International Journal of Medicine and Pharmaceutical Research

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Research Article **Open Access**

Development and Evaluation of Carvedilol Oral Disintegrating Tablet by Solid Dispersion Technique

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A B S T R A C T

Carvedilol is a poorly water soluble oral antihypertensive agent. An attempt has been made to develop fast dissolving the tablet of carvedilol by direct compression and solid dispersion technique the solid dispersion of carvedilol with peg-4000(1:4 molar ratio) by fusion extrusion method with a view to enhance the water solubility. The fast dissolving tablets were prepared using different concentrations of super disintegrants such as cross carmellose, sodium starch glycolate, cross povidone, the formulations were evaluated for physicho-chemical parameters, subjected to disintegration and dissolution test. When super disintegrating agents were added in one formulation, an increase in the disintegration time and *in-vitro* cumulative percent drug dissolution was observed.

Keywords: Fast disintegrating tablet, Super disintegrants, Carvedilol, Solid dispersion.

A R T I C L E I N F O

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Article History: Received 21 June 2015, **Accepted** 25 July 2015, **Available Online** 10 August 2015

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Manuscript ID: IJMPR2633

PAPER-QR CODE

Citation: Balachandrudu, et al. Development and Evaluation of Carvedilol Oral Disintegrating Tablet by Solid Dispersion Technique. *Int. J. Med. Pharm, Res*., 2015, 3(4): 1115-1119.

1. Introduction

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms [1, 5]. For many decades treatment of an acute disease or chronic illness has mostly Carvedilol

accomplished by delivery of drugs to patients using conventional drug delivery system [2,4,7].

Even today these conventional drug delivery systems are the primary pharmaceutical products commonly seen in the prescription. Conventional oral drug products are formulated to release the active principle immediately after oral administration to obtain rapid and complete systemic drug absorption. Systemic drug absorption from a drug product consists of a succession of rate process for solid oral, immediate release drug products [10-14].

The rate process includes

a. Dissolution of the drug in aqueous environments.
b. Absorption across cell membranes into systemic circulation.

Definition of solid dispersions:

Chiou and Riegelman defined the term solid dispersion as a "dispersion of one or more active ingredients in an inert carrier or matrix at a solid state prepared by the melting (fusion), solvent or melting solvent method [8,9,15,16]. Carvedilol is a mixed alpha beta blocker used in the treatment of conjestive heart failure and as anti hypertensive drug. Carvedilol produces its anti hypertensive effect partly by reducing total peripheral resistance by blocking alpha1 adreno receptor and by preventing beta-adrenoreceptor mediated compensatory mechanisms. This combined action avoids many of the un wanted effects associated with traditional beta-blocker or vasodilator theraphy [6].

Carvedilol is an alpha and a beta adrenoreceptor-blocking agent used in the treatment of various cardiovascular disorders such as angina pectoris, cardiac arrhythmia and hypertension.[17,18] Carvedilol is indicated for the treatment of mild to severe chronic heart failure, Left ventricular dysfunction following myocardial infraction in clinically stable patients and hypertension. [19, 20]

Carvedilol is a poorly water-soluble oral antihypertensive agent, with problems of variable bioavailability and bio-equivalence related to its poor water-solubility. In present work attempt will be made to design and evaluation of Fast dissolving tablets of Carvedilol for the effective management of angina pectoris, hypertension etc.[21] In view of substantial first pass effect and its shorter plasma half life therefore is an ideal drug candidate for Fast dissolving drug delivery system.

2. Materials and Methods

Carvedilol was found to the Amoli organics Pvt. Ltd. Microcrystalline cellulose were obtained from Gift Sample from KAPL, Bangalore, Magnesium stearate was obtained from Himedia Laboratories, Mumbai, Cross povidone was obtained from Gift Sample from KAPL, Bangalore.

Evaluation of Carvedilol Solid Dispersions:

Estimation of Drug Content:

A quantity, which was equivalent to 10 mg of drug, was accurately weighed and transferred to 100ml volumetric flask. Then the volume was made up with, PH-6.8 phosphate buffer and shaken or 10 min to ensure complete solubility of the drug. Then the solution was filtered. Same concentration of standard solution was prepared by dissolving 10 mg of standard drug in PH-6.8 phosphate buffer. For both the sample and standard solutions absorbance was measured at 275 nm in UV-Visible spectrophotometer are shown in table-20.

***In-vitro* dissolution study:**

The prepared solid dispersions were subjected to *in-vitro* dissolution. Dissolution test was carried out using USP23 paddle method [apparatus 2]. The stirring rate was 50 rpm, PH-6.8 phosphate buffer was used as dissolution medium and dissolution medium was maintained at 37±1^{o}C. Samples of 5 ml were withdrawn at regular intervals of time, filtered and replaced with 5 ml of fresh dissolution medium, dilutions were made wherever necessary and were analyzed for Carvedilol at 275 nm by using UV-visible spectrophotometer

X-ray diffraction:

The crystalline state of the different samples was evaluated with X-ray powder diffraction. Diffraction pattarns were obtained using XPERT-PRO diffractometer(PANanalytical) with a radious of 2240nm.The cu and kα radiation (kα1.54060A^{0}) was Ni filtered.A system of diverging and receiving slitsof 1^{0} and 0.1nm recepetively was used. The patteren was collected with 40kv of tube voltage and 30mA and scanned over the 2_{ψ} range og of 5-60^{0}.

Evaluation of Tablets:

Hardness, Friability, Weight variation, Estimation of drug content, Disintegration, Uniformity of dispersion.

Stability Studies:

In designing a solid dosage form it is necessary to know the inherent stability of the drug substance, to have an idea of what excipients to use, as well as how best to put them together with the drug and to know that no toxic substance are formed Limits of acceptability and therefore compromises must be reasonably defined.

3. Results and Discussion

Evaluation of Carvedilol Solid Dispersions:

Estimation of drug content:

Table 1: Drug content of prepared solid dispersions:
(Avg of three determinations)

Solid Dispersions	Drug: Carrier	Ratio	% of Carvedilol Present
Solid dispersion 1	Carvedilol: PEG (4000)	1:1	99.0
		1:2	99.5
		1:3	98.0
		1:4	97.8
Solid dispersion 2		1:1	99.0
		1:2	98.5
		1:3	98.0
		1:4	99.5
		1:1	97.5
		1:2	99.0
Solid dispersion3		1:3	99.5
		1:4	98.0

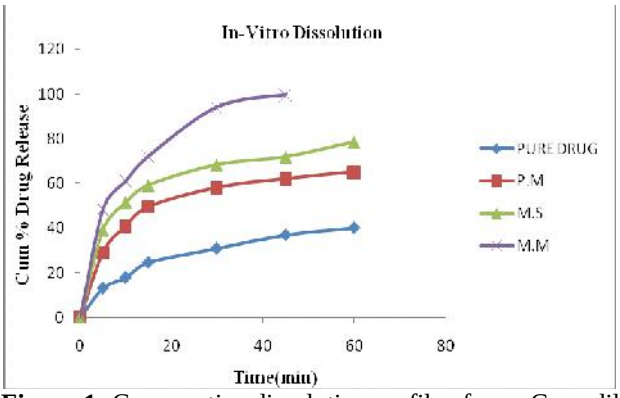

Figure 1: Comparative dissolution profile of pure Carvedilol and Carvedilol: PEG (4000) (1:4)

The drug content was estimated in the prepared dispersions was found to be uniform with low S.D. values. The best prepared dispersion that is CARVEDILOL: PEG (4000) (1:4) MM was tested for reproducibility of the method by preparing three batches of solid dispersion containing CARVEDILOL: PEG(4000) (1:4) MM under similar set of conditions. The yield was found to be 99.0%, 99.5% and 98.0% respectively in the three different batches prepared.

***In- vitro* dissolution studies:**

Dissolution of Carvedilol was increased in carrier dispersions prepared by physical mixture, melt solvent method and by melting method when compared to pure drug.

Dissolution of Carvedilol was increased in carrier dispersions prepared by physical mixture, melt solvent method and by melting method when compared to pure drug.

X-ray diffraction:

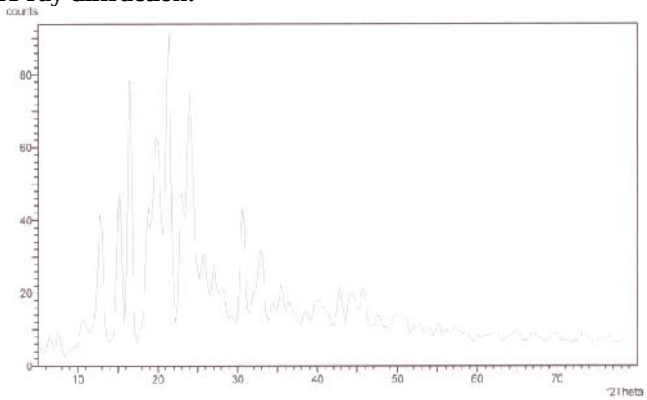

Figure 2: X-ray Diffraction spectra for Carvedilol

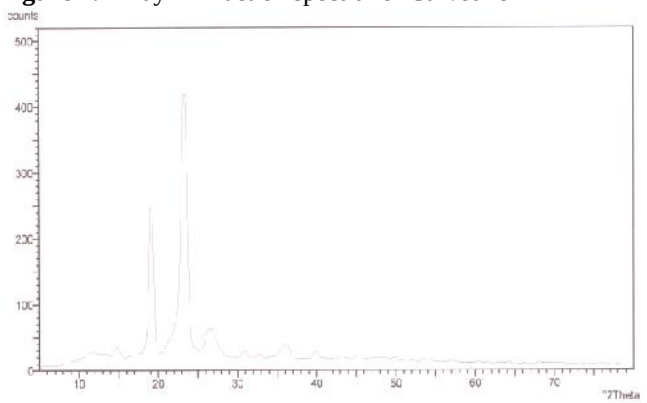

Figure 3: X-ray Diffraction for PEG (4000)

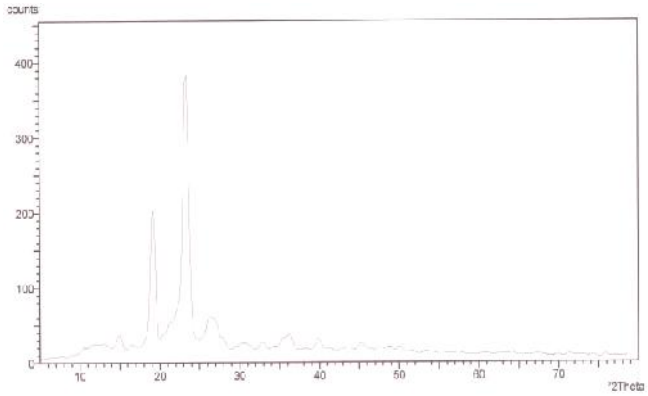

Figure 4: X-ray Diffraction for Carvedilol:PEG (4000)(1:4)

XRPD of pure Carvedilol shows sharp intence peaks in between 20-25 theta and 90-95 counts. XRPD of PEG4000 shows peaks in between 20-25 theta and 400-500 counts. XRPD solid dispersion of CARVEDILOL and PEG4000 (1:4) shows peaks in between 20-25 and 80-90 counts.

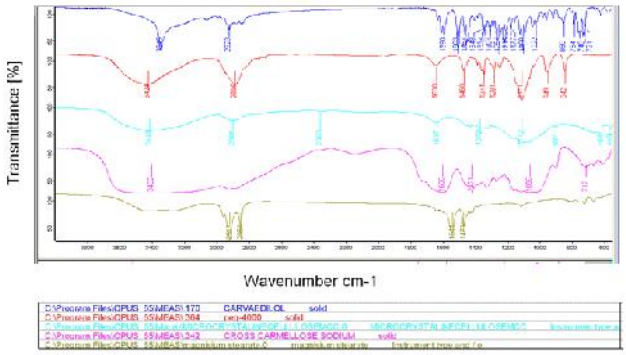

Figure 5: FT-IR Interpretation Spectra for Optimized Formula

FT-IR spectra of pure Carvedilol, PEG (4000), CCS, SSG, Carvedilol: PEG (4000) (1:4) (MM) and CARVEDILOL: PEG (4000) (1:4) (MM) with CCS was shown in Figs. FT-IR spectrum of pure CARVEDILOL was shown in Fig.4. The characteristic peaks of CARVEDILOL spectrum are 3342.92 due to N-H stretching, 1590.23 due to C-O stretching, 1503.26 due to N-H stretching, 2923.10 due to O-H stretching.

FT-IR spectrum of CARVEDILOL: PEG(4000) (1:4) (MM) with CCS was shown in Fig. 10, CARVEDILOL : PEG(4000) with CCS spectrum shows characteristic absorption peaks 344121.92 due to complex, 3342.92 due to N-H stretching, 2923.10 due to O-H stretching, 1590.23 due to C-O stretching,1503.26 due to N-H stretching. FTIR spectra of optimised formulation shows the same characteristic peaks related to Carvedilol without any significant spectral shift, hence this suggests that there is compatibility between the drug and excipients. All the micrometric properties and physical parameters of tested formulations were found to be within the acceptable range. The maximum % of drug release for the tested formulations are 68.12 ±0.5,63.10±0.5,62.18±0.8 at 60 minutes interval for the formulations F1,F2&F3 and 99.22 ±0.8, 98.22±0.8,

97.18±0.2 at 45 minutes interval for the formulations F4, F5& F6 respectively. The comparative dissolution profile of Carvedilol and Carvedilol: PEG 4000(1:4) (MM) tablets were performed and analysis that both of them follows first order kinetics. Stability studies of the optimized formulation was performed and confirmed that it is stable for 3months.

Table 2: Formulation of carvedilol tablets:

S. No	Ingredients	F1	F2	F3	F4	F5	F6
1	Carvedilol	6.25	6.25	6.25	---	---	---
2	Carvedilol: PEG (4000) (1:4)	---	---	---	31.25	31.25	31.25
3	MCC (AvicelPH 102)	10	10	10	5	5	5
4	CCS	3.75	---	---	3.75	---	---
5	SSG	---	3.75	---	---	3.75	---
6	CP	---	---	3.75	---	---	3.75
7	Sorbitol	20	20	20	5	5	5
8	Magnesium Stearate	10	10	10	5	5	5
	Total	50	50	50	50	50	50

Table 2: Micromeritic Properties of formulae

S.No	Parameter	F1	F2	F3	F4	F5	F6
1	Bulk density (g/mL)	0.61	0.59	0.64	0.621	0.652	0.686
2	True density (g/mL)	0.714	0.685	0.667	0.756	0.653	0.635
3	Compressibility Index (%)	14	13	15	17	15	14
4	Hausner's ratio	1.17	1.16	1.15	1.12	1.145	1.182
5	Angle of repose	17±0.9°	22±0.8°	20±0.2°	24±0.9°	24±0.8°	25±0.2°

Table 3: Physical Parameters of prepared tablets

Formula	F1	F2	F3	F4	F5	F6
Hardness (Kg/cm2±S.D)	3.26±0.15	3.95±0.35	3.58±0.25	2.5±0.12	2.75±0.26	2.5±0.52
D.T(Sec)	124	190	214	58	78	70
Wt. Variation (%)*	98.5±0.05	99.5±0.12	99±0.15	99.5±0.25	98.5±0.35	97.5±0.15
Drug Content (%)±S.D*	99.95±0.15	100.0±0.005	99±0.12	99±0.16	98.1±0.62	97.5±0.19
Friability (% w/w)	0.96	0.4	0.78	0.4	0.6	0.68
Uniformity of dispersion	Pass	Pass	Pass	Pass	Pass	Pass

Table 4: Stability Studies of Physical and Chemical Parameters

F1	Time	Appearance	Drug Content (%) ±S.D*	Hardness (Kg/cm2±S.D)*
40°C ± 2°C/75% ± 5%	Initial	No change	99.5±0.15	3.50±0.12
	1month	No change	99.2±0.2	3.42 ±0.21
	2 month	No change	98.9±0.5	3.37±0.31
RH 25°C ± 2°C / 60%±5%	3 month	No change	98.6±0.9	3.34±0.12
	1month	No change	99.2 ±0.61	3.50±0.12
	2 month	No change	98.9±1.0	3.48±0.61
RH	3 month	No change	98.6±0.8	3.47±0.58

4. Conclusion

Fast disintegrating tablet is a promising approach with a view of obtaining faster action of the drug and would be advantageous in comparison to currently available conventional forms. The present study was done to develop oral disintegrating tablets of the drug carvedilol by using super disintegrating and solid dispersion technique. The preformulation studies shows good characteristics of drug; suitable for formulation and within acceptable limits. The *in-vitro* release data showed that the drug has released faster from the dosage form as per the ratios of super disintegrants & technique employed. Optimised formulation was found to be stable for the period and conditions examined. All the above results clearly indicate that the problems of carvedilol. Amongst all formulations, formulation F4 prepared by drug: PEG (4000) (1:4) ratio MM with cross carmellose sodium showed least dispersion time and faster dissolution. Thus it can be concluded that combination of solid dispersion and addition of optimum concentration of super disintegrants is found to be a promising approach to prepare fast disintegrating tablet of poorly water soluble non steroidal anti inflammatory drug carvedilol and such other poorly water soluble drugs like carvedilol.

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