

Research Article



Enhancement of Solubility and Dissolution Rate of Carvedilol by Using Fluidized-bed Granulation Technique.

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ABSTRACT

Carvedilol is a non-selective beta- blocker with alpha-1-receptor blocking activity. Carvedilol drug is widely used in treatment of cardiovascular disease. Carvedilol is belonging to BCS Class II drug, It characterized by poor water solubility and high permeability. The main objective of this study is to enhance the solubility and dissolution rate of Carvedilol drug to achieve desired concentration of drug in systemic circulation for achieving the required pharmacological response by using Novel technique i.e., fluidized bed granulation technique by using wide variety of carriers such as PVP K30, Poloxamer 188 as a super disintegrant. The formulation F6 showed Enhance Solubility and Dissolution rate of Carvedilol drug released approximately 95.18% for 30min. So, it was selected as the best formulation among all the nine formulations.

Keywords: Carvedilol, Fluidized bed granulation technique, Dissolution, Solubility.

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INTRODUCTION

The Drug is administered by the oral route it go through a next process that are dissolution and permeation across the gastrointestinal membrane before they reach in systemic circulation. Number of factors that are affect in bioavailability of the drug, one of the major factor is that solubility and dissolution. Solubility of drug aqueous gastrointestinal fluid is major problem with the most drugs. At least 40% of newly developed chemical entity tested are drug having poor aqueous solubility this leads to fluctuating the bioavailability Among the various solubility enhancement technique, Solid dispersion is most preferable and effective strategies to enhance the solubility, dissolution rate, and oral bioavailability of poorly aqueous soluble drugs. In solid dispersion method reduction in particle size and an increase in surface area of poorly water-soluble drugs, resulting in enhanced solubility and dissolution rate. The main objective of this study is to enhance the solubility and dissolution rate of Carvedilol drug to achieve desired concentration of drug in systemic circulation for achieving the required pharmacological response by using Novel technique i.e., fluidized bed granulation technique. FBG used in this study over conventional granulation method because instability due to huge ratio of excipients to drug to drug substances. Chemical instability due to drug having greater surface exposure excipients, moisture and

manufacturing equipments. Low potency due to manufacturing loss. Variations in content uniformity can cause more problems in low dose drug than high dose.

Fluidized Bed Processor

In 1953 Dale Wruster invented the coating of tablets by spraying the coating solution on tablets bed stream of warm air suspended in warm air in 1953 this process also known as wruster process. In 1960 Dr. Dale Wruster further carried out the granulation of powders.

Fluid bed processing involves coating, granulation, drug layering and drying of particulate material.

Fluidized Bed Granulation^{1-7, 19, 30}

Granulation is also known as agglomeration. Fluidized bed granulator (FBG), a highly economical and efficient one pot process, is a popular technique in the pharmaceutical industry for achieving particle size enlargement. Fluidized bed granulation technique recently, a method for preparation of solid dispersion using fluid bed granulation process. Solid dispersion using fluidized bed granulation process has been attracting attention as a manufacturing process because it overcomes so many drawbacks and problems arising in other multistep granulation and solid dispersion manufacturing processes. With the help of fluid bed granulator, we can perform several unit operations, such as preblending, drying and granulation and the granules produced in this process are processed by tableting process and filling in capsule shell. This is important for scale up. Manufacturing process steps get reduces in fluidized bed granulation therefore requires less manufacturing time. Handling of raw materials also reduced by the fluid bed granulation and drying, and therefore reduces operator exposure to toxic and irritating compounds. Fluidized bed granulation it is the critical



process in which both process and product variables affects the various characteristics of the granules.

Principle

The fluid bed it is the bed of powder material or solid particle bed. The hot air passed at high pressure through the air distribution plate which is place in bottom then particles are lifted from bottom and suspended in air stream this process known as fluidization process. Fluid bed granulation process involves the spraying of binder solution, dispersion or suspension onto a physical mixture i.e. powder bed, where particles are suspended in air stream. These particles are wet by binder solution and when they collide to each other then formation of the liquid bridges and then dried which leads to acquisition of granules.

Advantages

- To improve compressibility for tableting & Continuous operation.
- Applicable for large or small-scale operations & saving labor cost.
- Time and cost effective. Improve housekeeping and workers safety.

Disadvantages

- Cleaning was labor intensive and time consuming
- Due to the complexity of fluidized bed behavior, there are often difficulties in attempting to scale-up from smaller scale to industrial units

In present study we are going to Enhance solubility and dissolution rate of different formulations of Carvedilol by using Novel technique such as Fluidized bed granulation technique. We also focus on the formulate granules by using fluidized bed granulation technique (FBP – Top spraying). And to study the effect of process on dissolution efficiency of carvedilol. And other formulation related properties by applying suitable optimization techniques for the development of formulation using control

Method of Preparation

strategies. Finally, we are going to compare the Optimized formulation of Carvedilol with marketed formulation.

MATERIALS^{13,14,15,21,26}

Carvedilol obtained from IPCA Pharmaceuticals, PVP K30, poloxamer 188, citric acid, coloring agent, magnesium stearate, lactose, talc.

Preformulation Study^{21,27,28}

- a) **Organoleptic Properties** – Color, odor, appearance
- b) **Solubility** – Solubility was observed in various solvent
- c) **Melting point** - Determined by using Thiele's tube technique.

d) Ultraviolet visible (UV) spectroscopy^{21, 27,28}

Wavelength of maximum absorption (λ max) determination

Stock solutions (100 μ g/ml) of Carvedilol were prepared in methanol. The UV spectrum was recorded in the range 200-400 nm by using UV spectrophotometer. The wavelength of maximum absorption (λ max) was determined.

Preparation of Carvedilol standard stock solution (100 μ g/ml) in Methanol

A standard stock solution – Dissolving accurate weighed 10mg of Carvedilol in small quantity of methanol in 100ml of volumetric flask. The volume was then make up to 100ml using methanol to obtain a stock solution of 100 μ g/ml.

Standard calibration curve of Carvedilol in HCL pH 1.45

Accurately weighed 10 mg of Carvedilol was dissolved in 100 ml of Methanol to produce a 100 μ g/ml concentration stock solution. The aliquots 2, 4, 6, 8, 10ml of stock solution pipette out into 10 ml volumetric flask. The volume was made up to the mark with HCL pH 1.45. This dilution gives 20, 40, 60, 80 and 100 μ g/ml concentration of Carvedilol respectively. Then all solutions were scanned at wavelength (max 242nm using UV spectrophotometer against the blank solution of HCL pH 1.45).

Table 1: Formulation code for each Batch

Sr. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Carvedilol	12.5mg	12.5mg	12.5mg	12.5mg	12.5mg	12.5mg	12.5mg	12.5mg	12.5mg
2.	PVP K30	10%	15%	12.5 %	10%	12.5%	15%	12.5%	10%	15%
3.	Poloxamer 188	5%	10%	7.5%	7.5%	5%	7.5%	10%	10%	5%
4.	Citric Acid	1 mg	1 mg	1 mg	1 mg	1mg	1 mg	1 mg	1 mg	1 mg
5.	Mg.Stearate	2 mg	2 mg	2mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
6.	Talc	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
7.	Color	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
8.	Lactose	Upto 200 mg	Upto 200 mg	Upto 200 mg	Upto 200 mg	Upto 200 mg	Upto 200 mg	Upto 200 mg	Upto 200 mg	Upto 200 mg



Method of Preparation

Using a top spray technique in fluidized bed granulator solid dispersion granules was prepared. Polymer (PVP K30) and nonionic surfactant (Poloxamer 188) were dissolved in methanol. Then Carvedilol powder slowly added in solution and stirred for 5 min to obtained homogenous state. This resulting solution was sprayed under appropriate conditions i.e. Spray rate(1.50- 2 rpm), Atomizing air pressure(1.0-1.5 bar), Product temperature (40-50 ° C), Inlet temperature (50-60 ° C), Fluidizing pressure (1.0-1.5 bar)on flowing mixture it contain citric acid, lactose, talc in fluidized bed granulator simultaneously fluidizing air passed and granules was dried. Granules were prepared accordingly to the amount which is described in formulation table. After the formation of granules in fluidized bed granulator an additional drying process was carried out for 15-20 min. for lubrication efficacy magnesium stearate was added in obtained solid dispersion granules and powder containing the solid dispersion granules was passed through a sieve and then compressed into tablets.

Evaluation 6,7, 8, 9, 10-25, 31, 32

Pre-Compression evaluation

Bulk density

Apparent bulk density was determined by pouring a weighed quantity of powder into graduated cylinder and measuring the volume of packing.

Bulk density = Weight of the powder / Volume of the packing

Tapped density

Tapped density was determined by tapping method. Weighed quantity of powder was placed in a graduated cylinder, after the initial volume was observed, and tapped until no further change in volume of powder was noted and the volume of tapped packing was noted.

Tapped density = weight of the powder / volume of the tapped packing

Angle of repose (θ)

Angle of repose was determined by using fixed funnel method. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by the angle of repose.

$$\tan\theta = h / r \quad \text{or} \quad \theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, h, is height of pile, r is radius of the base of the pile,

Hausner's ratio

Hausner's ratio is an indirect index of ease of power flow.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

% compressibility index

(%) Carr's Index can be calculated by using the following formula

$$\text{Car's consolidation index \%} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

Post-Compression parameters

Hardness test

The hardness of the tablets was determined using Digital Hardness tester. It is expressed in Kg/cm². Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability test

The friability of tablets was determined by using Electro lab, USP EF 2 friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_{initial}) and transferred into friabilator. The friabilator was operated at 25 RPM for 4 minutes. The tablets were weighed again (F_{final}).

$$F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100$$

% Friability of tablets less than 1% is considered acceptable.

Weight variation test

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed. Average weight of a tablet -200mg or less their % deviation was 10 %; More than 190 mg and less than 200 mg- % Deviation was 7.5 %; or more average weight tablet than 200 mg – and 5 their % deviation was 5 %.

Uniformity of thickness

The thickness of individual tablet may be measured with a digital vernier calliper, which permits accurate measurements and provides information on the variation between tablets.

Drug content ²¹

Weighed tablets (5) were powdered using glass mortar and pestle. Accurately weighed quantity of powder equivalent to 12.5 mg of carvedilol was taken into 50 ml volumetric flask dissolved in methanol and the solution was filtered through whatmann filter paper. The filtrate was collected and suitably diluted with methanol to volume to prepare a solution having a known concentration of about 0.125 mg per mL. The drug content was determined at 241 nm by UV- Spectrophotometer should compare with that of a reference standard solution similarly prepared.



Disintegration time

The disintegration time of the tablets was determined as per Indian pharmacopoeia. The test was carried out using tablet disintegration apparatus. 900 ml Distilled water was used as a disintegrating media at 37 ± 0.2 °C. The time required to obtain complete disintegration of all the tablets were noted.

In vitro drug release ²¹

In vitro Release of the drug was determined by estimating the dissolution profile, USP II Paddle apparatus was used and paddle was allowed to rotate at 50 rpm, Hydrochloric acid adjusted to pH of 1.45, (900 ml) was used as a dissolution medium. Temperature of dissolution medium was 37 ± 0.5 °C 5ml samples were withdrawn at predetermined intervals upto 30 min and replacements were done with fresh dissolution medium. The samples were suitably diluted and analyzed for drug content Absorbance measured at 242 nm by UV spectroscopy.

Comparative Study With Marketed Preparation

In this test comparison of different parameters of formulation like weight, color, shape, weight variation, friability, hardness, diameter, drug content, Disintegration time and % CDR. This all are the parameters will compared with Marketed formulation.

Saturation Solubility

Preparing saturated solution of pure drug and its granules by using FBG Technique in constant volume of distilled water, acidic buffer (pH 1.45). These mixtures were stirred in a mechanical shaker for 24 Hrs at room temperature. Visual inspection was carefully made to ensure there were excess particles in the mixture, indicating saturation has been reached. Aliquots from each sample were filtered through 0.45 µm whatman filter paper and filtrate was diluted suitably to determine the saturation solubility of samples. Drug solubility was evaluated spectrophotometrically using UV visible spectrometer at 242 nm using respective medium as a reference. Saturation solubility measurements were performed in triplicate.

Stability Studies ²⁹

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf life and recommended storage conditions.

RESULTS AND DISCUSSION

Preformulation study

Identification and Characterization of drug

Organoleptic properties

Carvedilol has white color, Odorless, Crystalline powder. Hence, the all characteristics of drug are complies as per I.P. 2014 therefore it's confirmed that the model drug has good properties.

Melting point

The melting point was determine by capillary method and it was found to be $116-117$ °C (observed value) and $114-115$ °C (standard value). I.e. the melting point of Carvedilol was complies with I.P. 2014

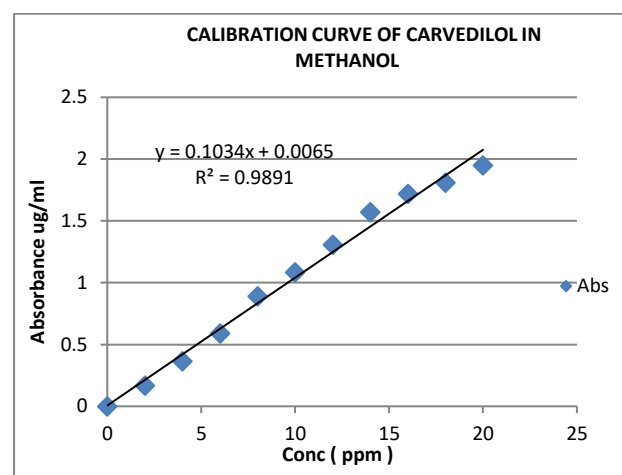
Solubility

The solubility of Carvedilol was checked in different solvents like Methanol (Freely soluble), Chloroform (soluble), Ethanol (Sparingly Soluble), Water (insoluble) etc.

UV-Spectrum of Carvedilol ^{23, 24}

Determination of λ max of Carvedilol in Methanol

The Ultra-violet spectroscopic absorbance of Carvedilol was done in Methanol at the 242 nm max.



The equation of the regression line was obtained $Y=0.103X+0.006$ and the correlation coefficient was obtained 0.989. The calibration curve yields a straight line, which shows that the drug follows Beer's law in the concentration range 2 to $20 \mu\text{g/ml}$.

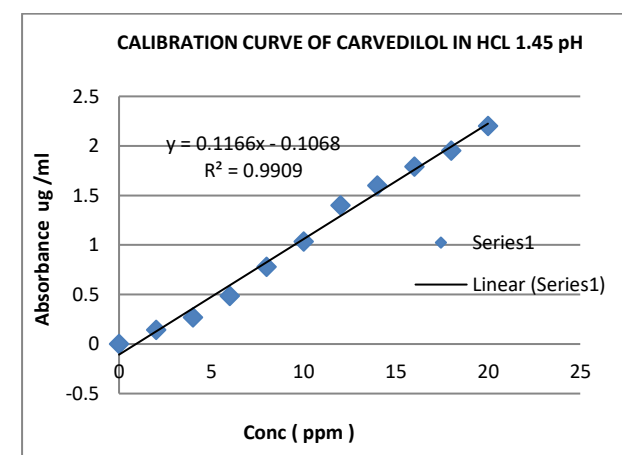


Figure 1: Calibration curve of Carvedilol in a) Methanol b) HCL pH 1.45

The equation of the regression line was obtained $Y=0.116X-0.106$ and the correlation coefficient was obtained 0.990.

Evaluation of Final Batches

Table 2: Pre-compression evaluations of formulations

Sr. No.	Formulation Code	Bulk Density ($\mu\text{g/ml}$)	Tapped Density ($\mu\text{g/ml}$)	Carr's Index (%)	Hausner's Ratio	Angle of Repose ($^{\circ}$)
1	F1	0.48	0.602	20	1.25	26.29
2	F2	0.4	0.5	20	1.25	27.02
3	F3	0.254	0.31	18.06	1.22	25.3
4	F4	0.62	0.78	20.5	1.25	28.41
5	F5	0.385	0.394	15	1.19	28.2
6	F6	0.345	0.399	13.53	1.15	24.21
7	F7	0.278	0.452	16.3	1.6	26.32
8	F8	0.258	0.324	20.3	1.27	25.48
9	F9	0.61	0.72	15.49	1.18	26.32

DISCUSSION

The bulk density, tapped density, Angle of repose, Carr's index and Hausner's ratio obtained for all the formulations

which is in the good or in the acceptable range and All these results indicated that, the powder mixture possess good flow of powder and compressibility properties.

Table 3: Post-compression evaluation of formulations

Sr. No.	Formulation Code	Weight Variation (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	D.T. (min/sec)	Drug Content (%)
1	F1	198	8	3.61	4.35	0.81	2	89.76
2	F2	200	8	3.64	4.2	0.83	2.1	87.67
3	F3	195	8	3.68	4.28	0.92	2.2	92.76
4	F4	198	8	3.63	4.3	0.9	1.5	93.56
5	F5	197	8	3.7	4.27	0.98	1.5	91.22
6	F6	199	8	3.68	4.37	0.95	1	98.7
7	F7	197	8	3.72	4.3	0.92	2	88.78
8	F8	198	8	3.68	4.24	0.94	2.5	91.31
9	F9	192	8	3.62	4.2	0.91	1.7	94.42

Discussion

The weight variation, diameter, Thickness, Hardness, friability, and Disintegration time obtained for all the

formulations in the range which is in the good or in the acceptable range.

Dissolution Study of Final Batches:

Table 4: *In-vitro* dissolution study of Different formulation

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	19.73	20.11	22.13	20.67	25.71	30.16	28.14	25.20	28.41
10	25.67	28.19	30.68	35.10	40.22	48.71	31.67	38.41	42.10
15	38.18	41.67	42.20	45.91	48.67	55.10	40.78	43.67	49.89
20	47.61	48.16	46.87	49.28	66.17	73.24	64.23	60.79	70.22
25	56.98	57.88	58.12	65.38	75.12	85.82	70.88	66.23	81.12
30	66.53	68.21	68.89	72.88	80.45	95.18	76.42	75.61	81.66



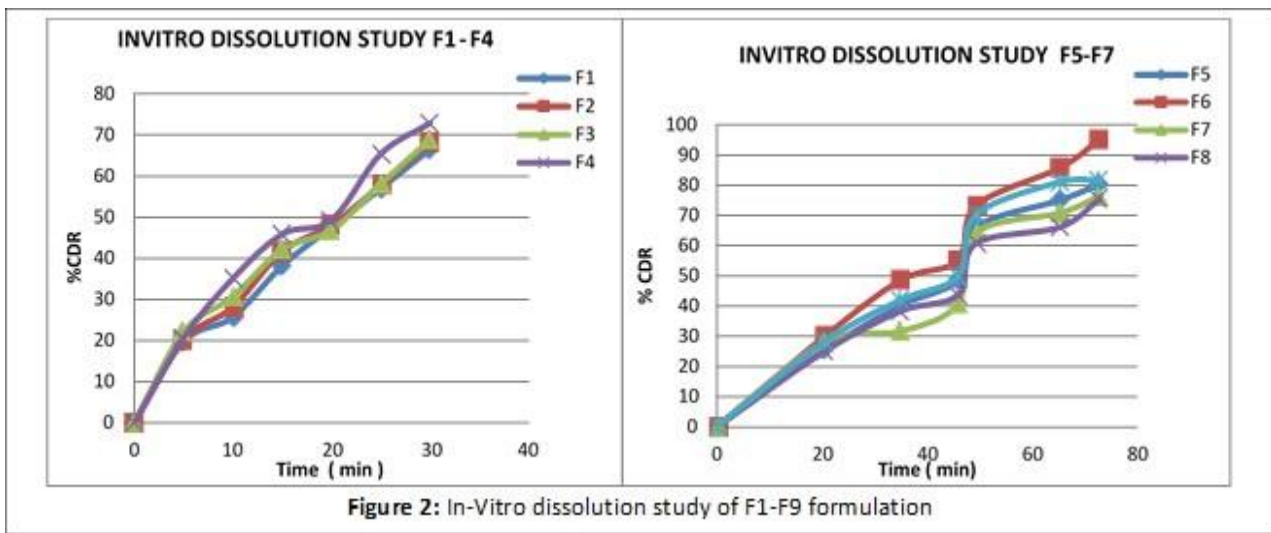


Figure 2: In-Vitro dissolution study of F1-F9 formulation

Formulation F6 shown best appropriate drug release rate.

Comparison of in-vitro dissolution study of pure drug (carvedilol), marketed formulation and optimized formulation.

Table 5: In-Vitro Dissolution Comparative Study

Time(min)	PURE DRUG (P.D)	MARKETED PRODUCT (M.P)	OPTIMIZED PRODUCT (F6) (O.P.)
0	0	0	0
5	8.21	50.21	35.16
10	9.78	59.43	48.71
15	12.53	69.12	65.1
20	16.05	80.15	78.24
25	20.61	88.83	85.89
30	27.1	94.92	95.18

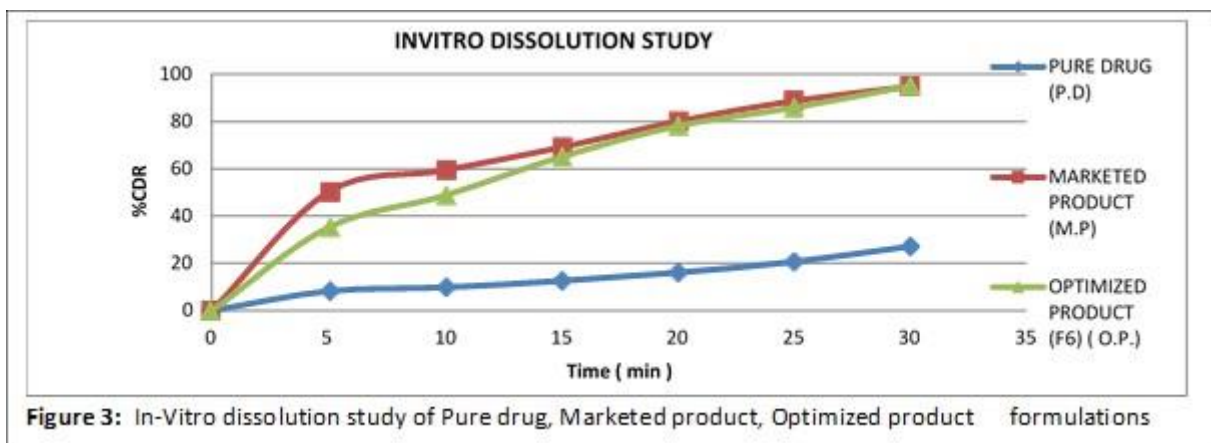


Figure 3: In-Vitro dissolution study of Pure drug, Marketed product, Optimized product formulations

Saturation Solubility

The saturation solubility study of pure drug and prepared granules in different physiological mediums. The results of solubility study indicated that Carvedilol granules possess a very high solubility in all physiological medium than pure

drug. The saturation solubility of Carvedilol pure drug in distilled water and HCL pH 1.45 medium was found to be 8.58 ug/ ml and 7.98 ug/ ml. And the saturation solubility of Carvedilol granules in distilled water and HCL pH 1.45 medium was found to be 21.49 ug/ ml and 130 ug/ ml.

Comparative Study (Marketed preparation)

Stability Study

There was no physical change in color. There is no any significant change in the weight variation, drug content, %CDR, and friability of tablets in comparison with the

initial samples of optimized batch. This formulation stable at 2 months.



Table 6: Comparative study of optimized formulation with marketed formulation

Test	Optimized formulation	Marketed formulation
Weight	200mg.	200mg.
Color	Orange	Yellow
Shape	Rounded	Rounded
Weight variation	199mg.	199mg
Friability	0.95%	0.70%
Hardness	4.37kg/cm ²	5.012 kg/cm ²
Diameter	8mm.	8mm.
Drug content	98.70%	99.69%
Disintegration time	1min / (60 sec)	51.20 sec
% CDR	95.18%	94.92%

CONCLUSION

This study demonstrate that the method, Fluidized Bed Granulation technique is suitable for the Enhancement of Solubility and Dissolution rate of Carvedilol drug by using various hydrophilic and hydrophobic polymers for in-vitro studies of Carvedilol Tablet. Different polymers like PVP K30 and Poloxamer 188. However, the granules produced by FBG technique it showed good flowability and other parameters, indicating that this technique seems to be the best alternative for large production of solid dosage forms. The formulation F6 showed Enhance Solubility and Dissolution rate of carvedilol drug released approximately 95.18% for 30min. So it was selected as the best formulation among all the nine formulations.

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