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DEVELOPMENT AND *IN VITRO* EVALUATION OF MICRONIZED SUSTAINED RELEASE MATRIX TABLET OF CARVEDILOL

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ABSTRACT

Carvedilol, a non selective β blocking drug under the biopharmaceutical classification system (BCS) class II, is widely used in the treatment of hypertension. Solubility of this drug is very low which affects in low dissolution rate and in turn affect the bioavailability of this drug following oral administration. The micronization of drug is one of the technological procedures to improve the dissolution rate. The purpose of the present study is to design a sustained release matrix tablet containing micronized carvedilol phosphate. Phospahte salt of carvedilol possesses better aqueous solubility than it's free base. Hydroxy propyl substituted β cyclodextrin and poly ethylene oxide are used as release modifying polymer to develop the matrix tablet. The comparative in vitro evaluation between the developed micronized sustained release and non-micronized sustained release matrix tablet of carvedilol are done. A significant increase in *in vitro* drug release rate is observed in case of the micronized product over the non micronized one. The sustained release matrix tablet of micronized carvedilol may be used as a once daily formulation after relevant pharmacokinetic studies.

INTRODUCTION: Drugs under biopharmaceutical classification system (BCS) class II exhibit low solubility and high permeability characteristics [1]. The solubility in gastro intestinal fluids and the dissolution rate are the limiting factors in most of the BCS class II drugs [2]. Thus research for strategies of drug dissolution enhancement is of special interest which leads to improvement of bioavailability. Particle size reduction of a drug is a promising way to improve the bioavailability of poorly water soluble substances due to increased dissolution rate of micron or nano size substances [3, 4]. There are numerous examples of research work on this aspect of enhancing bioavailability of poorly water soluble drugs [5, 6, 7]. Several methods are followed to produce a drug of small particle size. The most common way is the size reduction of larger particles using different milling processes such as jet-milling, pearl-ball milling or high pressure homogenization [2].

Carcedilol, chemically (2 RS) - 1- (9H-Carbazol- 4yloxy)- 3- [[2- (2- methoxy phenoxy) ethyl] amino] propan- 2- ol is a non selective β and α_1 adrenergic receptor blocking agent [8, 9, 10]. It also has multiple spectrums of activities such as antioxidant property, inhibition of smooth muscle proliferation and calcium antagonistic blocking activity [10, 11, 12]. Carvedilol is widely used as immediate-release (IR) tablet formulation to treat essential hypertension and mild to severe congestive heart failure [13]. Carvedilol free base is practically insoluble in water and thus poorly absorbed from gastro intestinal tract. It exhibits poor absolute bioavailability of 25-35% [14]. Half life of carvedilol is 6-8 hrs [15]. Recently a phosphate salt of carvedilol is developed with improved aqueous solubility and chemical stability by protonation of the secondary amine as a salt [16]. A new controlled release capsule of carvedilol phosphate was recently marketed with dose strength of 10, 20, 40 and 80 mg free base of carvedilol administered once daily [13]. The goal to design controlled release drug delivery systems (CRDDS) was to deliver drug at a rate necessary to achieve and maintain a constant drug-blood level. The key advantages to the use of CRDDS are prolonged activity, fewer doses, fewer side effects and reduced toxicity.

To the best of our knowledge there is no published literature till the date describing controlled release or sustained release (SR) tablet formulation containing micronized carvedilol phosphate. In the present investigation we have approached to develop a SR matrix tablet formulation containing carvedilol phosphate with the reduced drug particle size. Micronization of the drug has been done by jet milling to improve the dissolution rate and the matrix tablet was formulated with hydroxyl propyl β cyclodextrin (HP β CD), as a bioavailability enhancing agent and polyethylene oxide (PEO) as release retarding polymer. Cyclodextrin increases the permeability of poorly soluble hydrophobic drug available at the surface of the biological barrier such as skin, mucosa from where it partitions into the membrane [17, 18]. HP β CD is widely used in SR formulation of poorly water soluble drug to improve aqueous solubility and dissolution rate [19]. Uses of PEO, a hydrophilic polymer in the design of SR matrix tablet are reported by several researchers [20, 21, 22].

In this paper, formulation of a SR matrix tablet containing micronized carvedilol phosphate employing direct compression technique has been reported. Our aim was to enhance the dissolution rate by particle size reduction which has been evaluated by in-vitro drug release study.

MATERIALS AND METHOD:

Material: The active pharmaceutical ingredient used, in accordance with pharmaceutical grade of purity, was carvedilol phosphate (gifted by Dr. Reddy's Laboratories Ltd., India). HP β CD, microcrystalline cellulose (MCC), polyethylene oxide (PEO 301), magnesium stearate and talc

were donated as gift sample by Stadmed Pharmaceuticals Pvt. Ltd., India). The reagents of analytical grade were di-potassium hydrogen phosphate and hydrochloric acid (both were purchased from Merck Pvt. Ltd., India).

Micronization of raw drug & study of particle size distribution: Size reduction of carvedilol phosphate was done by an air jet mill (Midas Micronizer, M-50, R&D Model, Microtech Eng. Company, India). 200gm of carvedilol phosphate was used as feed to the jet mill after drying in a hot air oven at 40 ^{o}C for 2 hrs. The micronized fine particles were collected and subject to size distribution. Separations of micronized carvedilol phosphate were done by an electromagnetic sieve shaker (EMS–8, Electrolab, India) fitted with different sieves of 63, 53, 43 and 38µ in descending order.

The different ranges of carvedilol phosphate particles were retained over each sieve after 30 min of operation. The particles passed through the 38 µ sieve were collected from the lower lid of sieve. The results of particle size separation were expressed as weight percentage of distribution vs. particle size range. The particle size of under size particles of 38 µ sieve, over size particles of all other sieves and non-micronized carvedilol phosphate were measured by particle size analyzer (Master Sizer 2000SM, Malvern, UK) which works on the principle of laser diffraction. The drug particles were dispersed in water containing tween 20(0.1% v/v, as dispersing agent) and used to analyze the particle size. The results were expressed as plots of volume percentage vs. particle size (µm).

Preparation of Matrix Tablet: The particles passed through the 38µ sieve were used to prepare SR matrix tablet of micronized carvedilol phosphate (MC). After severe trial and evaluation process the suitable composition (**Table 1**) was fixed and the preparation was done by direct compression technique. All the ingredients except glidant and lubricant were weighed accurately and blended well in laboratory scale planetory mixer for 10 min. The appropriate quantity of mixture was then compressed by 6.4 mm flat punch using an eight station rotary compression machine (Labpress) after addition of talc and magnesium stearate.

TABLE 1: COMPOSITION OF ALL BATCHES OF MICRONIZED CARVEDILOL MATRIX FORMULATION

Ingredients (mg)	Quantity								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carvedilol Phosphate	50.528	50.528	50.528	50.528	50.528	50.528	50.528	50.528	50.528
HP β CD	30	30	30.00	35	35	35	40	40	40
PEO 301	20	25	30.00	20	25	30	20	25	30
MCC	31.872	26.872	21.872	26.872	21.872	16.872	21.872	16.872	11.872
Talc	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Mg. St.	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Total wt.	135	135	135	135	135	135	135	135	135

Physicochemical evaluation of fabricated matrix tablet: Hardness, friability, diameter and thickness, weight variation and content uniformity are to be measured to evaluate physicochemical property of tablets [23]. Tablet hardness were measured by Monsanto hardness tester and expressed by kg/sq.cm. Roche friabilator was used to determine friability of the fabricated matrix tablets taking 20 tablets. Thickness was measured by digital slide calipers (Mitutoyo, Japan). The weight variation of prepared matrix tablets were determined by taking 20 tablets as per the USP guidelines [24]. Content uniformity of carvedilol SR matrix

tablets was studied as per the assay method described in the USP 32-NF 27, First supplement.

***In vitro* Release Studies:** The *in vitro* release studies of carvedilol from the prepared matrix tablet were conducted by USP type II apparatus with paddle speed of 100 rpm at a constant temperature of 37 ± 0.5 ˚C. The dissolution studies were carried out for 24 hrs duration. The medium of dissolution (900ml) were 0.1 (N) hydrochloric acid for initial 2 hrs and phosphate buffer (pH 6.8) for 3 to 24 hrs. The drug release from the matrix tablets were determined by a double beam UV spectrophotometer at a wavelength of 242 nm. There was no interference of the ingredients of prepared tablet at the said wavelength. Six replicates of each tablet were taken for the *in vitro* dissolution study and the cumulative percentage release was plotted vs. time in hr.

RESULT AND DISCUSSION: Sustained release matrix tablets each containing micronized carvedilol phosphate equivalent to 40 mg free base were prepared by direct compression method. Direct compression method is known to be more economical than wet granulation and also avoids heat and moisture which may affect the drug stability [25]. Results of different physiochemical property evaluation are described in the **Table 2**. Hardness of the tablets was within the range of 3.7 to 3.9 kg/sq.cm. All formulations were compliant with official compatibility, which allow not more than 1% of mass lost on 20 tablets weight. Weight variation and thickness, studied with all batches of tablet were within the satisfactory limit. The content of the drug in the tablets were within the acceptable range of 90 to 110 %.

TABLE 2: PHYSICOCHEMICAL PROPERTIES OF ALL BATCHES OF TABLET

Formulation Batch Code	Hardness (kg/cm^2) n = 6	Friability (%) n = 20	Thickness (mm) n = 5	Weight variation (mg) n = 10	Drug Content (%) n = 20
F1	3.70 ± 0.12	0.08	4.11 ± 0.01	131.12 ± 0.77	96.78 ± 1.38
F2	3.80 ± 0.08	0.05	4.11 ± 0.01	130.92 ± 1.22	97.50 ± 0.64
F3	3.80 ± 0.11	0.08	4.11 ± 0.02	130.23 ± 1.18	96.05 ± 1.58
F4	3.80 ± 0.09	0.09	4.11 ± 0.02	130.09 ± 0.97	97.95 ± 1.79
F5	3.80 ± 0.13	0.05	4.11 ± 0.02	130.91 ± 1.48	95.90 ± 1.22
F6	3.80 ± 0.11	0.08	4.12 ± 0.03	130.31 ± 2.26	97.13 ± 0.80
F7	3.90 ± 0.07	0.05	4.11 ± 0.03	131.36 ± 2.14	98.87 ± 1.57
F8	3.80 ± 0.16	0.06	4.10 ± 0.01	129.69 ± 0.75	96.44 ± 0.67
F9	3.80 ± 0.06	0.08	4.10 ± 0.02	130.33 ± 2.14	97.42 ± 0.83

n = Number of tablet taken for each test

After micronization, drug particles were separated by Electro Magnetic Sieve Shaker (EMS – 8, Electrolab, India). The particles which were distributed in different range of sizes (38 µ to 63 µ) were shown in **Figure 1**. The figure indicates that the particle size distribution after milling follows the normal size distribution. Micronized pure carvedilol phosphate was analyzed by Malvern Particle Size Analyzer (Mater Sizer, 2000) to determine the particle size distribution.

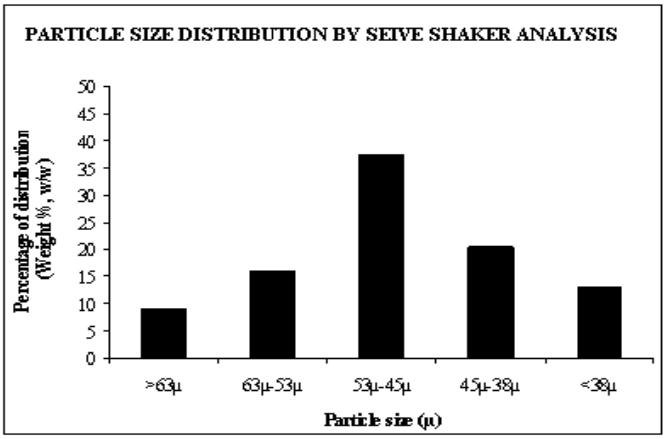

FIG. 1: **PARTICLE SIZE DISTRIBUTION BY SIEVE SHAKER ANALYSIS AFTER MICRONIZATION**

The 10 % by volume [d (0.1)], 50 % by volume [d (0.5)], and 90 % by volume [d (0.9)] values of the under size particles of 38 µ sieve, oversize particles of all other sieves and non-micronized carvedilol phosphate are presented in **Table 3**. Normal size distribution is considered as the main feature of good micronization.

TABLE 3: SIZE DISTRIBUTION OF MICRONIZED PARTICLE BY VOLUME %

Sieve aperture (µ)	Over size (OS)/ Under size (US)	d (0.1) by volume % (µ)	d (0.5) by volume % (µ)	d (0.9) by volume % (µ)
38	US	5.02	9.85	23.18
38	OS	10.44	39.58	116.23
45	OS	16.95	50.89	115.94
53	OS	21.06	60.05	129.46
63	OS	28.55	65.88	160.59
Non-micronized	N.A	54.32	108.72	210.45

US = under size, OS = Over size; d (0.1) = 10 % volume of particles under that size; d (0.5) = 50 % volume of particles under that size; d (0.9) = 90 % volume of particles under that size

Carvedilol phosphate exhibits better water solubility than it's free base carvedilol but it still shows low solubility in aqueous medium. HP-β-CD, because of its dissolution enhancing effect was found to be effective in development of SR formulation of poorly water soluble drug [26]. PEO is a common choice of the researcher to develop SR matrix formulation because of its low toxicity and pH dependent swelling and drug release properties [27]. From the in vitro release study (Figure 2) it was revealed that the carvedilol 40 mg SR matrix tablet of F5 batch composed of the ingredients containing HP-β-CD and PEO exhibit a release rate more than 25% and 99% in 1st hr and 24 hrs respectively.

This implies that the developed tablet have shown a prolonged drug release over a period of 24 hrs. With increasing amount of HP-β-CD and PEO it was observed that release rate of carvedilol was decreasing (in case of F8 and F9). Formulations with low quantity of HP-β-CD (F1 and F2) have shown more than 93% of drug release within 24 hrs which isn't desirable for a sustained release product for 24 hrs. PEO in association with HP-β-CD delayed the release of drug by controlling the extent and rate of swelling of the polymers. The *in vitro* drug release profiles of F5 batch tablets are most suitable for a once daily micronized SR carvedilol tablet.

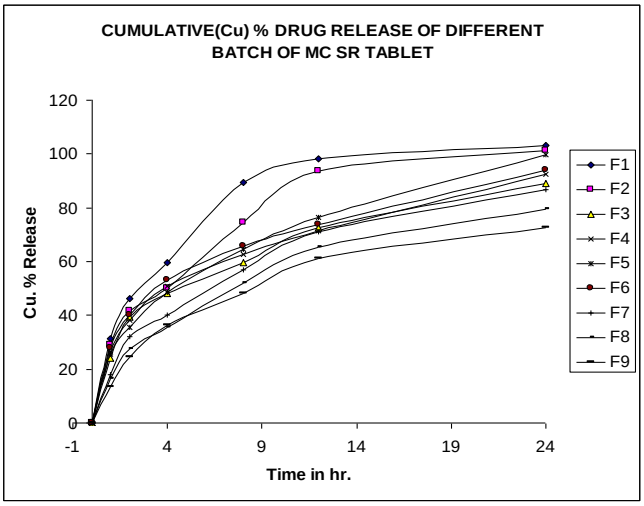

FIG. 2: IN VITRO DRUG RELEASE PROFILE OF ALL BATCHES OF MICRONIZED CARVEDILOL SR MATRIX TABLET

The in vitro release profile of SR matrix tablet micronized carvedilol 40 mg (MC) was compared with the in vitro release profile of SR matrix tablet of non - micronized carvedilol 40 mg (NMC) to evaluate the effect of micronization or particle size reduction of active pharmaceutical ingredient. The matrix tablet with non micronized carvedilol phosphate (NMC) was prepared as per the composition of F5 batch. The comparative in vitro release study was described by Figure 3. It was observed that the MC SR matrix tablet have shown a cumulative

percent release more than 99 % in 24 hrs, where as the NMC SR matrix tablet formulated with the same composition have shown a cumulative percent release below 75 %. This enhancement of dissolution is due to the reduced particle size of the drug. The dissolution of a drug at any point of time during an experiment is described by the Noyes-Whitney equation shown below [28]:

$$\frac{dC}{dt} = \frac{DS(C_S - C)}{Vh}$$

The dissolution rate dC/dt, is a function of the concentration of drug in the media (C), the diffusion coefficient (D), the saturation concentration of drug in the diffusion layer(h) and the surface area of the drug (S). Changes in any one of these terms in the equation can influence dissolution. Micronization leads to a decrease in particle size and thus increase the surface area term. This theory may be behind the enhanced in vitro release from SR tablet of micronized carvedilol phosphate over the non micronized formulation.

MC: Micronized carvedilol phosphate
NMC: Non- micronized carvedilol phosphate

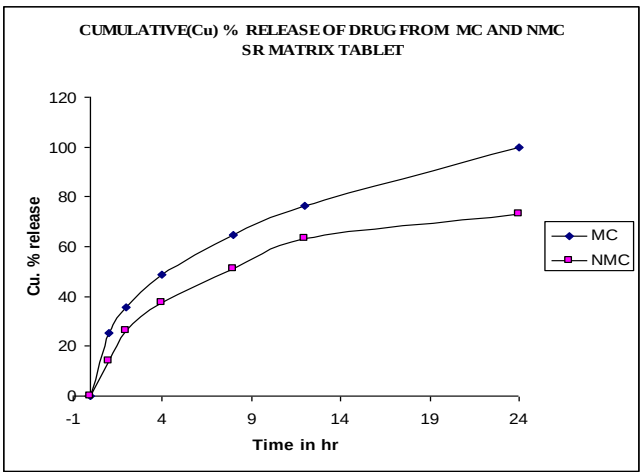

FIG. 3: IN VITRO DRUG RELEASE PROFILE OF MICRONIZED AND NON-MICRONIZED CARVEDILOL SR MATRIX TABLET

MC: Micronized carvedilol
NMC: Non micronized carvedilol

CONCLUSION: There is no SR formulation of carvedilol phosphate in Indian market. So the in vitro release profile of the developed SR matrix tablet containing micronized carvedilol phosphate was compared with the desirable theoretical sustained release needed to select the optimum formulation. The approach utilized a combination of distinct formulations containing hydroxyl propyl substituted cyclodextrin along with poly ethylene oxide and processes of size reduction to improve the dissolution of BCS class II drugs. The developed SR matrix tablet containing micronized carvedilol phosphate equivalent to 40 mg carvedilol may be used as a once daily formulation after suitable in vivo pharmacokinetic study. The strategy of micronization may be applied to the design and development of SR matrix tablet of poorly water soluble drugs.

REFERENCES:

1. Alex A: Absorption and Drug Development. John Wiley & Sons Inc, New Jercy, USA, 2003:20-21.
2. Rasenack N, Bernd W, Muller: Micron-size drug particles: common and novel micronization techniques. Pharmaceutical Development and Technology 2004; 9(1):1-13.
3. Kawashima Y: Nanoparticulate systems for improved drug delivery. Advanced Drug Delivery Review 2001; 47:1-2.
4. Chaumeil JC: Micronization: a method for improving the bioavailability of poorly soluble drugs. Methods and Findings in Experimental and Clinical Pharmacology 1998; 20:211-15.
5. Farinha A, Bica A, Tavares P: Improved bioavailability of a micronized megestrol acetate tablet formulation in humans. Drug Delivery and Industrial Pharmacy 2000; 26(5):567-70.
6. Turk M, Hils P, Helfgen B, Schaber K, Marting HJ, Wahl MA: Micronization of pharmaceutical substances by the rapid expansion of supercritical solutions(RESS): a promising method to improve bioavailability of poorly soluble pharmaceutical agents. Journal of Supercritical Fluids 2002; 22(1):75-84
7. Kerc J, Srcic S, Knez Z, Sencar-Bozic P: Micronization of drugs using supercritical carbon dioxide. International Journal of Pharmaceutics 1999; 182(1):33-39.
8. Nicholas AJ, Sulpizio AC, Ashton DJ, Hieble JP, Ruffolo RR Jr: In vitro pharmacologic profile of the novel beta-adrenoreceptor antagonist and vasodialator,carvedilol. Pharmacology 1989; 39:327-336.
9. Ruffolo RR, Gellai M, Hieble JP, Willette RN, Nicholas AJ: The pharmacology of carvedilol. European Journal of Clinical Pharmacology 1990; 38:S82-88.

10. Nicholas AJ, Gellai M, Ruffolo RR Jr: Studies on the mechanism of arterial vasodialation produced by the novel anti hypertensive agent, carvedilol. Fundamental Clinical Pharmacology 1991; 5:25-38.
11. Feuerstein GZ, Rufflo RR Jr: Carvedilol, a novel multiple action antihypertensive agent with antioxidant activity and the potential for myocardial and vascular protection. European Heart Journal 1995; 16:38-42.
12. Sung CP, Arleth AJ, Ohlstein EH: Carvedilol inhibits vascular smooth muscle cell proliferation. Journal of Cardiovascular Pharmacology 1993; 21:221-27.
13. Tenero DM, Henderson LS, Charlotte A, Baidoo MM: Pharmacokinetic properties of a new controlled release carvedilol. The American Journal of Cardiology 2006; 98:5L-16L.
14. Kalimuthu S, Yadav A V: Formulation and evaluation of carvedilol loaded Eudragit e 100 nanoparticles. International Journal of Pharm Tech Research 2009; 1(2):179-83.
15. McTavish D, Campoli-Richards D, Sorkin EM: Carvedilol: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. Drugs 1993; 45:232-58.
16. Chakarborty S, Shukla D, Jain A, Mishra B, Singh S: Assesment of solubilization characteristics of different surfactant for carvedilol phosphate as a function of pH. Journal of Colloid and Interfence Science 2009; 335:242-49.
17. Uekama K, Otagiri M: Cyclodextrins in drug carrier systems. Critical Reviews in Therapeutic Drug Carrier System 1987; 3:1-40.
18. Szejtli J: Medicinal applications of cyclodextrins. Medicinal Research Review 1994; 14:353-86.
19. Challa R, Ahuja A, Ali J, Khar R K: Cyclodextrins in drug delivery: An updated review. AAPS PharmSciTech 2005; 6(3):E329-55.
20. Zhang F, McGinity JW: Properties of sustained-release tablets prepared by hot-melt extrusion. Pharmaceutical Development and Technology 1999; 4:241-50.
21. Razaghi AM, Schwartz JB: Investigation of Cyclobenzaprine Hcl release fron oral osmotic delivery systems containing a water soluble polymer. Drug Delivery and Industrial Pharmacy 2002; 28:631-9.
22. Jamzad S, Fassihi R: Development of a controlled release low dose class II drug-Glipizide. International Journal of Pharmaceutics 2006; 312:24-32.
23. Lachman L, Leiberman H A, Kaning J I: The Theory and Practice of Industrial Pharmacy. Varghese Publishing House, 3rd Edition 1991.
24. U.S. Pharmacopoeia and National Formulary (USP 24, NF 19). United States for Pharmacopoeial Convention Inc, Asian Edition 2000.
25. Rudnic E M, Kottke M K: In Modern Pharmaceutics. Marcel Dekker Inc, New York, Edition 3, 1995:333-94.
26. Chowdhury KPR, Reddy GK: Complexes of Nifedipine with β and hydroxyl propyl β cyclodextrin in the design of Nifedipine SR tablets. Indian Journal of Pharmaceutical Science 2002; 64:142-46.
27. Apicella A, Cappello B, Del Nobile M a, La Rotonda M I, Mensitieri G, Nicolais L: Poly (ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release. Biomaterials 1993; 14(2):83-90.
28. Lipinski C A, Lombardo F, Dominy B W, Feeney P J: Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Review 1997; 23(1-3):3-25.

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