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EFFECT OF HYDROPHILIC POLYMERS ON SOLID DISPERSIONS OF CARVEDILOL FOR ENHANCING ITS DISSOLUTION RATE

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ABSTRACT

Carvedilol, a lipophilic drug, belongs to BCS Class II due to its poor aqueous solubility and exhibits an oral .bioavailability of 25 – 35%. As such it needs enhancement in the dissolution rate and bioavailability to derive its maximum therapeutic efficacy. The objective of the present study was to prepare solid dispersions of carvedilol employing two hydrophilic polymers, namely PVA and HPMC 6cps by three different methods of preparation - physical mixing, kneading and solvent evaporation in ratios of 1:1, 1:2 and 1:4. The prepared carvidelol-hydrophilic polymer dispersions were evaluated by *in vitro* methods. The dissolution data was fitted into various mathematical models such as zero order, first order and Hixson-Crowell's cube root model to assess the kinetics and mechanism of dissolution. Dispersions prepared by kneading method gave higher dissolution rate and DE_{20} values than those prepared by co-precipitation and physical mixing methods. The dissolution data of all the solid dispersions prepared obeyed first order kinetic model as well as Hixson-Crowell's cube root model. Solid dispersions prepared, employing HPMC gave higher values than those prepared from PVA. As the concentration of HPMC increased, the dissolution rate increased, whereas in the case of PVA, as the concentration of the carrier increased the dissolution rate decreased. Solid dispersions, carvidelol –HPMC (1:4) and carvidelol –PVA (1:1) ratio gave higher dissolution rate and dissolution efficiency values than all other dispersions. Carvidelol –HPMC (1:4) ratio gave a 19.7 fold increase in dissolution rate of carvidelol whereas in the presence of PVA (1:1) ratio, it gave an 8.33 fold increase.

Keywords: Carvidelol, Solid Dispersion, HPMC 6cps, PVA, Dissolution rate.

INTRODUCTION:

About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pHs and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters and pose challenging problems in their pharmaceutical product development process. Carvedilol is a third-generation, nonselective β-adrenergic blocking agent with multiple activities. Carvedilol, a lipophilic drug, belongs to BCS Class II due to its poor aqueous solubility and exhibits an oral .bioavailability of 25 – 35%. As such it needs enhancement in the dissolution rate and bioavailability to derive its maximum therapeutic efficacy.

Several techniques[1] such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility , microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among the various approaches, solid dispersion[2, 3] in water soluble and water dispersible excipients is a simple, industrially useful approach for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs. In solid dispersions the poorly soluble drug is dispersed in an inert water-soluble carrier such as urea, polyethylene glycol and poly vinyl pyrrolidone at solid state. In the case of solvent deposited dispersions the drug is deposited in miniscular form on an inert water insoluble excipient such as silica gel and starch at solid state. Surfactants are also used as carriers in solid dispersions of poorly soluble drugs to enhance their solubility and dissolution rates.

The objective of the present study is to prepare solid dispersions of carvedilol in PVA and HPMC 6cps and to evaluate the feasibility of enhancing the dissolution rate and dissolution efficiency of carvedilol, a BCS class II drug.

EXPERIMENTAL:

Materials and Methods:

Carvedilol was a gift sample from Orchid Healthcare Pvt. Ltd., Chennai. Hydroxy Propyl Methyl Cellulose 6cps was a gift sample from Orchid Healthcare Pvt. Ltd., Chennai. Polyvinylalcohol (PVA, Sigma Chemical Co.), Methanol (Qualigens) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Estimation of Carvedilol:

An UV Spectrophotometric method based on the measurement of absorbance at 243 nm in 0.1 N HCl was used for the estimation of carvedilol. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1-10 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative standard deviation was found to be less than 1.0%. No interference by the excipients used in the study was observed.

Preparation of Solid Dispersions:

In each case, solid dispersions of drug and hydrophilic polymer were prepared in 1:1, 1:2 and 1:4 ratio by three methods namely, kneading, solvent evaporation and physical mixing methods.

Kneading Method:

Drug (carvedilol) and hydrophilic polymers were triturated in a mortar with a small volume of a solvent blend of water: methanol (1:1). The thick slurry formed was

kneaded for 45 min and then dried at 55 ºC until dry. The dried mass was powdered and sieved through mesh No. 120.

Solvent Evaporation Method:

Drug (carvedilol) and carrier were dissolved in a common solvent (ethanol) and solvent was evaporated to form the solid mass. The contents were dried at 55 ºC until dry. The dried mass was powdered and sieved through mesh No. 120.

Physical Mixing:

The physical mixtures of respective ratios were prepared by mixing powders of drug and hydrophilic polymer in a dry mortar and the powder was sieved through mesh No. 120.

Estimation of Drug Content of Solid Dispersions:

From each batch four samples of solid dispersion equivalent to 20mg of the medicament was taken into a 100 ml conical flask and extracted with 3 x 10 ml quantities of methanol. The methanolic extracts were filtered and collected into 50 ml volumetric flask and the volume was made up to 50 ml with methanol. The solution was subsequently diluted with water and assayed for the drug content at 243 nm.

Dissolution Rate Study:

The dissolution rate of carvedilol as such and from solid dispersions prepared was studied respectively in 900 ml of 0.1 N HCl using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37±1^{o}C was maintained throughout the study. Drug or solid dispersion equivalent to 25 mg of carvedilol was used in each test. Samples of dissolution media (5ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed at 243 nm. The samples of dissolution fluid withdrawn at each time were replaced with fresh fluid. The dissolution experiments were replicated three times each (n=3).

RESULTS AND DISCUSSION:

Carvedilol, a lipophilic drug, belongs to BCS Class II due to its poor aqueous solubility and exhibits an oral .bioavailability of 25 – 35%. As such it needs enhancement in the dissolution rate and bioavailability to derive its maximum therapeutic efficacy. In the present study solid dispersions of carvedilol employing two hydrophilic polymers- HPMC and PVA in 1:1, 1:2 and 1:4 ratios were prepared by three methods namely (i) physical mixing, (ii) kneading and (iii) solvent evaporation. All the complexes prepared were found to be fine and free flowing powders. There was no significant loss of drug during the preparation of solid dispersions in any of the methods. Low RSD values (< 1.5%) in the percent drug content indicated uniformity of drug content in each batch.

The dissolution rate of carvedilol from dispersions was studied in 0.1N HCl as prescribed in IP 2010. The dissolution of carvidelol from all the solid dispersions was rapid and higher when compared to carvidelol pure drug. The dissolution data was fitted into various mathematical models such as zero order, first order and Hixson-Crowell's cube root model to assess the kinetics and mechanism of dissolution. The dissolution data obeyed first order kinetic model as well as Hixson-Crowell's cube root model in all the cases. The correlation coefficient (r) values were higher in the first order model than in zero order model indicating that the dissolution of carvidelol as such and from its solid dispersions followed first order kinetics. The correlation coefficient (r) values of Hixson-Crowell's cube root model were found to > 0.8 indicating a change in surface area and diameter of the solid dispersions. The dissolution data of all solid dispersions prepared obeyed Hixson-Crowell's cube root model indicating that the dissolution of

carvedilol has occurred from discretely suspended solid dispersions. This is because the Hixson-Crowell's cube root model is applicable to describe the dissolution of discrete particles of uniform size.

The first order dissolution rates (K_1) were calculated from the slopes of the corresponding linear plots. Dissolution efficiency (DE_{20}) values were calculated as per Khan[4].T_{50} (time taken for 50% dissolution) values were recorded from the dissolution profiles. Hixson-Crowell's rate constants were calculated from the slopes of the corresponding linear plots. The dissolution parameters and Hixson – Crowell's rate constants are summarized in Tables 1 and 2.

Table 1: Dissolution Parameters of Carvedilol – Hydrophilic Polymer Systems

Complex System	Method of Preparation								
	Physical Mixing			Solvent Evaporation			Kneading		
	T_{50} (min)	DE_{20} (%)	K_1 (min^{-1})	T_{50} (min)	DE_{20} (%)	K_1 (min^{-1})	T_{50} (min)	DE_{20} (%)	K_1 (min^{-1})
C-HPMC(1:1)	>60	15.07	0.0043	>60	28.36	0.0122	4.7	52.72	0.0231
C- PMC(1:2)	>60	18.41	0.0044	50	39.92	0.0150	3.6	67.00	0.0466
C-HPMC(1:4)	>60	20.84	0.0046	15.4	45.66	0.0227	3.5	70.72	0.0591
C-PVA (1:1)	>60	18.15	0.0057	>60	20.84	0.0063	7.79	49.00	0.0250
C- PVA (1:2)	>60	14.57	0.0034	>60	15.81	0.0053	45.3	34.14	0.0107
C- PVA (1:4)	>60	10.55	0.0030	>60	11.46	0.0032	60	31.83	0.0080

Table 2: Hixson – Crowell's Cube Root Dissolution Rate as Per Hixson-Crowell's Cube Root Model

Complex System	Method of Preparation		
	Hixson – Crowell's Cube Root Dissolution Rate (K_H) ($mg^{1/3}.min^{-1}$)		
	Physical Mixing	Solvent Evaporation	Kneading
C-HPMC(1:1)	0.0042	0.0100	0.0166
C-HPMC(1:2)	0.0040	0.0117	0.0242
C-HPMC(1:4)	0.0039	0.0163	0.0304
C-PVA (1:1)	0.0051	0.0055	0.0173
C- PVA (1:2)	0.0031	0.0048	0.0075
C- PVA (1:4)	0.0028	0.0030	0.0069

All solid dispersions prepared exhibited higher rates of dissolution and dissolution efficiency values than pure drug, carvedilol, indicating rapid andhigher dissolution of carvedilol from its solid dispersion complexes. Solid dispersion complexes prepared, employing HPMC gave higher values than those prepared from PVA. The K_1, DE_{20} and Hixson Crowell's dissolution rate values increased as the proportion of HPMC in all the solid dispersion complexes increased whereas in the case of solid dispersions containing PVA, K_1, DE_{20} and Hixson Crowell's dissolution rate values decreased as the proportion of the PVA in the solid dispersion complex system increased. Solid dispersions prepared by kneading method gave higher dissolution rates and DE values than those prepared by solvent evaporation and physical mixing methods. The increase in K_1 (no. of folds) with various solid dispersions is shown in Table 3.

Table 3: Enhancement of Dissolution Rate of Carvedilol by Various SD Systems

S. No	Complex System	Method of Preparation		
		Increase in K_1 (No of Folds)*		
		Physical Mixing	Solvent Evaporation	Kneading
1	C-HPMC(1:1)	1.433	4.06	7.7
2	C-HPMC(1:2)	1.466	5.00	15.3
3	C-HPMC(1:4)	1.533	7.56	19.7
4	C-PVA (1:1)	1.9	2.1	8.33
5	C-PVA (1:2)	1.13	1.76	3.56
6	C-PVA (1:4)	1.0	1.06	2.66

* Ratio of K_1 of SD systems and uncomplexed drug.

Solid dispersions, carvidelol – HPMC (1:4) and carvidelol –PVA (1:1) ratio gave higher dissolution rate and dissolution efficiency values than all other dispersions. Carvidelol –HPMC (1:4) ratio gave a 19.7 fold increase in dissolution rate of carvidelol whereas in the presence of PVA (1:1) ratio, it gave an 8.33 fold increase. The higher dissolution rates and DE_{20} values were observed with kneaded dispersions containing HPMC may be attributed to stronger drug amorphization of the carvidelol with the hydrophilic polymer during the kneading process.

CONCLUSION:

Solid dispersions of carvedilol employing two hydrophilic polymers- HPMC and PVA in 1:1, 1:2 and 1:4 ratios were prepared by three methods namely (i) physical mixing, (ii) kneading and (iii) solvent evaporation. The prepared carvidelol- hydrophilic polymer dispersions were evaluated by *in vitro* methods. The dissolution data was fitted into various mathematical models such as zero order, first order and Hixson-Crowell's cube root model to assess the kinetics and mechanism of dissolution. Dispersions prepared by

kneading method gave higher dissolution rate and DE_{20} values than those prepared by co-precipitation and physical mixing methods. The dissolution data of all the solid dispersions prepared obeyed first order kinetic model as well as Hixson-Crowell's cube root model. Solid dispersions prepared, employing HPMC gave higher values than those prepared from PVA. As the concentration of HPMC increased, the dissolution rate increased, whereas in the case of PVA, as the concentration of the carrier increased the dissolution rate decreased. Solid dispersions, carvidelol – HPMC (1:4) and carvidelol –PVA (1:1) ratio gave higher dissolution rate and dissolution efficiency values than all other dispersions. Carvidelol –HPMC (1:4) ratio gave a 19.7 fold increase in dissolution rate of carvidelol whereas in the presence of PVA (1:1) ratio, it gave an 8.33 fold increase.

REFERENCES:

1. Chowdary KPR and Madhavi BLR, **Indian Drugs,** 42(9), 557, 2005.
2. Dhirendra K, Lewis S, Udupa N and Atin K., **Pak. J. Pharm. Sci,** 22(2), 234, 2009.
3. Patidar Kalpana, Soni Manish, Sharma K. Dinesh and Jain K. Surendra., **Drug Invention Today,** 2(7), 349, 2010.
4. Khan K. A., **J. Pharm. Pharmacol.** 27, 48, 1975.