

Research Article**DISSOLUTION ENHANCEMENT OF CARVEDILOL BY USING SURFACTANT AS A COATING MATERIAL**

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ABSTRACT

Carvedilol is a poorly water-soluble oral antihypertensive agent, with problems of variable bioavailability and bio-in equivalence. This work was investigated to develop the carvedilol tablets, allowing fast, reproducible and complete drug dissolution, by using surfactant. The tablets were prepared by wet granulation technique. The prepared tablets were evaluated for thickness, uniformity of weight, hardness, friability, *in-vitro* disintegration time and *in-vitro* drug release. The tablets apart from fulfilling all official and other specifications, the Carvedilol dissolution profile from the newly developed tablets was clearly better than those batches without surfactants in the coating. The stability studies conducted as per ICH guidelines at $40^{\circ}\pm 2^{\circ}$ and $75\%\pm 5\%$ RH showed insignificant loss in drug content and on physical evaluations at the end of three months. So many techniques are available for the solubility enhancement such as micronization, spray drying, and complex formation. Some drugs such as carvedilol, zolpidem tartrate may show change in polymorphism by using above techniques. The purpose of the research was to increase the solubility of carvedilol by adding the surfactants in coating without changing its polymorph so as to develop an immediate release formulation. The study shows that the use of 3 % surfactant increases the dissolution rate up to 12 % in first 20 minutes in pH 6.8 Phosphate buffer, USP II, 50 rpm. Thus by incorporating the surfactants like tween 80, we can enhance the solubility of low solubility drugs.

KEY WORDS Antihypertensive, surfactant, tablet coating.

INTRODUCTION

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 hypertension¹. 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. Carvedilol is a poorly water-soluble oral antihypertensive agent, with problems of variable bioavailability and bio-inequivalence related to its poor water-solubility. Its biological half-life (2.2 hours) is very short and it is 90% absorbed from GIT. Earlier carvedilol fast dissolving tablets², transdermal patches³ are reported. In this work an attempt has been made to increase the dissolution of the carvedilol

tablets which ultimately increases the bioavailability, also to give the benefits in terms of patient compliance, rapid onset of action, low side effect and good stability which make these tablets popular as a dosage form for the treatment of hypertension.

MATERIAL AND METHODS

Carvedilol was procured from Zentiva; (Germany), povidone is taken as a gift sample from Cipla Ltd. (kurkumbh), lactose monohydrate from DMV (Germany), collidal silicon dioxide from Degussa (Bombay), polyplasdone INF 10 and magnesium stearate from Mallinckrodt and tween 80 were obtained as gift samples from Wockhardt R & D (Aurangabad). The rest of the chemical of analytical grade were supplied by S. D. fine chemicals, Mumbai.

Preparation of Carvedilol Tablets

The conventional wet granulation procedure was employed to formulate core tablets of carvedilol. The ingredients consisting of carvedilol, lactose monohydrate, polyplasdone INF 10 and colloidal silicon dioxide is taken intragranular and PVP-K 30 in water is used to granulate the mass. The mass is then dried and passed through the 25 mesh sieve. Extragranular polyplasdone INF 10, colloidal silicon dioxide and magnesium stearate is sifted through 60 mesh sieve and mixed with the dried granules. Tablets were prepared using 10 x 6.4 mm oval punch.

Aqueous Coating of the Tablets

Aqueous film coating procedure was applied. The different levels of tween 80, 0 %, 3 %, 6 % and 10 % was prepared to observe the solubility and dissolution rate of the carvedilol. Tween 80 was first dissolved in distilled water with stirring using a variable speed propeller stirrer and then polyvinyl alcohol (PVA), talc and triethyl citrate (TEC) was added with stirring to the mixture and stirring was continued to obtain homogenous dispersion. The coating dispersion was diluted sufficiently to produce the 15 % w/w of the solid content. Four batches of coated tablets T1, T2, T3 and T4 were prepared by applying PVA and Tween 80. Coated tablet contains 0 %, 3 %, 6 % and 10 % of Tween 80. The pan rotation was adjusted to 20 rpm for better tumbling effect to the tablets.

Evaluation of Tablets

Weight variation of core tablets/coated tablets was determined by official method. The percentage practical weight gain for each batch of coated tablets was computed from the average tablet weight of each tablet. Hardness of ten randomly selected tablets was

measured using a Stokes Monsanto Hardness Tester. The percentage friability of the core tablets was determined by following USP procedure. The friability was determined by subjecting a sample of core tablets equivalent to 6.5 g to abrasion in automated USP friabilater for 100 rotations. The dedusted tablets were weighed and percentage friability was calculated from the difference in the weight of tablets before and after the friability test. The disintegration test of the core tablets was carried out using USP XXIII disintegration tester (model ED-2, Electrolab, Mumbai). Six tablets were placed individually in each tube of the apparatus. The disintegration test was performed in distilled water; the temperature of water bath was maintained at $37\pm 0.5^\circ$ through out the test. Dissolution studies of the coated tablets were carried by employing the USP II dissolution test apparatus in pH 6.8 phosphate buffer, 900 ml. The temperature of the dissolution medium is maintained at $37\pm 0.5^\circ$ with a stirring speed of 50 rpm. Aliquot of the dissolution medium was withdrawn at 10 minute time interval for 60 minute and sampled volume is replaced with the equal volume of buffer maintained at same temperature.

RESULTS AND DISCUSSION

A wet granulation procedure was employed to produce a tablet of carvedilol. Lactose monohydrate was selected as filler in the formulation as tablets containing lactose are reported to show fast disintegration. Good friability and low wet variation with no signs of sticking, binding and capping. The formula was designed to have sufficient crospovidone as a superdisintegrant with intention to minimize the disintegration time and to generate a pulsed release during the dissolution. Crospovidone was incorporated in two steps, 3 % was added intragranular and dry mixed before wet granulation.

TABLE 1- The Physical properties of the final formulation

Physical Properties	Parameters Range	Actual Parameters
Weight variation (mg)	5.0 % (Between 2.850 g and 3.150 g)	2 %
Average weight (mg)	150.0 mg ± 5.0% (Between 142.5 mg and 157.5 mg)	151.4-152.0 mg
Thickness (mm)	Between 2.70 mm to 3.20 mm	2.89 mm
Hardness (kg)-(core tablets)	Between 6 to 12.5	8.5 kg
Friability (%)-(core tablets)	Not more than 1.0 % w/w	0.2 %
Disintegration (Min)	Should not be more than 15 min	1 min 4 seconds
Drug content (%)	Not less than 95.0 % and not more than 110.0 % of the labeled amount of Carvedilol	99.41 %

The remaining 3 % was incorporated as extragranular portion during the lubrication process. The two step of addition of disintegrant is reported to produce more complete disintegration as

30 is an excellent and versatile all purpose binder with a concentration 3 -5 % of the dry mass during the wet granulation step. Magnesium stearate used as an anti-adherent and lubricant. Colloidal silicon

Table 2- The detailed Processed Conditions

Tablet Composition	Coating dispersion composition	Processing conditions
Carvedilol, Povidone (PVP K 30), Lactose Monohydrate, Colloidal silicon dioxide, Polyplasdone INF 10 (crospovidone) Magnesium stearate	PVA, Tween 80, Triethyl citrate, purified talc	Bed temperature 40-45 Spray rate 5 g/min Spray nozzle diameter 1mm Spray pressure 4 kg/cm Pan speed 20 rpm

Table 3- The dissolution profile of the coated tablets with different weight gain

Time (min)	pH 6.8 Phosphate Buffer			
	T1	T2	T3	T4
0	0	0	0	0
5	28	46	34	33
10	51	74	54	52
20	70	83	71	70
30	78	88	77	78
45	85	92	86	87
60	86	96	87	88

the extragranular portion produces immediate disruption of the tablets in to the pre compressed granules. Intragranular portion produces further erosion of the granules to the primary particles. PVP-K

dioxide is used as a glidant. The physical properties are outlined in the Table 1. The core tablets passed the friability test as the friability of the core tablets was found to be within the specified limit of 1 %. The

tablet shows no evidence of capping, cracking, cleavage and breakage after tumbling in the Rochi Block friabilater. The mean value of the hardness and the thickness for entire batch of core tablets was found to be 2.94 mm and hardness 8-9 Kg. The presence of optimum amount of moisture (2-3 %) and PVPK-30 in the precompressed granules were the contributing factors for the low friability and good hardness of the tablets. The coated tablets passed the disintegration test as they were found to disintegrate in 1 min 4 seconds. The quick disintegration time of the tablets can be attributed to the presence of the super disintegrant crospovidone in optimum concentration in the formula.

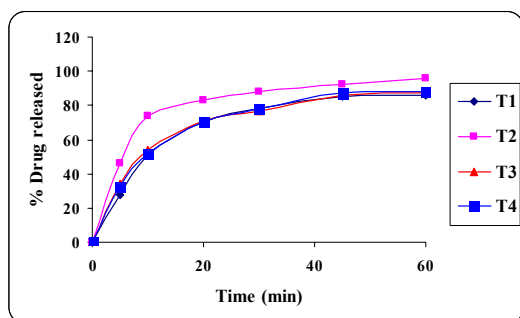


FIG.1-Dissolution Profile of Tablets In pH 6.8 Phosphate Buffer, USP II, 50 Rpm, 900 ml

Where T1-coating without Tween 80, T2-3 % Tween 80, T3-6 % Tween 80, T4-10 % Tween 80

The batch of the tablets was found to pass the weight variation test with an average tablet weight of 150 mg. The core tablets passed the content uniformity test with an average assay value 98.4 %. The uniformity in content could be related to the low weight variation of the core tablets which could be due to the narrow size distribution and free flowing nature of the precompressed granules. The tablet shows no signs of sticking, binding during the compression. The aqueous coating procedure was adopted to apply the PVA based coating on the core tablets. Triethyl citrate is used at a concentrate of 10 % w/w to lower the glass transition temperature and promote formation of a good elastic film. The coating dispersion flow during the coating process was

continuous with no spray system blocking during the coating. The detailed processed conditions are out lined in the Table 2.

The dissolution profile of the coated tablets with different weight gain is displayed in the Table 3. In case of normal PVA based coating (without tween 80) shows limited drug release which is increased in the tablets coated with 3 % tween in coating composition. Approximately 15-25% rise in dissolution is observed in first 20 minutes. Where in case of tablets with 6 and 10 % weight gain of tween 80, there is no further increase in dissolution rate. The details are given in Table III. The results collectively indicate that, Tablet compression and aqueous coating can be applied to successfully develop a formulation. A coat weight including 3 % tween 80 in coating was just sufficient to enhance the solubility and dissolution rate of the tablets. Dissolution profile of tablets is shown in Fig.1

CONCLUSION

The prepared tablet gives benefit in terms of patient compliance, rapid onset of action, low side effect and good stability which make these tablets popular as a dosage form for the treatment of hypertension.

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