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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF CARVEDILOL TABLET

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ABSTRACT
The aim of the study was to develop a formulation of Carvedilol 25 mg tablet that is equivalent to the reference product using similar excipients to match the *in-vitro* dissolution profile. A compressed coated tablet was formulated consisting of Carvedilol and excipients conforming to the USP / BP monograph and below maximum amount allowed per unit dose. The powder blends for core and coated tablet were evaluated for bulk density, tapped density, moisture content and pass through mesh #100. The compressed core and coated tablets were evaluated for thickness, hardness, average weight and friability, loss of drying, disintegration, dissolution, drug content and stability. The powder blends for all formulations showed satisfactory bulk density, tapped density, moisture content and pass through mesh #100. All the core and coated tablets showed acceptable pharmaco-technical properties in terms of thickness, hardness, weight variation, friability, loss of drying and disintegration. Dissolution performances were varied depending on the composition of formulated tablet. Finally a formulation batch B09 consisting of Carvedilol (14.28 %), Colloidal Silicon Dioxide (1.3 %), Lactose Monohydrate (60.79 %), Microcrystalline Cellulose (10.29 %), Sucrose (10.29 %), Crospovidone (1.51 %), Magnesium Stearate (1.54 %) and Opadry II (2.9 %) showed maximum similarity with the reference product. Using this formulation a pharmaceutical will be able to met regulatory compliance.
Keywords: Carvedilol, Hypertension, *In-vitro* Dissolution.

INTRODUCTION

The prevalence of hypertension is continuously rising in developed countries affecting more than 20 % of adult population[1] that ultimately causes coronary artery disease, heart failure and peripheral vascular disease. In developed countries 40.8 % men and 33.0 % women are suffering from hypertension[2]. The tablet formulation problem can be stated as follows: given the drug with its physical and chemical properties and the preferred drug dose in the tablet, find the 12 excipients and their amounts, when mixed they can be compressed into a tablet containing satisfactory properties. To formulate typically 25 % active ingredient is required. Filler is used increase bulk in order to produce a tablet of practical weight for compression (typically 65 %); binder is used to impart cohesive properties to the powders by the formulation of granules. Lubricants added to reduce interparticulate friction to prevent adhesion of powder to the surfaces of punches and dies and to facilitate tablet ejection from the dies. Disintegrating agent is incorporate to facilitate rapid breakup and disintegration after administration, Surfactant is used to aid wetting and dissolution of the drug[3]. Since it is imperative that the final tablet must conform to tight qualifications on, for instance, content uniformity, stability, label claim, disintegration time and dissolution and it is known that all these are influenced by both the formulation components and method of preparation, so it is clear that a tablet formulator requires a high degree of technical knowledge and expertise. Appropriate drug design is essential to export pharmaceutical products in highly regulated countries like Australia, Canada, USA etc. because it should be equivalent to the reference listed drug which is approved by the US FDA.

MATERIALS AND METHODS

The active ingredients, Excipients and coating materials shown in the Table 1 are used in the preparation of Carvedilol 25 mg tablet.

Reference Product

For experiment, Coreg 25 mg tablet manufactured by Glaxo Smith Kline is considered as reference listed drug (RLD).

Experiments

To develop a direct compressible formula for Carvedilol 25 mg tablet and to evaluate its physical and chemical characteristics, the following composition of raw and excipients were taken as percentages as batch (Table 2). Physical parameter of Carvedilol 25 mg tablet (Table 3).

Testing Procedure

Physical properties of powder blend which include: Bulk density, Tapped density, Loss on drying, Pass through mesh #100. After compression, tablet properties which include Thickness, Hardness, average Weight, Friability, Disintegration time, Dissolution and Assay were done. Stability study was done at 40°C + 75 % RH and 30°C + 65 % RH condition for about six months.

Pass through mesh # 100

Dry Sieving Method- Tare each test sieve to the nearest 0.1 g. Put a correctly weighed amount of test specimen on the top sieve and replace the lid. Agitate the nest of sieves for 5 minutes. Then cautiously take out each from the nest without loss of material. Then reweigh each sieve and calculate the weight of material on each sieve. Determine the weight of material in the collecting pan in a similar method. Rearrange the sieves and stir up for 5 minutes. Eliminate and weigh each sieve as previously mentioned. Replicate all steps until the endpoint are met. Upon completion of the analysis, reconcile the total weights of the materials. Total losses must not exceed 5 % of the weight of the original test specimen[5].

Disintegration

Except chewable tablet, Disintegration is a very important parameter which is intended by mouth. Six tablets were taken from each batch and performed disintegration time according to the official monogram.

Dissolution

In each experiment, twelve tablets were randomly selected and performed in accordance with the dissolution apparatus Shing Kwang Machinery, Type DT-6 dissolution test apparatus (Japan). The dissolution apparatus was used with paddles at 50 rpm and a bath temperature of 37°C ± 0.5°C. The dissolution media were evaluated using 0.1 N HCl solutions (pH 3.0) and acetate buffer (pH 4.5). Dissolution was carried out according to the drug release guidelines 900 ml of the freshly prepared medium was used in a rotating vessel[4]. The sampling times were 3, 5, 7, 11, 15, 20, 30, 45 and 60 minutes. At each sampling time point, the dissolution sample (5 ml) was collected from each vessel and filtered through a 0.45-µm porosity nitrocellulose membrane (Millipore, Bedford, MA). Fresh medium (5 ml) was replaced in each vessel after sampling. The dissolution performance of the test formulation compared to the dissolution performance of the RLD for similarity (f2) factor. f2 is the measurement of similarity of two different dissolution curves[5]. f2 value greater than 50 means the curves are similar. The value is determined by the following equation:

$$f_2 = 50 + \log \{[1+ (1 /n) \sum_{t=1} * n (R_t-T_t)^2]^{-0.5} *100\}$$

Where n indicates dissolution sample times, and R_t and T_t are the individual percentage dissolved at each time point t for the referent and test dissolution profiles respectively.

Assay

Standard solution: 0.025 mg / ml of USP Carvedilol prepared as follows: Dissolve a quantity of USP Carvedilol RS in a mixture of diluent and water (9:1) and sonicate until the solution is clear. To obtain the required final concentration, dilute with Methanol solution. Sample stock solution: Transfer a portion of the powdered Tablets (not less than 20), equivalent to 25 mg of Carvedilol to a 100 ml volumetric flask. Include 10 ml of water, then add 70 ml of diluents after shaking by hand and sonicate for 30 minutes. Shake on a mechanical shaker for about 30 minutes and dilute diluents to volume to prepare a 0.25 mg / ml solution. Centrifuge an appropriate amount (about 50 ml) at 2000 rpm for 10 minutes. Sample solution: 0.025 mg / ml of Carvedilol in methanol solution from the Sample stock solution. Pass a portion of the solution through a suitable 0.45-µm syringe filter, discard the first 5 ml and use the filtrate as the Sample solution. Procedure: A 20 µl aliquot of standard or sample preparation (test and reference products) was injected into the HPLC system described above. The quantity (in mg) of Carvedilol in the portion of tablets was obtained by the formula:

% Content = (Ru/Rs) X (Cs/Cu) X 100
Ru = Peak response from the sample solution
Rs = Peak response from the standard solution
Cs = Concentration of the sample solution (mg / mL)
Cu = Nominal Concentration of the sample solution (mg / mL)

Stability

To determine the shelf life of the product and to ensure the stable formulation throughout the specified shelf life of the product, stability study is performed. This guideline has been developed within the scope of the International Conference on Harmonization (ICH) which provides general instruction on the requirement of stability testing and encompasses the practical flexibility required for specific scientific situations and characteristic of the products being evaluated. Tablets were studied at 40°C ± 2°C temperature and relative humidity 75 % ± 5 % and at 30°C ± 2°C temperature and relative humidity 65 % ± 5 % for 3 and 6 months respectively. After 3 and 6 months the tablets were tested[3].

Table 1: List of Ingredients

Ingredients	Sources
Carvedilol	Mylan Laboratories, India
Lactose Monohydrate NF	DMV International, India
Mannitol NF	Eli Lilly, India
Crospovidone NF	ISP Technologies, Inc. USA
Colloidal Silicon Dioxide NF	DMV International, India
Sodium Lauryl Sulphate	Tianjin Kaiyi Chemical Factory , China
Magnesium Stearate NF	Nitika Chemicals, India
Sucrose NF	Ferro Pfanstieh Laboratories, Inc., USA
Microcrystalline Cellulose	Ranq Pharmaceuticals, India
Opadry II	Colorcon Asia Private Limited, India

Table 2: Materials Used in all Formulations

Ingredients (%)	B01	B02	B03	B04	B05	B06	B07	B08	B09
Carvedilol	13.89	13.89	13.89	13.89	13.89	14.28	14.28	14.28	14.28
Lactose NF (Pharmatose 200M)	36.72	26.38	26.38	37.49	15.95	10.41	10.41	13.35	13.36
Sucrose NF	-----	-----	-----	-----	----	----	10.29	10.29	10.29
Lactose NF (Pharmatose DCL 11)	20.00	54.92	53.42	45.96	55.00	56.54	56. 54	48.19	47.43
Microcrystalline Cellulose NF	----	----	-----	---	10.00	10.29	---	10.29	10.29
SLS	-----	-----	----	0.10	0.10	-----	---	----	----
Povidone NF	-----	1.00	5.00	---	---	-----	---	---	----
Mannitol NF	23.00	----	----	----	----	----	----	----	----
Crospovidone NF	5.00	3.00	0.50	1.00	2.56	1.03	1.03	1.03	1.51
CSD	0.12	----	-----	0.75	1.00	-----	----	1.03	1.30
Magnesium Stearate NF	1.27	0.81	0.81	0.81	1.50	1.45	1.45	1.54	1.54
Opadry II	2.86% along with suitable solvent for all batches								

[SLS: Sodium Lauryl Sulphate; CSD: Colloidal Silicon dioxide NF]

Table 3: Physical Parameters for All Formulations

Characteristics	For B01-B05		For B06-B09	
	Core Tablet	Coated	Core Tablet	Coated
Average wt. mg	180 ± 3 %	180 - 190	175 ± 3 %	175 - 185
Thickness (mm)	2.90 - 3.30	3.0 - 3.4	2.90 - 3.30	3.0 - 3.4
Hardness(NW)	60 - 520	60 - 520	60 - 520	60 - 520
Friability	NMT 1.0 %	NMT 1.0 %	NMT 1.0 %	NMT 1.0 %
Disintegration	NMT 5	30 minutes	NMT 5	30 minutes

Table 4: Characteristics of Blend and Weight Variation of Tablets

Batch no.	Bulk density (g / ml)	Tapped Density (g / ml)	Loss on Drying (%)	Pass100 mesh (% w/w)	Average wt (mg)	Min. (-) (%)	Max. (+) (%)
B01	0.58 ± 0.04	0.76 ± 0.06	1.50 ± 0.06	87.99	183.4	1.45	2.49
B02	0.59 ± 0.03	0.75 ± 0.05	1.27 ± 0.04	89.80	180.8	1.58	0.85
B03	0.57 ± 0.03	0.71 ± 0.05	1.54 ± 0.06	93.10	182.2	0.80	0.90
B04	0.65 ± 0.04	0.83 ± 0.04	1.12 ± 0.08	93.50	184.3	1.94	1.10
B05	0.61 ± 0.03	0.74 ± 0.06	1.29 ± 0.07	88.70	187.0	1.28	1.34
B06	0.58 ± 0.01	0.79 ± 0.06	1.45 ± 0.06	91.45	176.3	1.32	1.56
B07	0.63 ± 0.02	0.76 ± 0.07	1.30 ± 0.09	89.50	177.3	0.93	1.32
B08	0.62 ± 0.04	0.75 ± 0.06	1.34 ± 0.08	89.10	178.1	1.52	1.25
B09	0.61 ± 0.02	0.72 ± 0.05	1.28 ± 0.04	90.50	180.2	0.93	2.3

Table 5: Stability Data of B09 Batch Formulation

Frequency of analysis		1st Month	3rd Month		6th Month	
Date of analysis		06.04.12	10.07.12		10.10.12	
Sl. No	Parameters	Initial Result	30°C / RH 65 %	40°C / RH 75 %	30°C / RH 65 %	40°C / RH 75 %
1	Appearance	Complies	Complies	Complies	Complies	Complies
2	Identification	Complies	Complies	Complies	Complies	Complies
3	Average wt	181.5 mg	181.6 mg	181.8 mg	181.6 mg	181.7 mg
4	Disintegration	2'45"	2'45"	2'58"	2'15"	2'15"
5	Dissolution	100.53 %	98.99%	98.35%	98.28%	98.20%
6	Assay	25.06 mg	24.96 mg	24.78 mg	25.00 mg	24.92 mg

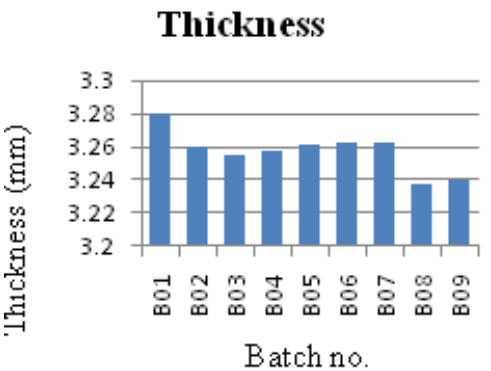

Figure 1: Thickness

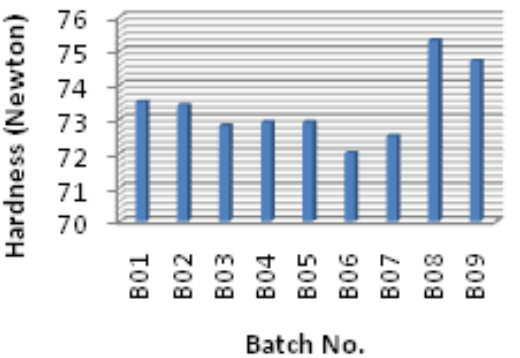

Figure 2: Hardness

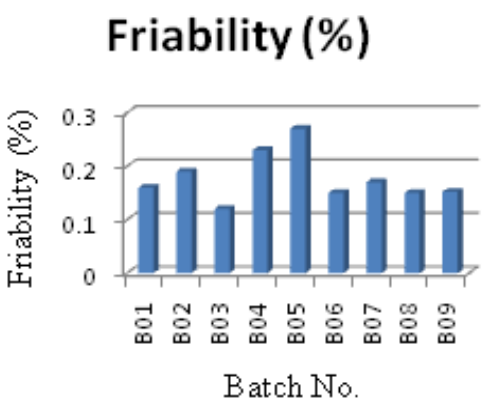

Figure 3: Friability

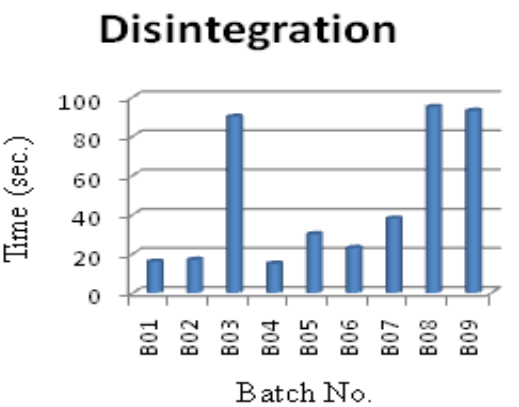

Figure 4: Disintegration

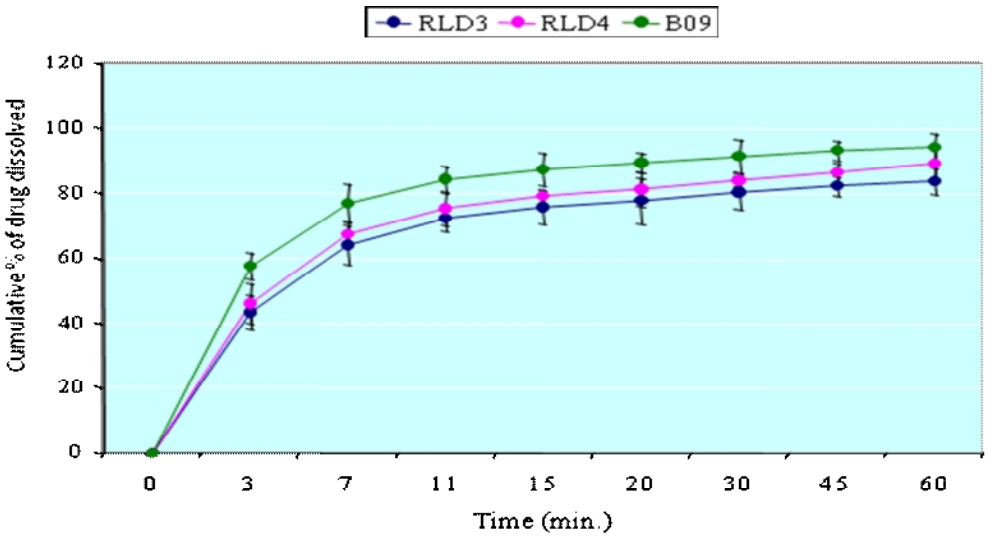

Figure 5 (A): Dissolution of B09 batch formulation (A) in pH 3.0

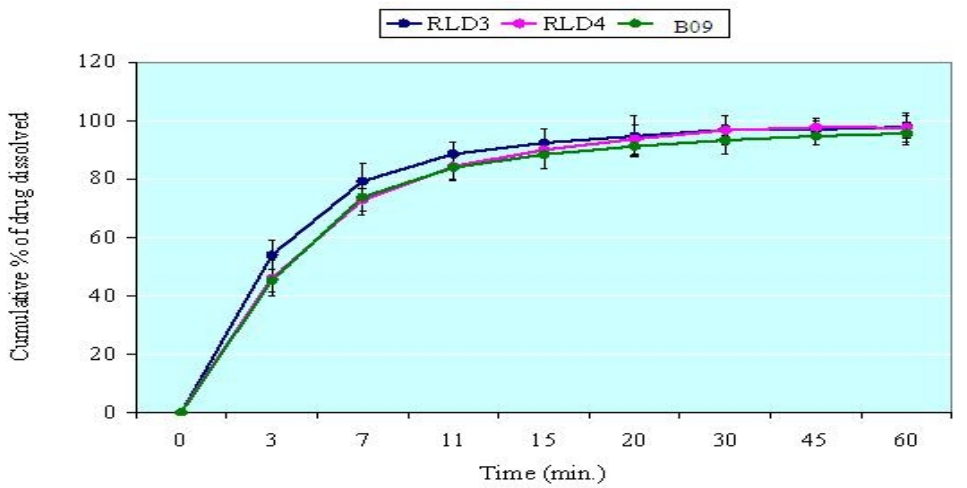

Figure 5 (B): Dissolution of B09 batch formulation (B) in pH 4.5

RESULT

The Powder blend and granules of different prepared formulations (B01- B09) were evaluated for Bulk density, Tapped density, LOD, pass through of mesh # 100 (Table 4). The results of Bulk density ranged from 0.57 ± 0.03 to 0.65 ± 0.04 g / ml and Tapped density ranged from 0.71 ± 0.05 to 0.83 ± 0.04 g / ml. Loss on drying also within the limit (2 %). Pass through of mesh #100 also showed satisfactory results (Table 4). In case thicknesses, found acceptable results (Figure 1). The hardness of core tablet and coated tablet of all batches was acceptable (Figure 2). The weight variation range was (-1.98 to + 2.49) (Table 4). The friability of all formulations was found less than 1.0 % (Figure 3). Formulation B03, B08 and B09 showed higher disintegration time (Figure 4). Drug release at 60th minute was 59.3 % (f2) for test tablets against 96.9 % for the reference product [Figure 5 (A), (B)]. Dissolution of the film coated tablets was similar to RLD in both pH 3.0 and 4.5 medium in case of B09. Rest the batches (B02-B09) were revealed the Pharmacopeias specification of drug content.

Stability Test

Average weight was gained; disintegration time decreased and drug content remained almost same after 3 and 6 months. But these change permits the specification of stability guidelines (Table 5).

DISCUSSION

From result of Table 4, listed blend characteristics of powder for core and coat layer showed satisfactory micromeritic properties. It is suggested that the effect of a binder on the relationship between the bulk density, tapped density and compatibility of lactose granulations was significantly influenced by the consolidation and compaction behavior of the lactose particles. All the blend formulations (B01-B09) met the specified specifications[6]. Thickness of all formulations did not vary significantly[7] (Figure 1). It can be seen that hardness of all batches was satisfactory (Figure 2). Highest thickness was seen in B08 (85N) and the lowest thickness was in B06 (67N)[8]. Average weight of all formulations was found in the range of 176.3-187 mg after coating. The friability of all formulations was less than 1.0 % and hence the tablets with lower friability may not break

during handling on machines and or shipping[9] (Figure 3). According to USP 32-NF27, Conventional compressed tablets that loose less than 0.5 to 1 % of their weight are generally considered acceptable. In all batches (B01-B09), core and coated tablets were disintegrated within 2 minutes (Figure 4). Formulation Batch 04 showed the lowest disintegration time (15 sec) where as formulation batch 09 showed the highest disintegration time (1 min. 50 Sec). After coating the weight gain achieved was 3.11 % w/w with 1 minute 32 seconds as the disintegration time of coated tablets. The dissolution performance of the tablets in batch B09 was similar to that of the RLD where the formulation with 1.51 % crospovidone was used. Stability showed that, there was no change in product's physical properties with little bit change in disintegration time. Dissolution also reduced in some batches insignificantly. The drug content remained almost same after 3 and 6 months. The assay of Carvedilol 25 mg tablet found 25.06 mg to 24.092 mg / tablet for accelerated condition which is under pharmacopoeias limit.

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