ml) and stirring at 50 rpm with a three- bladed mechanical stirrer for one day. This causes water absorption and swelling. Then the liquid was poured in a large Petri-dish and allowed for drying up to three days in an incubator at 37±1^{o} C and then the mass was pulverized and sifted through # 80 mesh sieve [16].

Preparation of Co grinding Mixtures:

Co-ground mixtures were prepared by using four carriers, namely, lactose, corn starch, treated agar and microcrystalline cellulose, in four different weight ratios, i.e., 1:1, 1:3, 1:4 and 1:9. All the ingredients were separately passed through # 80 mesh.

A physical mixture of the weighed quantities of the drug and carrier was ground for 20 minutes in a ceramic mortar and sifted through #100 mesh. To ascertain the effect of method, carrier or both on the dissolution rate of carvedilol (CDL), carvedilol alone was ground for 20 minutes and the resultant product is represented as CDL_1. All the samples were stored in desiccators at room temperature taking precaution to protect from light.

Physical Mixture:

The physical mixtures of carvedilol and carrier were obtained by simple blending of the drug and carrier in a 1:9 w/w ratio with a spatula. PM-L, PM-CS, PM-TAG, PM-MCC are used to represent the physical mixtures of carvedilol -lactose, carvedilol-corn starch, carvedilol-treated agar and carvedilol-microcrystalline cellulose respectively.

Drug Content Uniformity Studies:

25 mg of each coground mixture was accurately weighed and dispersed in 15 ml methanol and the mixture was vigorously shaken for 10 min. The methanolic extracts were filtered and collected into 25 ml volumetric flask and made up to the mark by passing more solvent through the filter. The above solutions were suitably diluted with methanol and the absorbance was measured at 285.5 nm against the solvent blank. The carvedilol content was calculated using calibration curve

Drug-Carrier Interaction Studies:

IR spectra of carvedilol and its formulations were obtained by KBr pellet method using Perkin Elmer FTIR series model-1615 spectrometer in order to rule out drug-carrier interactions occurring during the formulation process.

***In vitro* Dissolution Studies [17]**:

Dissolution of carvedilol from various coground mixtures was studied in 900 ml of 0.1N HCl containing 0.1% w/v sodium lauryl sulfate at 37$\pm$ 0.5^{0} C using XXIII dissolution test apparatus- II employing paddle stirrer at 50 rpm for 120 min. A sample of coground mixture equivalent to 12.5 mg of carvedilol was used in each test. At predetermined time intervals, 5 ml of the samples were collected by means of a syringe fitted with a pre-filter. These samples were analyzed for drug content by measuring the absorbance at 241.5 nm. The *in vitro* drug release data obtained for all formulations were fitted in three popular models of data treatment as follows:

1. Zero-order kinetic model (cumulative percent drug released vs time).
2. First order kinetic model (log cumulative percent drug remaining vs time).
3. Hixon-Crowell's cube-root law (cube root of cumulative % drug remaining vs time)

Dissolution Efficiency: As a model-independent approach, dissolution efficiency (DE) as suggested by Khan [18], was employed to evaluate the dissolution rate of CDL from different coground mixtures.

Preparation of Tablets:

A batch of 50 tablets were prepared for the promising coground mixtures, viz., MCC_9 and TAG_9 (M_{9tab} and T_{9tab}), using directly compressible lactose (Pharmatose DCL-11), magnesium stearate and purified talc as a lubricant and glidant respectively. The blend was compressed using 9 mm flat round punches to get tablets of 250 mg weight on 10-station rotary tablet machine (Clit, Ahmedabad). The prepared tablets were evaluated for drug release rate in comparision with commercial conventional tablets of carvedilol.

Stability testing:

Short-term stability studies on M_{9tab} and T_{9tab} formulations were carried out by storing 15 tablets in amber colored rubber stoppered vials at 40^o C/75% RH in a humidity chamber (model: JRIC-11, Osworld, Mumbai) over a period of three months. At intervals of one month, the tablets were visually examined for any physical changes and changes in drug content. At the end of three months period, the formulations were also subjected to dissolution rate studies.

RESULTS AND DISCUSSION

All the coground mixtures prepared were found to be white or almost white, fine and free flowing powders. The drug content estimated in various coground mixtures were found to be within $\pm$ 2.5% range of the expected percent drug content values. The low values of the standard deviation and coefficient of variation (<2%) for the estimated drug contents indicated the uniform distribution of the drug within the coground mixtures prepared.

From the dissolution study data of carvedilol in pure form of the drug shows slow dissolution (57.35% in 120 min), whereas the physical mixtures of the drug with various carriers, viz., lactose, corn starch, treated agar and microcrystalline cellulose in 1:9 drug carrier ratio showed a little improvement in the dissolution rate, when compared to pure drug; the ground drug (CDL_1) showed drug release of 58.13% in the same period, i.e., very slow dissolution. However, the coground mixtures have shown marked enhancement in the dissolution rate of carvedilol (up to 93.77% in 45 min for MCC_9, 97.04% in 60 min for TAG_9). The dissolution rate of carvedilol from coground mixtures is dependent on the drug-excipient ratio with each excipient studied. As the proportion of the excipient in coground mixtures was increased, the dissolution rate has also increased.

The efficiency of excipient in enhancing the dissolution rate of carvedilol can be evaluated on the basis of D_5, D_{10}, DE_{30min}, $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ values as shown in Table 1. From this data, it can be clearly seen that treated agar and microcrystalline cellulose gave rapid and very high rates of dissolution when compared to other carriers. This difference in dissolution rate is more obvious from $t_{50\%}$, $t_{70\%}$, $t_{90\%}$ and DE_{30min} values. The MCC_9 formulation with the drug excipient ratio 1:9 has shown $t_{50\%}$ value of 5 min, $t_{70\%}$ value of 9 min, $t_{90\%}$ value of 39 min and DE_{30min} value of 64.73% and the TAG_9 formulation shows $t_{50\%}$ value of 11 min, $t_{70\%}$ value of 19 min, $t_{90\%}$ value of 53 min and DE_{30min} value of 53.43%. Similarly L_9 and CS_9 formulations with the same drug-excipient ratio have shown $t_{50\%}$ values of 9 min, 9 min; $t_{70\%}$ values of 30 min, 17 min; t_{90}% values of >120, 75 min and DE_{30min} values of 49.83%, 49.93%, respectively.

The higher dissolution rate enhancement by microcrystalline cellulose and treated agar can be attributed to their aqueous solubility resulting in increased wettability of the micronized dug particles and increase in the effective surface area of the drug. The drug release from all the coground mixtures displayed nearly first order release kinetics with 'r' values ranging from approximately 0.935 to 0.992 and obeyed Hixon-Crowell's cube-root law ('r' values range from 0.922 to 0.980).

Out of 16 coground mixtures, the formulation MCC_9 prepared from microcrystalline cellulose was found to give optimum dissolution characteristics ($t_{50\%}$, $t_{70\%}$, $t_{90\%}$, DE_{30min}, $D_{5\%}$ and $D_{10\%}$ values of approximately 5 min, 9 min, 39 min, 64.73%, 52%, 73%, respectively). Therefore, this formulation was selected for further studies i.e., for designing tablets. These tablets (M_{9tab}) displayed much better dissolution parameters compared to the commercial conventional tablet formulation of carvedilol (CCF).

Table-1: Dissolution parameters for pure drug, co-ground mixtures by using various carriers, T_{9tab}, M_{9tab} and commercial formulation.

Formulation Code	Drug: excipient	Mean % drug content (CV)	D_5 (%)	D_{10} (%)	$t_{50\%}$ (min)	$t_{70\%}$ (min)	$t_{90\%}$ (min)	DE_{30}min (%)
CDL	-	-	09.00	24.00	59.00	>120	>120	23.03
CDL_1	-	-	10.00	23.00	56.00	>120	>120	24.89
L_1	1:1	49.00(0.828)	24.00	30.00	51.00	>120	>120	26.93
L_3	1:3	24.98(0.562)	27.00.	37.00	34.00	109.0	>120	38.56
L_4	1:4	20.25 0.634)	32.00	38.00	24.00	76.00	>120	39.40
L_9	1:9	09.60(0.416)	35.00	52.00	09.00	30.00	>120	49.83
CS_1	1:1	53.68(0.537)	25.00	32.00	35.00	>120	>120	32.60
CS_3	1:3	25.80 (0.85)	28.00	41.00	22.00	70.00	>120	38.53
CS_4	1:4	19.97(0.416)	33.00	42.00	20.00	45.00	99.00	41.70
CS_9	1:9	09.81(0.848)	37.00	54.00	09.00	17.00	75.00	49.93
TAG_1	1:1	50.02(0.402)	27.00	38.00	22.00	89.00	>120	35.30
TAG_3	1:3	24.96 0.974)	31.00	44.00	16.00	59.00	>120	41.26
TAG_4	1:4	19.54(0.718)	43.00	56.00	08.00	45.00	100.0	48.70
TAG_9	1:9	09.88(2.141)	45.00	58.00	11.00	19.00	53.00	53.43
MCC_1	1:1	41.11(3.879)	33.00	49.00	12.00	56.00	>120	44.23
MCC_3	1:3	23.54(0.573)	40.00	55.00	08.00	47.00	>120	49.86
MCC_4	1:4	21.49(0.488)	47.00	68.00	06.00	12.00	89.00	62.50
MCC_9	1:9	09.77(1.083)	52.00	72.00	05.00	09.00	39.00	64.73
M_{9tab}	-	-	52.00	69.00	05.00	12.00	45.00	64.23
T_{9tab}	-	-	44.00	56.00	08.00	19.00	53.00	58.00
CCF	-	-	31.00	44.00	15.00	36.00	106.0	44.73

L-Lactose, CS-Corn starch, TAG-Treated agar, MCC-Microcrystalline cellulose

The tablets made from MCC_9 formulation (M_{9tab}) have shown $t_{50\%}$, $t_{70\%}$, $t_{90\%}$, DE_{30min} and $D_{5\%}$, $D_{10\%}$ values of 5 min, 12 min, 45 min, 64.23% and 52%, 69% respectively. The marketed product has shown $t_{50\%}$ value of 15 min, $t_{70\%}$ value of 36 min, $t_{90\%}$ value of 106% and has shown only 44.73% dissolution in 30 min. The better dissolution parameters of the tablets made from MCC_9 formulation could be attributed to excellent swellability and disintegrant properties of MCC. The tablets prepared from TAG_9 coground mixture (T_{9tab}) displayed $t_{50\%}$, $t_{70\%}$, $t_{90\%}$, DE_{30min} and $D_{5\%}$, $D_{10\%}$ values of 8 min, 19 min, 53 min, 58.00% and 44%, 56% respectively. The marketed product has shown $t_{50\%}$ value of 15 min, $t_{70\%}$ value of 36 min, $t_{90\%}$ value of 106 min and has shown only 44.73% dissolution efficiency in 30 min. Therefore M_{9tab} and T_{9tab} tablet formulations have displayed 2-3 times faster drug release when

$t_{50\%}$ and $t_{70\%}$ values were considered. The dissolution profiles of carvedilol (CDL), CCF, M_{9tab} and T_{9tab} were shown in Figure. 1.

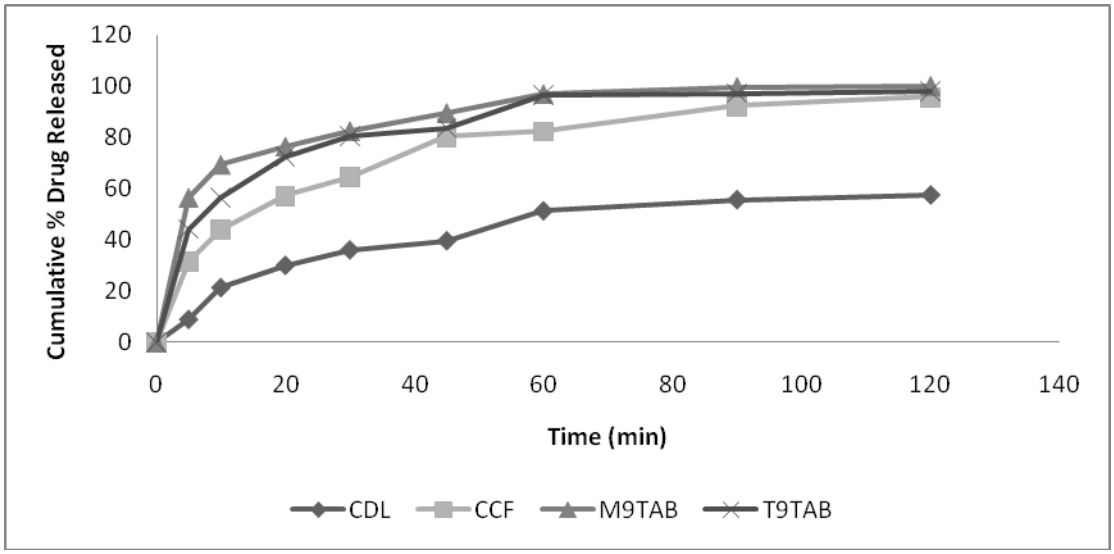

Fig-1: Drug release data for the pure drug, commercial formulation M_{9tab} and T_{9tab}

From the stability studies data, it is evident that the drug content and *in vitro* dissolution of M_{9tab} formulation ($t_{70\%}$) was not significantly affected by storage at 40^{o} C/75% RH for three months. The 't' values were found to be 1.05 and 2.08 respectively and for T_{9tab} formulation ($t_{70\%}$) 1.33 and 2.03 which were much lower than table value of 4.3 ($p<0.05$).

Infra-red Spectroscopy(IR Studies):

Drug-excipient interactions were ruled out by IR spectroscopic studies on the M_{9tab} and T_{9tab} formulations stored for 3 months at 40^{0} C/75% RH. The IR spectrum of the pure drug shows the characteristic peaks at 3341 cm^{-1} (OH group), 3056 cm^{-1} (-NH group), 1213 cm^{-1} (allyl aryl group), 1025 cm^{-1} (ether bending) and 2831cm^{-1} (-CH group).

The IR spectrum of M_{9tab} tablet formulation also exhibited peaks at 3334, 3270, 1209 and 1030 and 2895 cm^{-1} and the IR spectrum of T_{9tab} formulation shows peaks at 3343, 3280, 1213, 1025 and 2850 cm^{-1} respectively for the above groups. This confirms the undisturbed structure of drug in the formulations. Hence there are no drug-carrier interactions.

CONCLUSION

The efficiency of various excipients in enhancing the dissolution rate of carvedilol in increasing order according to DE_{30min} values can be given as: L<CS<TAG <MCC. Hence, cogrinding method can be used for enhancing the *in-vitro* dissolution rate of poorly water soluble drug carvedilol providing nearly first order drug release.

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