SOLUBILITY ENHANCEMENT OF CARVEDILOL USING MICROWAVE FUSION METHOD

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ABSTRACT

The solubility is an important property of any drug. The absorption and bioavailability of drug is decided by its solubility in gastric fluids. The bioavailability of drug can be enhanced by enhancing its solubility. So, to achieve this goal, formulating solid dispersion is an effective approach to increase the dissolution rate and solubility of drug like carvedilol which have low water solubility. The water-soluble carriers or polymers used in formulation, assists in increasing the solubility and dissolution rate of drug with low hydrophilicity. Numbers of methods are present to formulate solid dispersions, but amongst them Microwave Fusion method is more efficient. Using this method Amorphization of drug can be accomplished which help to increase the dissolution rate and solubility of drug.

Keyword: *Carvedilol, microwave fusion method, solubility, dissolution rate, bioavailability, amorphization*

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1.0 INTRODUCTION

Solubility and bioavailability are two very important factors for a drug to achieve therapeutic success. To attain pharmacological response, a certain concentration of drug needed to be present in systemic circulation which can be achieved if drug is soluble enough. Currently, among the new drugs, only a small percentage of drugs (8%) have both high solubility and permeability. [1, 2] In fact, most of the new drug entities are having low hydrophilicity and lacking in proper oral administration. [3] Also, most new drug entities, irrespective of their high permeability, are normally absorbed in the upper part of small intestine, absorption decrease after the ileum. These factors made absorption of drug difficult. [1, 4]

By enhancing the drug release, it become easy to improve bioavailability and minimize side-effects of drug. Solid dispersions are a very efficient and successful way of improving drug's dissolution rate and bioavailability of low hydrophilic drug through oral route. [5] This can be done by molecular mixing of low hydrophilic drugs with water soluble polymers like PEG. In this approach, polymer properties help to improve drug release profile. [6, 7]

Oral drug administration is the most common way of taking medications, which have various advantages like administration is easy, its cost effective, safe, convenient and avoids pain. Instead of having these advantages, achieving the desired bioavailability of lipophilic and low water-soluble drugs is becomes very difficult. [8] The drugs having low water solubility have so many limitations like administration frequency is more, increased doses and these may result in side effects. Also, for drug with low hydrophilicity, rate-limiting step is their dissolution rate in GI fluids.[9]

Use of microwaves has become good technique for making the solid dispersions. [10-14] Microwave radiation is electromagnetic radiation having frequencies between the infrared and radio_in the range of 0.3–300 GHz. Microwaves can be directly converted into heat inside the material. This happens because of dipolar moment of

molecules, causes the them to oscillate, resulting in heat generation. Because of this phenomenon even heating throughout the material is possible, which is not possible in conventional heating methods. Microwaves helps to change the crystalline nature of drug into amorphous nature. The solid dispersions made by this method contains drug with amorphous nature having high water solubility, distributed evenly in hydrophilic polymer. Microwave fusion method is an efficient technique for increasing solubility of low hydrophilic drugs. [15-16] Amorphous APIs have greater solubility than their crystalline equivalents. [17]

In this study, microwave radiation was used to make solid dispersion of the poorly water-soluble Carvedilol. Carvedilol is a nonselective β + weak selective α1 blocker which act as vasodilator and have free radical scavenging properties. It is BCS Class II drug having low water solubility and high permeability. [18] It is also a diabetes friendly drug. In this study, we investigated that use of microwave radiation help to increase solubility and dissolution rate of the poorly water-soluble Carvedilol.

2.0 MATERIALS AND METHODS

2.1 Materials

Carvedilol and PEG 6000 were purchased from local vendor.

All other materials used were of analytical grade.

2.2 Methods

Preparation of solid dispersions

Physical mixture

The physical mixture of Carvedilol and PEG 6000 was prepared by mixing these ingredients in mortar and pestle in different ratios such as 1:1, 1:3, 1:5 w/w.

Development of the optimized batch

Based on the statistical evaluations, the software recommended one optimum batch from each solid dispersion. These batches of solid dispersion along with other batches were used for the further studies and comparisons.

Microwave fusion method

Solid dispersions having different ratios of Carvedilol and PEG 6000 were prepared using the microwave fusion method. The optimized ratio was found to be 1:5 w/w. Carvedilol and PEG 6000 were weighed and batches of different ratios were prepared (1:1, 1:3, 1:5). A fixed amount of physical mixture (2 g) from each batch was exposed to microwaves for different times, like 1, 3 and 5 minutes at a constant power of 590 W in a microwave oven instrument. Only one beaker was placed at a time inside the instrument. After the completion time of exposure, beaker was placed at room temperature to get solidify. Solid dispersions were collected and product was crushed using a mortar and pestle. And powders of solid dispersions were passed through 80 number sieves. [19]

3.0 PREFORMULATION STUDIES

Pre-formulation studies were carried out on the drug, which included solubility, determination of melting point. [20-28]

3.1 Solubility of drug

It was tested at room temperature in various solvents. 5 mg of drug is liquefied in 5 ml of various solvents such as DW, methanol, ethanol, and acetone.

3.2 Determination of melting point

Determination of melting of drug was done by capillary method.

3.3 Determining the λ max

A 100 µg/ml solution of Carvedilol was made by adding 10 mg of pure API in 100ml dist. water. The solution was clarified and scanned in between 200-600 nm by employing UV spectrophotometer.

4.0 EVALUATION OF SOLID DISPERSION [1]

4.1 Drug content (%)

100 mg of optimized solid dispersion was accurately weighed and taken into a 50 ml volume flask and dissolved in 40 ml methanol. The solution was made up to the sufficient volume with methanol. Then solution was diluted with 0.1N HCl and assay for drug content was takes place using the UV spectrophotometry at 242 nm. [29-31]

4.2 Percentage drug release

Using the USP dissolution apparatus II, the analysis of *in-vitro* dissolution was carried out. The dissolution test was carried out using 900 ml PBS of pH 7.4. At 37.0 ± 0.5 °C & 50 rpm. At specific time intervals, 5ml sample from the solution of dissolution system was removed and replace the sample with a new dissolution medium. Through Whatman filter paper the samples were filtered. UV spectrophotometer was used to estimating the absorbance of these solutions at 242 nm.

4.3 Selection of optimized batch of solid dispersion

Based on the statistical evaluations using Design expert 12 statistical software, nine formulations batches were prepared according to Factorial design to find optimized batch of solid dispersion. The formulations batches were F1 to F9. With addition to this data from % DR and % drug content was observed to find out optimized batch.

4.4 Evaluation of pre-compression parameters of optimized solid dispersion

- **Bulk Density**

Known mass of the solid dispersion, transferred to a graded 100 ml cylinder. Level adjustments were made without compacting and apparent unsettled volume was measured. Using bulk density apparatus (Bio-technics, India). The following formula was used to quantify the apparent BD in gm/cm^3

Bulk Density (BD) = Wt. of granules/ Bulk volume.

- **Tapped density**

Known solid dispersion mass transferred in a cylinder of 100 ml. Original volume was observed. Originally, the cylinder tapped 100 times and checked the tapped volume. It was estimated by the given formula in gm/cm^3

Tapped density (TD) = Mass of the powder/ Tapped volume.

- **Angle of repose**

It was evaluated by the funnel technique. Approximately 3 gm solid dispersion was poured from a height of 6 centimetres into a level bench top through a glass funnel. The angle between side of the heap and horizontal plane was recorded.

It was calculated by:

$\tan \theta = h/r$

where,

θ - is the angle of repose; h- height; r- radius of powder cone.

- **Compressibility index**

Measurements of bulk density and tap density were used to estimate a material's Carr's index and Husner's ratio.

Carr's index (in %) = [(T D – BD)/tapped density] * 100

Hausner's ratio = Taped Density / Bulk Density

5.0 PREPARATION OF TABLETS OF OPTIMIZED SOLID DISPERSION

Tablets of optimized solid dispersion were prepared by direct compression method. Talc and Magnesium stearate were also used in tablet preparation. All the ingredients were mixed properly. The mixture of powders was compressed in to tablets using single punch tablet.

6.0 EVALUATION OF TABLETS OF OPTIMIZED SOLID DISPERSION

1. Weight variation test

Twenty tablets are selected randomly according to USP requirements for weight uniformity testing and their average weights were evaluated by using balance (Elder, Mumbai). The percentage weight differences were assessed and tested using USP specifications.

2. Thickness

Three tablets are taken randomly and their thickness was measured with a vernier calliper (Mitutoyo Co., Japan) as per pharmacopeial specification.

3. Hardness

Three tablets are randomly taken and hardness of the same was analysed via Monsanto hardness tester. The tablet's hardness was stated as kg / cm^2.

4. Friability

Using friability test apparatus (Bio-technics, India) the friability test is conducted according USP requirements. Because the tablet weight (500 mg) was always < than 650 mg, an accurate weighing of a random selection for complete tablets corresponding to 6.50gm and kept in a Roche Friability tester drum. Drum was revolved 100 times, extracting, de-dusting and measuring tablets correctly.

$$\%\text{friability} = \frac{\text{Original weight} - \text{End weight}}{\text{Original weight}} \times 100.$$

% Friability of tablets lower than 1.0 % is okay.

5. Disintegration test

The in-vitro disintegration test for tablets was carried out by means of the Disintegrating Test Apparatus. In each disintegration test apparatus tube, three tablets were placed separately and disks were put over each table. Medium was distilled water, kept at 37.00 ± 2.0 ° C and the time it took for each tablet to disintegrate totally was reported.

6. % Drug content

Crushing three tablets calculated the product content and dissolved powder equivalent to hundred mg of the medication in 100ml of PBS pH 7.4 filtered and with required dilution examined using UV-spectrophotometry at 242nm. The concentration of drug was estimated via a standard calibration curve.

7. % Drug release

Using the USP dissolution apparatus II, the analysis of *in-vitro* dissolution was carried out. The dissolution test was carried out using 900 ml PBS of pH 7.4. At 37.0 ± 0.5 °C & 50 rpm. At specific time intervals, 5ml sample from the solution of dissolution system was removed and replace the sample with a new dissolution. medium. Through Whatman filter paper the samples were filtered. UV spectrophotometer was used to estimating the absorbance of these solutions at 242 nm.

7.0 RESULTS AND DISCUSSION

7.1 PRE-FORMULATION STUDY

1. Solubility of drug

The test for solubility of the drug was carried out in different solvent. The results obtained are given in the table 1.

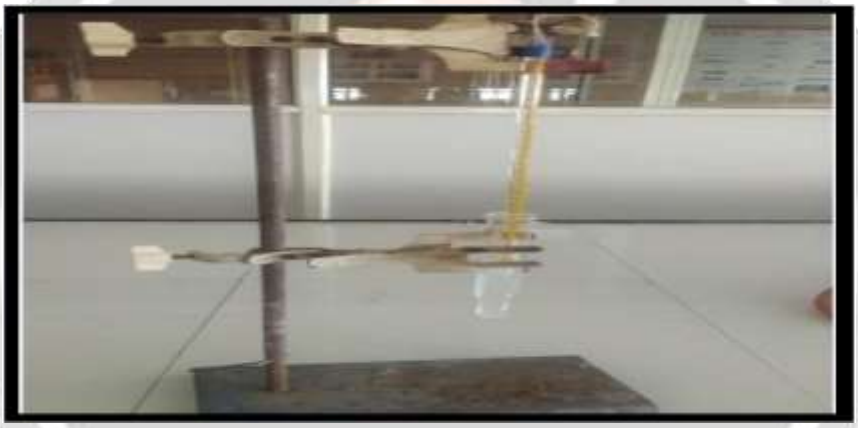
Table-1: The solubility of Carvedilol

Solubility	Solvent
Freely soluble	Dimethyl sulfoxide
Soluble	Methylene chloride, Methanol, Acetone
Insoluble	Water

2. Determination of melting point

Melting point of pure drug was determined by using capillary method. Melting point was noticed to be in range between 112-115 ^{0}C.

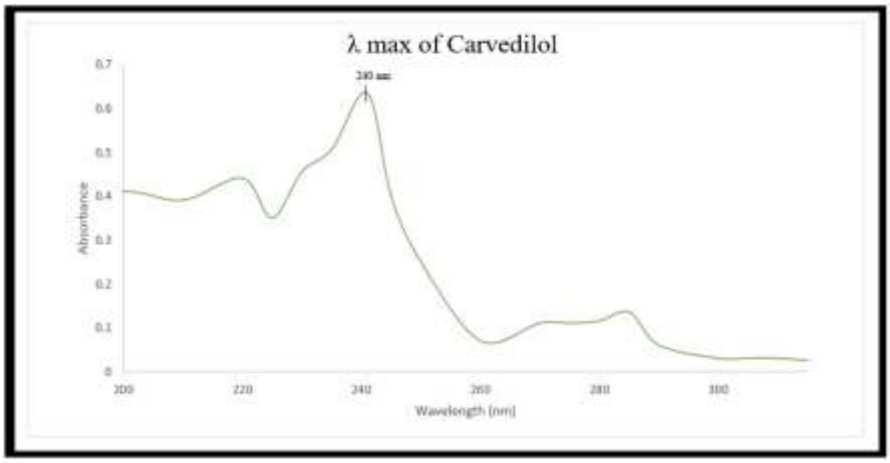
Fig-1: Melting point



3. Determining the λ max

The lambda max of drug Carvedilol was determined using UV Spectrophotometry. The standard solution of concentration 10µg/ml exhibited max absorbance at 240 nm.

Fig-2: λ max of Carvedilol



7.2 EVALUATION OF SOLID DISPERSION

1. Drug content (%)

The % drug content of solid dispersion was found to be in the range of 65.11% to 98.08 %. Batch F7 had the highest drug content. As the conc. of polymer PEG increases the % drug content also increases. The % drug content of all batches is shown in table 2.

Table-2: % drug content

Batch code	drug content (%)
F1	68.38 ± 0.27
F2	76.84 ± 0.11
F3	94.64 ± 0.09
F4	75.14 ± 0.04
F5	65.11 ± 0.34
F6	86.79 ± 0.17
F7	98.08 ± 0.15
F8	90.30 ± 0.18
F9	70.08 ± 0.21

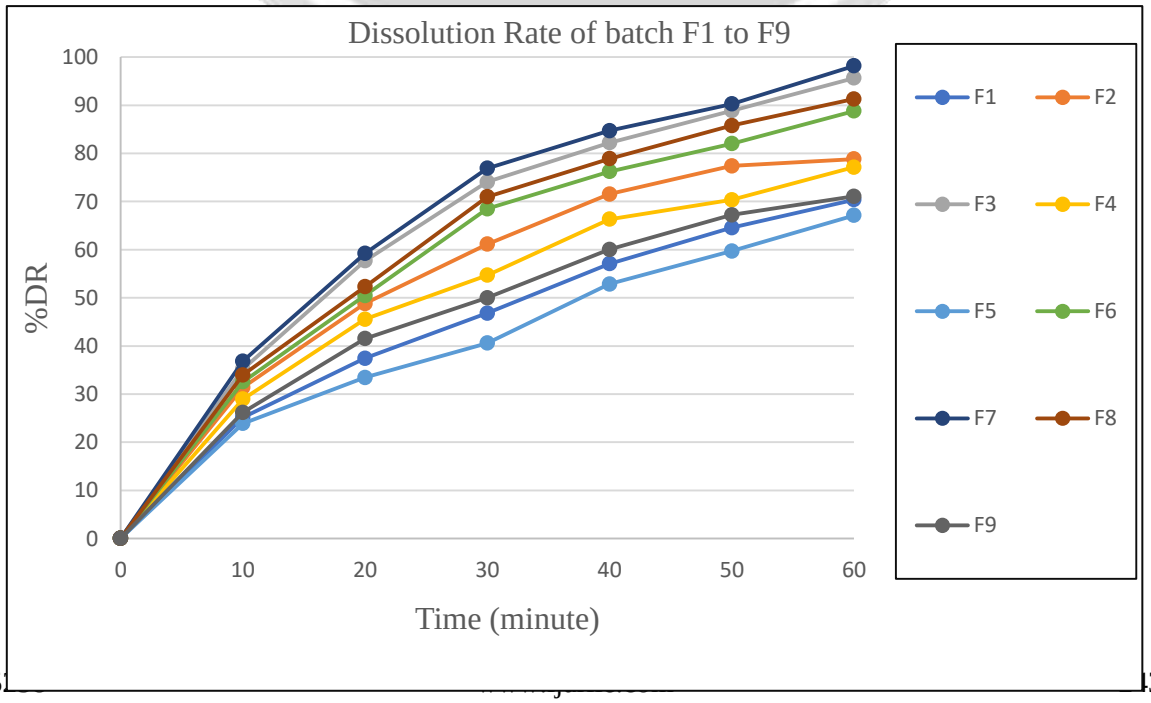
2. Percentage drug release

In-vitro drug release examinations of all the solid dispersion batches were performed. The study was performed for 60 minutes & drug release was calculated at different time intervals. It was found that, as concentration of polymer and exposure period to microwaves increased drug release also increased. All the batches showed drug release in range of 67.11 % to 98.18%. While batch F7 exhibited highest drug release of 98.18 %. The % drug release data of all batches is given in table 3.

Table-3: % Drug release

Time (Minute)	Drug release (%)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
10	25.16 ±0.15	31.37 ±0.51	35.19 ±0.74	28.94 ±0.32	23.90 ±0.81	32.54 ±0.68	36.81 ±0.70	33.96 ±0.52	26.18 ±0.81
20	37.42 ±0.22	48.81 ±0.12	57.68 ±0.11	45.55 ±0.39	33.43 ±0.24	50.47 ±0.42	59.21 ±0.04	52.29 ±0.36	41.51 ±0.26
30	46.81 ±0.09	61.12 ±0.61	74.06 ±0.72	54.67 ±0.29	40.59 ±0.14	68.47 ±0.59	76.89 ±0.13	70.98 ±0.92	49.99 ±0.47
40	57.08 ±0.51	71.54 ±0.08	82.22 ±0.05	66.31 ±0.44	52.86 ±0.27	76.23 ±0.33	84.70 ±0.20	78.89 ±0.43	60.03 ±0.10
50	64.55 ±0.23	77.39 ±0.15	88.88 ±0.32	70.36 ±0.08	59.72 ±0.11	82.01 ±0.21	90.26 ±0.71	85.79 ±0.16	67.23 ±0.35
60	70.38 ±0.27	78.84 ±0.34	95.64 ±0.07	77.14 ±0.19	67.11 ±0.17	88.79 ±0.39	98.18 ±0.26	91.30 ±0.08	71.08 ±0.66

Fig-3: In-vitro Drug release of batch F1 to F9



3. Selection of optimized batch of solid dispersion

Based on the statistical evaluations (design expert 12) and experimental data the optimized batch of solid dispersion found was batch F7 having drug to polymer ratio 1:5 and its exposure time to microwave radiation was 5 minutes.

7.3 PRE-COMPRESSION EVALUATION OF OPTIMIZED SOLID DISPERSION

Solid dispersion was evaluated for different pre-compression parameters. The data of evaluation is depicted in table 4.

Table-4: Pre compression evaluation

Parameters	Result
Bulk Density (gm/cm^3)	0.645
Tapped Density (gm/cm^3)	0.701
Angle of Repose(θ)	26.04
Carr 's Index	9.39
Hausner's Ratio	1.09

7.4 PREPARATION OF TABLETS OF OPTIMIZED SOLID DISPERSION

The ingredients used for tablet preparation are depicted in table 5.

Table-5: Preparation of tablets of optimized solid dispersion

Sr. No.	Ingredients	Quantity (mg/tablet)
1.	Solid dispersion of Carvedilol and PEG	480
2.	Talc	10
3.	Magnesium stearate	10
	Total weight	**500**

7.5 EVALUATION OF TABLETS OF OPTIMIZED SOLID DISPERSION

The tablets were evaluated for various post compression parameters and dissolution studies also carried out. All results are found in standard ranges as per USP. All the data of post compression parameters is given in table 6.

Table-6: Post-compression parameters

Parameters	Result
Weight Variation (mg)	496 ± 0.72
Thickness (mm)	4.1 ± 0.29
Hardness (kg/cm^2)	4.83 ± 0.21
% Friability	0.49 ± 0.19

Disintegration Time (sec)	54
Drug Content (%)	98.45 ± 0.12
%DR at 60 min	97.06 ± 0.24

7.6 COMPARISON BETWEEN MARKETED TABLET AND OPTIMIZED SOLID DISPERSION TABLET

1. Comparison of %DR between marketed, optimized solid dispersion and pure drug tablet

To find out the drug release efficiency of optimized solid dispersion tablet, its dissolution rate was compared with marketed tablet and tabled prepared from pure drug. And it was found that, optimized solid dispersion tablet had highest dissolution rate. The data of comparison is depicted in table 7.

Table-7: Comparison of %DR between marketed, optimized solid dispersion and pure drug tablet

Time (minute)	%DR		
	Marketed tablet	Optimized solid dispersion tablet	Pure drug
0	0	0	0
10	46.53	35.87	9.65
20	61.23	57.91	14.79
30	70.56	76.10	17.30
40	79.12	83.68	20.10
50	85.27	89.36	22.37
60	93.68	97.06	24.49

2. Comparison of Post-compression parameters between marketed and optimized solid dispersion tablet

The data for Comparison of Post-compression parameters between marketed and optimized solid dispersion tablet is depicted in table 8.

Table-8: Comparison of Post-compression parameters between marketed and optimized solid dispersion tablet

Parameters	Result	
	Marketed Tablet	Optimized solid dispersion Tablet
Weight Variation (mg)	Pass	496 ± 0.72
Thickness (mm)	3.8 ± 0.34	4.1 ± 0.29
Hardness (kg/cm^2)	5.3 ± 0.17	5 ± 0.21
%Friability	0.68 ± 0.22	0.49 ± 0.19
Drug Content (%)	96.71 ± 0.19	98.45 ± 0.12

4. CONCLUSION

From this study, it was found that dissolution rate and solubility of carvedilol increased after preparation solid dispersions using microwave fusion method. Solubility studies exhibited the solubilizing effect of polymer properties on carvedilol. Solubility studies showed increased dissolution rate of carvedilol after preparation solid dispersions indicated that amorphization of drug was successful. The results obtained from evaluations of pre-compression and post compression parameters are within the standard limits. It is

possible to formulate tablets of optimized solid dispersions of carvedilol using direct compression method. The comparison data between optimized solid dispersion tablet showed faster drug release than marketed tablet. From the data obtained, it is clear that a higher carrier concentration and exposure to microwaves increases the drug release. Hence, solid dispersion prepared using microwave fusion method is one of efficient methods used to enhance the solubility and dissolution rate of poorly water-soluble drug.

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