BJPS

Brazilian Journal of
Pharmaceutical Sciences
vol. 47, n. 4, oct./dec., 2011

Article

Development and validation of dissolution method for carvedilol compression-coated tablets

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The present study describes the development and validation of a dissolution method for carvedilol compression-coated tablets. Dissolution test was performed using a TDT-06T dissolution apparatus. Based on the physiological conditions of the body, 0.1N hydrochloric acid was used as dissolution medium and release was monitored for 2 hours to verify the immediate release pattern of the drug in acidic pH, followed by pH 6.8 in citric-phosphate buffer for 22 hours, to simulate a sustained release pattern in the intestine. Influences of rotation speed and surfactant concentration in medium were evaluated. Samples were analysed by validated UV visible spectrophotometric method at 286 nm. 1% sodium lauryl sulphate (SLS) was found to be optimum for improving carvedilol solubility in pH 6.8 citric-phosphate buffer. Analysis of variance showed no significant difference between the results obtained at 50 and 100 rpm. The discriminating dissolution method was successfully developed for carvedilol compression-coated tablets. The conditions that allowed dissolution determination were USP type I apparatus at 100 rpm, containing 1000 ml of 0.1N HCl for 2 hours, followed by pH 6.8 citric-phosphate buffer with 1% SLS for 22 hours at 37.0 ± 0.5 ºC. Samples were analysed by UV spectrophotometric method and validated as per ICH guidelines.

Uniterms: Carvedilol/coated tablets. Compression coated tablets/dissolution. pH 6.8 citric-phosphate buffer. Hydrochloric acid. Sodium lauryl sulphate.

O presente estudo descreve o desenvolvimento e a validação de método de dissolução para comprimidos revestidos de carvedilol. O teste de dissolução foi efetuado utilizando-se o aparelho para dissolução TDT-06T. Com base nas condições fisiológicas do organismo, utilizou-se ácido clorídrico 0,1 N como meio de dissolução e a liberação foi monitorada por 2 horas para se verificar o padrão de liberação imediata do fármaco em condições de pH baixo, seguidas por pH 6,8 em tampão cítrico-fosfato por 22 horas, para simular o padrão de liberação controlada no intestino. Avaliou-se a influência da velocidade de rotação e a concentração de tensoativo no meio. As amostras foram analisadas por método espectrofotométrico UV-visível validado, em 286 nm. O laurilsulfato sódico a 1% (SLS) mostrou-se ótimo para aumentar a solubilidade do carvedilol em pH 6,8 em tampão cítrico-fosfato. A análise da variância não mostrou diferença significativa entre os resultados obtidos a 50 e a 100 rpm. O método da dissolução discriminante foi desenvolvido com sucesso para os comprimidos revestidos de carvedilol. As condições que permitiram a determinação da dissolução foram: aparelho USP tipo I a 100 rpm, contendo 1000 mL de HCL 0,1 N por 2 horas, seguido de pH 6,8 com tampão cítrico-fosfato, com 1% de SLS por 22 horas a 37,0 ± 0,5 ºC. Amostras foram analisadas por método espectrofotométrico e validadas pelas normas ICH.

Unitermos: Carvedilol/comprimidos revestidos. Comprimidos revestidos por compressão/dissolução. Tampão cítrico-fosfato pH 6.8. Ácido clorídrico. Laurilsulfato de sódio.

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INTRODUCTION

Dissolution testing has been proven to be important tool for evaluating the performance of solid dosage forms (Dressman *et al.*, 1998). Developing an appropriate *in vitro* dissolution test for drug products with limited water solubility has been a challenge for scientists. Lipophilic drugs are classified into classes II or IV by the Biopharmaceutical Classification System (BCS), depending on their apparent permeability (*P*app values). Drug release is usually the rate-limiting step for oral absorption of these substances (Lobenberg *et al.*, 2000; Soni *et al.*, 2008).

An ideal dissolution test should provide product quality information as well as some preliminary *in vivo/in vitro* correlation (IVIVC) or biorelevance (Emani, 2006). For insoluble compounds, surfactants may be employed, such as sodium lauryl sulfate (SLS) or polysorbate 80 (e.g. Tween® 80), to assist in drug dissolution and solubilisation (Balakrishnan *et al.*, 2004). Usually, biorelevant dissolution testing is performed separately using media such as simulated gastric fluid (SGF), simulated intestinal fluid (SIF), milk and fasted-state or fed-state simulated intestinal fluid (FaSSIF or FeSSIF) (Nicolaides *et al.*,1999).

Dissolution testing is used to guide the development of new drug products and to assess the lot-to-lot variability of drug products. Analytical methods are validated to ensure that they are suitable for their intended use and provide accurate and reliable data. Validation of a dissolution method typically involves validation of the end analysis method (Galia *et al.*, 1998; ICH, 2005).

The present study describes the development and validation of a dissolution method for compression-coated tablets with quick and slow release characteristics. Carvedilol, or (±)-1-9*H*-(carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol (Figure 1), is an antihypertensive agent with β and α_1-adrenergic receptor-blocking activities (Ruffolo *et al.*, 1990; Nichols *et al.*, 1991; De *et al.*, 1994).

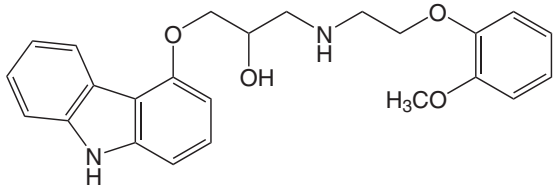

FIGURE 1 - Chemical structure of carvedilol.

Carvedilol has a greater antioxidant activity than other commonly-used β blockers (Nakamura *et al.*, 2002; Kukin *et al.*, 1999). It is widely prescribed for the treatment of essential hypertension, angina pectoris (Packer *et al.*, 2002; Ruffolo *et al.*, 1992) and congestive heart failure (Poole-wilson *et al.*, 2002). Its biological half-life is 6 to 10 hours and its usual dose is 3.125, 6.25, 12.5 and 25mg, two to three times a day. Short biological half-life and high frequency of administration make carvedilol a suitable candidate for administration by a quick/slow delivery system. Conventional controlled dosage forms delay the release of the drug but do not provide a rapid onset of action. This can be overcome by quick/slow release pattern of compression-coated tablets. The present study describes the process of selection, development and validation of a dissolution method for 25 mg carvedilol compression-coated tablets. A dissolution method for carvedilol compression coated tablets had not been reported in the literature.

MATERIAL AND METHODS

Material

Carvedilol BP was received as a gift sample from Unichem India Laboratories. All chemicals and solvents used were of analytical reagent grade. Hydroxy propyl methyl cellulose (HPMC)K_4M (Colorcon India), polyox WSR 205 (Dow chemical's), microcrystalline cellulose, magnesium stearate, talc, sodium starch glycollate, starch, disodium hydrogen ortho phosphate, citric acid, hydrochloric acid, sodium lauryl sulfate (SLS) (Sd fine chem pvt. Ltd, Mumbai) were used.

Instrumentation

Equipment and instruments used in the present study included: electronic balance (Reputed Micro System), tablet compression machine (Rimek mini press- I), hardness tester (Monsanto), Roche friabilator, UV Spectrophotometer (UV-1800 Shimadzu), Dissolution test apparatus TDT-06T (Electrolab, Mumbai, India) and laboratory stirrer (Remi Instruments division).

Methodology

Solubility of drug in different dissolution media

The selection of a dissolution medium may be based on the solubility data and dosage range of the drug product. The saturation solubility of carvedilol was determined in distilled water, hydrochloric acid solution (pH 1.2), citric-phosphate buffer (pH 4.5, 6.8, 7.4) and pH 6.8 citric-phosphate buffer with sodium lauryl sulphate (0.1%, 0.5%, and 1.0%). Fifty miligrams of carvedilol were accurately weighed and added to 15 ml of the afforementioned

dissolution medium in a 25 ml volumetric flask and then agitated continuously at room temperature for 24 hours using a mechanical shaker. The solutions were kept aside for 24 hours for equilibrium, at the same temperature. After equilibrium, solutions were filtered through Whatman fiters (0.45 micron); filtrates were suitably diluted and analysed by UV spectrophotometer at 286 nm. Solubility of drug in each medium was determined in triplicate.

Dissolution test conditions

The dissolution method was developed using a TDT-06T dissolution apparatus. Volume of dissolution medium was selected based on the solubility data. Influences of rotation speed and surfactant concentration in pH 6.8 citric-phosphate buffer were evaluated. At 30, 45, 60 minutes time interval, 10 ml sample aliquots were withdrawn and replaced with an equal volume of fresh medium to maintain a constant total volume. Aliquots were passed through a filter and analysed using the previously validated UV spectrophotometric method at 286 nm, with dissolution medium in reference cell.

Discrimination power of selected dissolution method

Discriminatory dissolution profiles are highly desirable for differentiating between products having differences in pharmaceutical attributes (formulation and/or manufacturing process differences) that may reflect corresponding differences *in vivo*.

Two formulations were prepared which differed in concentration of HPMC and MCC in core tablets, in order to challenge the discrimination power for the dissolution method (Table I). The core tablets were prepared by direct compression method, where the desired amount of blend (equivalent to 50 mg tablet weight) was compressed into tablets using a rotary tablet-compression machine equipped with a 5.5 mm concave punch. The immediate release layer (coat layer) was composed of drug (5 mg), starch, sodium starch glycollate, microcrystalline cellulose, magnesium stearate and talc, for both formulations. To prepare the compression-coated tablets, half the amount of immediate release powder blend was put into the die cavity with 8 mm diameter to make a powder bed, on the center of which a core tablet was placed. Once more, half the amount of powder was added to cover the core tablet, and the layers were compressed at a compression force of 5 kN.

Dissolution profiles of batch F1 and F2 were compared using a similarity factor (f2) and dissimilarity factor (f1). Values for f1 and f2 were calculated using equations 1 and 2, respectively. The f2 factor measures the closeness between the two profiles and f1 measures difference between the two profiles:

$$f1 = \left\{\frac{[\Sigma \mid Rt - Tt \mid]}{[\Sigma\, [Rt]}\right\} \times 100, \text{ where t = 1 to n} \quad (1)$$

$$f2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n} [[(Rt - Tt)^2]]\right]^{-0.5} \times 100\right\} \quad (2)$$

where Rt and Tt are the percentage of drug dissolved at each time point for the test and reference products, respectively. A value of f1 over 15 indicates significant dissimilarity and a value of f2 over 50 indicates significant similarity in results (Gupta *et al.*, 2010).

Method validation

UV/VIS spectrophotometry and high performance liquid chromatography are analytical methods widely used for quantifying drug release in dissolution tests (Wang *et al.*, 2006). In the present research work, the UV spectrophotometric method was used to analyse carvedilol released in the dissolution medium. It was validated as per ICH guideline (ICH, 2005).

RESULTS AND DISCUSSION

Solubility of drug in different media

Saturation solubility and relative sink conditions of carvedilol in different dissolution medium are shown

TABLE I - Composition of two batches of core tablets of carvedilol compression-coated tablets to challenge the discriminating power of the dissolution

Batch no.	Weight of drug (mg)	Weight of PEO WSR 205 (mg)	Weight of HPMC K_4M (mg)	Weight of MCC (mg)	Weight of magnesium stearate (mg)	Weight of talc (mg)
F1	20	5	5	18	1	1
F2	20	5	10	13	1	1

PEO, HPMC and MCC stand for polyethylene oxide, hydroxypropyl methyl cellulose and microcrystalline cellulose, respectively.

TABLE II - Saturation solubility and relative sink conditions of carvedilol in different dissolution media (n=3)

Dissolution medium	Solubility (μg/mL)	S value = Cs/C_d (25 mg tablet)
Water	0.98 ± 0.12	0.040
0.1 N HCl	89.2 ± 0.03	3.568
pH 4.5 citric-phosphate buffer	44.2 ± 0.012	1.768
pH 6.8 citric-phosphate buffer	15.7 ± 0.05	0.063
pH 7.4 citric-phosphate buffer	10.6 ± 0.01	0.424
pH 6.8 citric-phosphate buffer + 0.1 % SLS	29.4 ± 0.03	1.176
pH 6.8 citric-phosphate buffer + 0.5% SLS	54.2 ± 0.02	2.168
pH 6.8 citric-phosphate buffer + 1% SLS	79.8 ± 0.13	3.192

C_S stands for saturation solubility of carvedilol; C_d stands for concentration of carvedilol after complete dissolution; SLS stands for sodium lauryl sulfate.

in Table II. Carvedilol showed good solubility in acidic medium (0.1 N HCl) and solubility decreased at higher pH values. For poorly soluble drugs, surfactants can be used to enhance drug solubility (Wang *et al.*, 2006). The FDA recommended the use of SLS in dissolution media for many lipophilic drugs. Using 3% of SLS has been suggested for conducting dissolution tests for insoluble drugs, such as acetracin and orlistate (Amit *et al.*, 2010). The ratio of solubility to drug concentration, expressed as C_S/C_D (S value), represents the closeness to the sink conditions, with values greater than 3 considered as sink according to USP (Jamzad *et al., 2006)*. In the present study, 1.0 % w/v SLS in pH 6.8 citric-phosphate buffer medium provided sink conditions, hence 1.0% SLS was chosen to enhance the solubility of the drug in 6.8 citric-phosphate buffer.

Development of dissolution test conditions

Retention times of formulations in the stomach depend on the dosage size and on whether or not the formulation is taken with a meal. To develop dissolution tests on the basis of gastrointestinal physiology, mean residence times in various segments of the gastrointestinal tract are considered (Klein *et al.*, 2005). Patients are advised to take carvedilol after eating a meal (White *et al.*, 2007). Postprandial mean residence time of pellet and non-disintegrating tablet in the stomach ranges from 2-4 hours (Klein *et al.*, 2005); hence 0.1N HCl was used as dissolution medium for 2 hours, to check the immediate release pattern of the drug in acidic pH. A value of S greater than 3 (Table II) at 0.1 N HCl eliminates the need for surfactants in the dissolution medium. After 2 hours, a pH 6.8 citric-phosphate buffer with 1% SLS was chosen to study the dissolution of compression-coated tablets for 22 hours, in order to simulate the slow release pattern in the small and large intestines.

The influence of the rotation speed was evaluated and the analysis of variance showed no significant difference between the results obtained at 50 and 100 rpm ($p<0.05$). The drug release percentage in pH 6.8 citric-phosphate buffer medium at 100 rpm was slightly higher than the release at 50 rpm (Table III).

TABLE III - *In vitro* drug release of carvedilol compression-coated tablet

Sr. No.	Time (hours)	% Drug release
	Immediate layer of tablet (5 mg)	
1	0	0
2	1	80.75
3	2	100.8
	Sustained layer of tablet (20 mg)	
4	3	21.29
5	4	23.92
6	6	28.62
7	8	34.81
8	10	40.79
9	12	47.45
10	16	65.76
11	20	84.28
12	24	97.97

A Basket apparatus was selected for dissolution of compression-coated carvedilol tablets as it allowed for easy change of the dissolution medium after 2 hours, without disturbing the dosage form. The volume of the dissolution medium was selected as 1000 mL, based on the solubility data.

Based on these results and on requirements of dosage form, the optimised conditions for the dissolution test of compression-coated carvedilol tablets were a USP apparatus I containing 1000 ml of 0.1N HCl for the first 2 hours, followed by a pH 6.8 citric-phosphate buffer with 1% of SLS for 22 hours with a stirring speed of 100 rpm. Under these conditions, the optimised batch of carvedilol compression-coated tablets showed a drug release of 100.8% from the immediate layer in the first 2 hours and a drug release of 97.97% from the sustained release layer after 22 hours (Table III, Figure 2). The drug was stable for 24 hours in the dissolution medium (variation less than 2%). Acceptance criteria are derived in the form of "Q factors", a minimum amount dissolved at a given time as a percentage of the labeled content. Acceptance criteria, Q, for the compression-coated tablets were in the range of 75% to 80%.

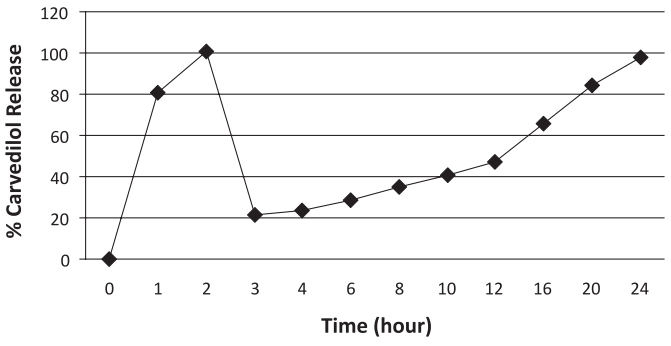

FIGURE 2 - *In vitro* drug release profile of carvedilol compression-coated tablet in 0.1 N HCl for 2 hours and in pH 6.8 citric-phosphate buffer for the next 22 hours at 100 rpm.

Discrimination power of selected dissolution method

Results of the dissolution study for both formulations, F1 and F2, are given in Table IV. Comparison of the dissolution profile for batches F1 and F2 was conducted by Model-Independent analysis, using the values of f1 and f2 to confirm the discriminating power of the dissolution method. The optimised dissolution conditions in this study enabled differentiation between the two formulations, having varying concentrations of HPMC and MCC, with f1 and f2 values of 17.65 and 41.46, respectively. Student's t-test was used to find maximum significant difference in the dissolution profile to represent discrimination power. The p value was found to be 0.4657 for formulations F1 and F2, indicating maximum significant difference in the *in vitro* drug release profile for both batches.

TABLE IV - Comparison of *in vitro* drug release profile of two batches of carvedilol compression-coated tablets to challenge discriminating power

Time (hours)	% drug release	
	Batch F1	Batch F2
0	0	0
1	17.23	15.69
2	21.71	23.54
3	35.02	26.09
4	41.3	30.42
6	57.93	35.79
8	66.5	45.92
10	77.55	56.44
12	85.62	62.91
16	100.51	77.58
20	100.18	101.02
24	99.37	103.46

Method validation

Specificity

The UV spectrophotometric method may be used if the drug has a UV chromophore and no UV interferences, due to excipients used in the formulation being observed (Fortunato, 2005). Specificity was examined by analysing a placebo solution, which consisted of all the excipients without the drug. The absorption spectrum of the drug in dissolution medium showed an absorbance peak at 286 nm. At this wavelength, no interference of excipients was observed (Figure 3).

Linearity

Linearity of the method was evaluated with a six-point calibration curve, spanning a concentration range of 5-30 µg/mL of drug substance in 0.1 N HCl and in 6.8 citric-phosphate buffer with 1% SLS. Three independent determinations were performed for each concentration. Linearity curves were plotted for media, 0.1 N HCl (Figure 4) and 6.8 citric-phosphate buffer with 1% SLS (Figure 5), considering mean absorbance and standard deviation (SD) for each concentration. These data indicated that the absorbance was linear over the concentration range of 5-30 µg/mL of drug substance. The correlation coefficient (R^2) value for the regression line was 0.999, with a slope of 0.136 and *y*-intercept of 0.049 in 0.1 N HCl. The R^2 value for the regression line was found to be 0.999 in 6.8 citric-phosphate buffer with 1% SLS, with a slope of 0.134 and *y*-intercept of 0.049. These results were

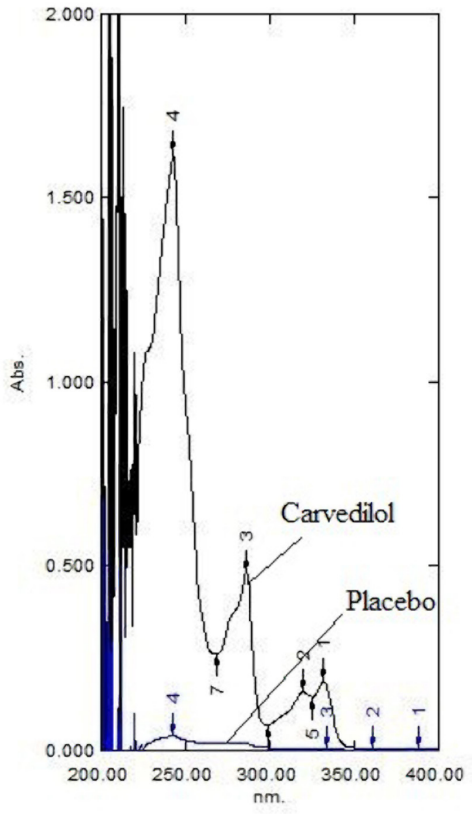

FIGURE 3 – UV spectra of drug and placebo.

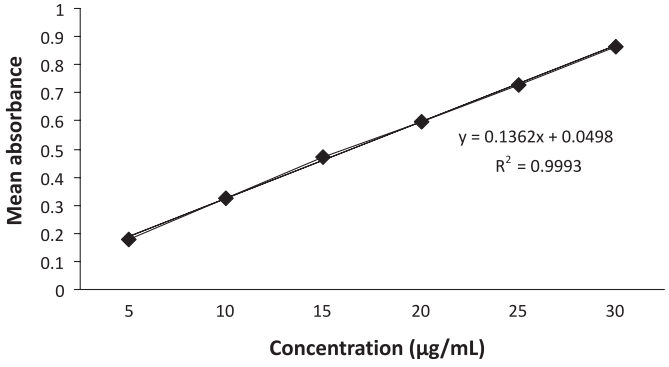

FIGURE 4 - Linearity curve of carvedilol in 0.1 N HCL.

considered acceptable and the linearity curves were used to calculate *in vitro* drug release studies.

Range

The specified range is normally derived from linearity studies and depends on the intended application of the procedure. As per ICH guideline, if the specifications for a controlled released product cover a region from 20% after 1 hour, up to 90% after 24 hours, the validated range would be 0-110% of the label claim. In the present study, 100% drug was released from the immediate release layer in up to 2 hours, 21.29% drug was released at 3 hours from the sustained release layer and 99.99% drug was released after 24 hours, so the validated range would be 0-110% of the label claim.

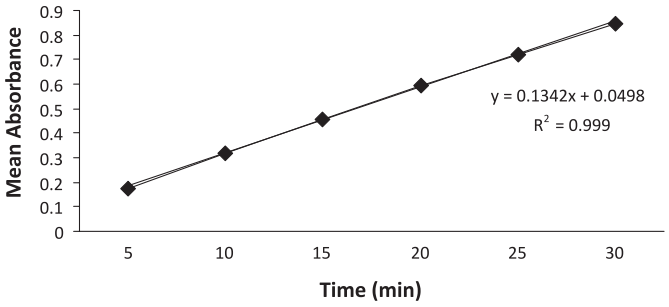

FIGURE 5 - Linearity curve of carvedilol in 6.8 citric-phosphate buffer with 1 % SLS.

Precision

Precision of the method was determined by measuring the repeatability, intraday precision and interday precision. The repeatability study (n = 6) carried out showed a maximum percentage relative SD of 0.72% among samples prepared on the same day under the same conditions. At interday and intraday, the maximum percentages of relative SD were found to be 1.32 and 0.97, respectively.

The method also showed intermediate precision with maximum difference in RSD percentage of 0.26%, among the results of six analytical solutions prepared by two different analysts on different days (n=3).

Accuracy

The accuracy was demonstrated by the recovery of known amounts of carvedilol in the dissolution vessels. In the present study, four concentrations were evaluated (15, 20, 25 and 30 µg/mL) and each concentration was measured three times. The recovery percentage found ranged from 99.26 to 101.40, which indicates the accuracy of the method. The recovery percentage was calculated in triplicate and the mean value was considered.

Solution stability

Solution stability was determined by measuring absorbance of 15µg/ml of carvedilol solution under the dissolution test conditions for up to 30 hours. All of the assay results during this period of time were within 98–102% of the initial value.

CONCLUSION

The discriminating dissolution method was successfully developed for carvedilol compression-coated tablets.

The conditions that allowed the dissolution determination were USP type I apparatus at 100 rpm, containing 1000 mL of 0.1 N HCl for first 2 hours and pH 6.8 citric-phosphate buffer with 1% SLS for the next 22 hours at 37.0 ± 0.5 ºC. Carvedilol stability was ensured under the developed dissolution conditions. Samples were analysed using the validated UV spectrophotometric method.

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Received for publication on 17th March 2011
Accepted for publication on 30th July 2011