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Comparative study of dissolution behavior on solid dispersions and inclusion complexes of rofecoxib.

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ABSTRACT

The drug dissolution studies are essential for the assessment of drug absorption and many pharmaceutical agents show the poor aqueous solubility results with poor absorption. The present study is aimed at improving the dissolution of poorly water-soluble NSAID, rofecoxib. It is very slightly soluble in water and hence orally administered drug is showing less bioavailability. In order to enhance the bioavailability it is necessary to improve its solubility of drug. The physical mixtures and solid dispersions were prepared in different proportions using hydrophilic carriers like polyvinylpyrrolidone (PVP) and polyvinylpyrrolidonevinyl alcohol (PVPVA). Inclusion complexes of β-cyclodextrin (βCD) were also prepared in 1:1 and 1:2 molar ratios to study the influence on the solubility and dissolution rate of rofecoxib. The prepared formulations were characterized for percentage yield, drug content, average particle size, hygroscopic studies and IR spectral studies. The dissolution rate studies were performed in phosphate buffer, pH 7.4 and the dissolution rates were found to be in the following order: β-CD >solid dispersion >physical mixture > pure drug. The enhancement in solubility of rofecoxib helps in improving its bioavailability and also to reduce its dose.

Key Words: Rofecoxib, Dissolution rate, β-cyclodextrin, Solid Dispersion, Solubility.

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INTRODUCTION

The drug absorption is an important parameter for drug action in the body. The drugs solubility or dissolution is the pre requisite step for absorption. The solubility enhancement of poorly water-soluble drugs has been the subject of many studies published in literature. The various techniques to enhance solubility like co-solvency, hydrotrophy, surfactants, inclusion complexes etc., were studied [1]. Cyclodextrins and their derivatives are the inclusion complexes play an important role in formulation development of poorly water-soluble drugs, due to their effect on solubility, dissolution rate, chemical stability and absorption of drugs [2]. Cyclodextrins have been studied during the past two decades; their commercial application in pharmaceutical formulation widely used in enhancement of solubility of is drugs such as phenyl butazone, nimesulide and piroxicam [3].

Solid dispersion is another approach widely used for the enhancement of solubility of poorly water soluble drugs [4]. The concept of solid dispersion was introduced by Sekiguchi and Obi [5]. In solid dispersion method the drug is dispersed in extremely fine state in an inert water-soluble carrier in solid state. A number of freely water-soluble materials such as citric acid, bile acids, sterols and related compounds and polymers like Polyvinylpyrrolidone and Polyethylene glycols were used as carriers for solid dispersions [6]. By this approach the dissolution rate and bioavailability of poorly soluble drug can be increased [7].

Rofecoxib is a non-steroidal anti-inflammatory agent, which has very low solubility in water and therefore shows very low bioavailability. Rofecoxib is having good anti-inflammatory and analgesic properties and useful in the conditions like inflammation, spondylitis, rheumatoid arthritis and osteoarthritis. Rofecoxib is very slightly soluble in water and its bioavailability is very less[8]. In the present investigation an attempt has been made to improve and compare the solubility and thereby the bioavailability of rofecoxib by solid dispersions and inclusion complexes using β-cyclodextrins.

MATERIALS AND METHODS

Rofecoxib was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad. PVP and PVPVA were obtained as gift samples from Noveon laboratories, Mumbai and all other chemicals were of analytical grade.

Preparation of Physical Mixtures

The physical mixtures were prepared by mixing pre-weighed amounts of rofecoxib and carriers (PVP/ PVPVA) in 1: 0.5, 1:1 and 1:2, ratios. Four batches of drug: carrier in different ratios was prepared in similar manner (Table 1).

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Preparation of Solid Dispersions

Solid dispersions of rofecoxib were prepared with carriers (PVP / PVPVA) in, 1:0.5, 1:1 and 1:2 weight ratios by fusion method[9,10]. A known weight of carrier and drug were mixed thoroughly and the mixture was subjected to thermal fusion with constant stirring. The melted mass was shock cooled on an ice cooled ceramic tile. Solidified mass obtained was powdered and passed through Sieve No 100. The powdered solid dispersion was further dried and stored in desiccators.

Preparation of β-cyclodextrin Inclusion Complexes

Inclusion complexes of rofecoxib and β-cyclodextrin (βCD) were prepared in 1:1 and 1:2 molar ratios using kneading method [11] in which known weight of βCD (Table 1) was taken in a glass mortar, water was added slowly and mixed to obtain a homogeneous paste. Then weighed quantity of drug was added slowly by grinding for one hour. Appropriate quantity of water was added during grinding to maintain the suitable consistency. Finally the mixture was dried in an oven at 40°C for 48 hours. Then the product obtained was powdered and passed through sieve 100 # and further dried in vacuum oven at 40° C, and stored in a desiccators for further studies.

EVALUATION PARAMETERES

Compatibility of the drug and carriers was studied by comparing the IR spectra taken for the drug, carriers and the formulations separately. The products obtained were analyzed for appearance, shape, colour and texture. All the formulations were prepared under similar set of conditions. The percentage yield was estimated on the basis of dry weight of the substances taken and the final weight of the product obtained.

Drug content

Drug content in various formulations was determined by UV spectrophotometric method. Fifty mg of formulation was accurately weighed and dissolved in 100ml of 20% v/v acetic acid, from that 1ml of solution was diluted to 10ml and assayed for drug content using UV-visible spectrophotometer at 261nm[12].

Particle size analysis

The prepared formulations were evaluated for particle size distribution and average diameter by optical microscopy method. The calibrated optical microscope was used for the study. Small quantity of the formulation was dispersed using liquid paraffin and spread into a thin film on a microscopic slide, Particles were observed under high power (45×) of microscope and the size of 150 randomly selected particles at different locations were measured, Size distribution and average size of the particles was calculated [13].

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Moisture absorption studies

Moisture absorption studies were done to study the extent of moisture absorbed by the formulations when they are stored under different storage conditions. Fifty mg of each of the formulations (dried in a desiccator under anhydrous $CaCl_2$) was accurately weighed and exposed to ambient atmospheric conditions (70±5% RH, 30±2°C) and accelerated humidity condition (99±1%RH, 30°C±2) for 2 days. The gain in their weight was determined and the percentage moisture absorbed was calculated [14].

***In vitro* dissolution study**

Dissolution studies were performed using USP XXII basket type dissolution test apparatus in 900ml of phosphate buffer, pH 7.4 at 50 rpm and 37° ± 0.5°C for 2 hours. The samples (pure drug/ physical mixture/ solid dispersion/ βCD complexes) equivalent to 100 mg of drug were filled into a capsule and placed into the basket of the dissolution test apparatus. Known volume of samples was withdrawn at different time intervals and the amount of drug dissoluted was calculated after suitable dilution by spectrophotometric method [15].

Anti-inflammatory activity

Anti-inflammatory activity was studied by paw edema method using rats as test animals. The animals were divided into 4 groups, each containing 6 animals. First group was served as control for which 0.5% of sodium CMC suspensions, for second group, suspension of pure drug in 0.5% sodium CMC, for third group the suspension of selected solid dispersion in 0.5% sodium CMC and for last group βCD complexes in 0.5% sodium CMC were administered orally. The inflammation was induced by administering 0.1% w/v carrageenan by sub plantar route. Percent reduction in the oedema produce in the paw of the rats in each group was determined for the evaluation of anti-inflammatory activity [16].

RESULTS AND DISCUSSION

All the formulations were found to be free flowing under dry conditions. Percentage yield of prepared formulations with reference to the weight ranged between 94-97% (Table-1).

Percentage drug content in different batches of formulations was found to be in confirmation with the theoretically calculated values, which indicated that there was no degradation of the drug during the preparation and it was stable in the formulations (Table-1). Low values of standard deviation in % drug content indicate the reproducibility of the method.

Particle size of all the prepared formulations ranged from 25-150μ and the average diameter was in the range of 51μ to 65μ (Table-1).

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The moisture absorption studies revealed that the tendency of moisture absorption was maximum with solid dispersions followed by β-CD complexes. Formulations containing PVPVA as carrier were more hygroscopic in comparison with those containing PVA (Table-1).

Table 1: Physical Characteristics of the formulations

Composition	Drug: Carrier Ratio	Percent Yield	Drug content μg/ml*	Average particle size (μm)	% Moisture absorption	
					Ambient humidity conditions	Accelerated humidity conditions
Pure drug	-	-	-	56.21	0.8	1.4
Solid Dispersion PVP	1:0.5	95.5	9.8	64.33	0.7	1.0
	1:1	93.9	9.9	66.51	0.6	1.1
	1:2	96.9	9.8	51.27	0.9	1.9
Solid Dispersion PVPVA	1:0.5	95.3	9.6	63.27	0.9	2.0
	1:1	94.9	9.9	71.04	1.0	3.4
	1:2	84.1	9.8	57.83	1.3	5.2
β-CD Complex	1:1M	92.9	9.8	60.59	1.2	3.7
	1:2M	97.2	9.9	61.22	1.0	3.9

*The theoretical value is 10μg/ml.

Stability of the drug in the formulations and absence of interaction between drug and carriers was confirmed from the IR spectra obtained for pure drug, solid dispersions and βCD complexes. The spectra have shown the characteristic peaks corresponding to the drug and carriers used.

The results obtained from dissolution studies have shown that the dissolution profile in the following order: βCD complexes>solid dispersion > physical mixture > pure drug. The increase in dissolution rate from βCD complexes is due to the formation of water-soluble inclusion complexes with the β-cyclodextrin. Moreover, the dissolution rate of the drug β-CD complexes in 1:2 M ratio was found to be superior in comparison to other ratios (Table-2).

While in case of solid dispersions reason for increased solubility may be attributed to the reduction in the particle size and/or the presence of drug in the form of solid solution in a water-soluble carrier in molecular form/high energy amorphous form. Greater solubility of drug from the physical mixture than the pure drug can be attributed to the wetting of hydrophobic surface of aceclofenac due to solubilization of water-soluble carrier. In the above studies, formulations containing PVPVA as carrier showed better dissolution rate than PVP and the optimized drug-carrier ratio was 1:2. From the results it is observed that the use of water-soluble carriers improves the wettability of the drug particles and hence increases the dissolution rate.

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Table 2: Dissolution of the Formulations in Phosphate Buffer.

Composition	Ratio	Percent release at 2hr in Phosphate buffer (pH 7.4)	
Pure Drug	1:0	16.5	
		Physical mixture	**Formulation**
Solid Dispersion PVP	1:0.5	19.9	26.7
	1:1	24.6	31.2
	1:2	32.7	42.3
Solid Dispersion PVPVA	1:0.5	22.4	31.0
	1:1	29.3	39.8
	1:2	40.2	49.8
β-CD Complex	1:1M	27.9	56.5
	1:2M	33.2	70.6

The study of anti-inflammatory activity revealed that the percentage inhibition of oedema with β-CD complex, solid dispersions and pure drug was 58%, 46% and 27% respectively (Figure-1).

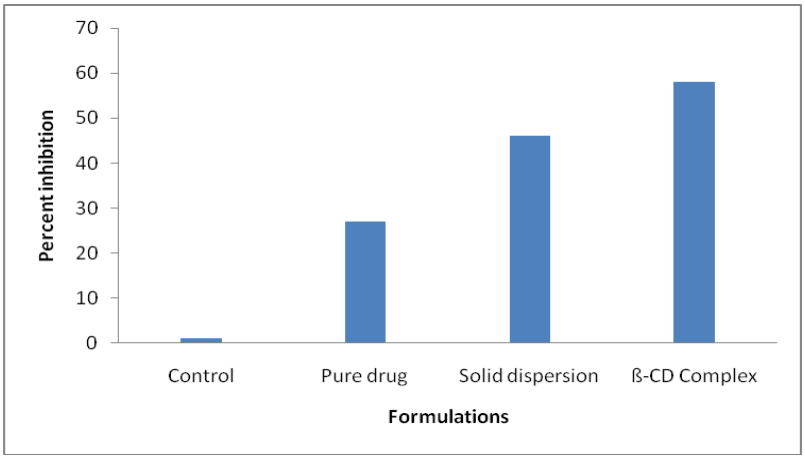

Figure-1. Anti-inflammatory activity of various formulations

CONCLUSION

From the above studies it can be concluded that the techniques of enhancing solubility like molecular inclusion complexation and solid dispersions can enhance the dissolution profile of rofecoxib. The β-CD complexation technique has showed highest rate of dissolution when compared to solid dispersion, which has the advantage to produce a faster absorption results with better onset of action and also be helpful in dose reduction.

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