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Research Article

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STUDIES TO ENHANCE DISSOLUTION PROPERTIES OF CELECOXIB

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ABSTRACT

Celecoxib is a selective cox-2 inhibitor is indicated to the treatment of Osteoarthritis, Rheumatoid arthritis, and acute painful primary Dysmenorrhoea. It is also superior to other NSAID's, due to lower incidences of symptomatic gastrointestinal ulcer complications than other NSAID's. Celecoxib is practically insoluble in water. The present investigation deals with enhancement of dissolution rate of Celecoxib using PVPK30 as carrier at various proportions (1:1, 1:2, 1:4 and 1:6) with different techniques like physical mixtures, kneading method and solvent evaporation method. The release profiles was studied in water containing 2 % SLS. UV Spectrophotometric method was selected for assay as well as dissolution studies at 254 nm .The dispersions were evaluated for drug content uniformity, dissolution rate study, T50, DE20, ANOVA. The FTIR & DSC were used to characterize solid state of solid dispersions. Amarked increase in the dissolution rate was observed with all solid dispersions, among that Celecoxib with PVPK30 by solvent evaporation method showed maximum drug release.

Keywords: Solid Dispersion, Celecoxib, Physical mixtures, Kneading Method, Solvent Evaporation Method and Polyvinyl Pyrrolidone.

INTRODUCTION

Celecoxib (CXB) is a NSAID, which exhibits potent anti inflammatory and analgesic action by inhibiting prostaglandin synthesis by specifically inhibiting the COX-2 enzyme. It exhibits anti-inflammatory, analgesic and antipyretic action; it is mainly used for Osteoarthritis, Rheumatoid arthritis, and acute painful conditions, primary Dysmenorrhoea and Ankylosing spondylitis.[1] Celecoxib is preferred over conventional NSAIDs, as the latter may lead to serious gastrointestinal complications like ulcer, severe bleeding and perforation, resulting in hospitalization and even death. The rate and extent of dissolution of the drug from any solid dosage form, determines the rate and extent of absorption of drug. In case of poorly soluble drugs dissolution is the rate limiting step in the process of drug absorption Potential Bio availability problems are prevalent with extremely hydrophobic drugs (aqueous solubility less than 0.1mg/ml at 37°C) due to erratic (or) incomplete absorption from G.I.T. The solid dispersion (SD) approach has been widely and successfully applied to improve the solubility, dissolution rate and consequently the bioavailability of poorly soluble drugs.[2-4] A number of drugs have been shown to improve their dissolution character when converted to solid dispersions. Aceclofenac[5], Sulphamethoxazole[6], Nifedipine[7], Glyburide[8], Melaxicam[9], Valdecoxib[10], Rofecoxib[11]. Various hydrophilic carriers, such as PEG[12], PVP[13], HPMC[14], Gums[15], Sugars[16], Mannitol[17] and Urea[18] have been investigated for improving the dissolution rate and bioavailability of poorly aqueous soluble drugs. In the present work, solid dispersion of Celecoxib with PVP K30[19], prepared in different Drug: carrier ratios (1:1, 1:2, 1:4, 1:6) with different techniques like physical mixture (PM), kneading method (KM), solvent evaporation method (SE) to improve solubility and dissolution characteristics UV Spectrophotometric method was selected for assay as well as *in-vitro* dissolution study at 254nm in 900 ml water containing 2% SLS[20]. The dissolution profile of best solid dispersion i.e. CXB: PVP K30 1:4 SE, showed maximum dissolution rate. The increase in dissolution rate of the drug may be due to increased wettability, hydrophilic nature of the carrier and also possibility due to reduction in drug crystalinity.

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MATERIALS AND METHODS

Celecoxib was procured from Karup Pharma Pvt. Ltd., Hyderabad. PVP-K30 and SLS were purchased from SD Fine chemicals Ltd, Mumbai. Methanol and Dichloromethane were purchased from Qualigens fine Chemicals, Mumbai.

Preparation of physical mixtures

Physical mixtures were prepared by simple blending of accurately weighed quantities of drug(s) and carrier(s) sifted through sieve # 100 in a closed glass bottle. The powders were then stored in a dessicator.

Preparation of Solid Dispersions

Kneading method

The weighed quantities of drug and carrier were triturated in a mortar with a small volume of methanol. The thick

slurry was kneaded for 45 min and then dried at 50ºc to constant weight. The dried mass was pulverized and sifted through sieve # 100 and stored in a desiccator.

Solvent evaporation method

The accurately weighed amounts of drug and polymer were dissolved in sufficient quantity (60 ml) of solvent blend to obtain clear solution. Dichloromethane and methanol in the ration of 2:1 was used as solvent blend for PVPK-30. The solvent blend was removed by evaporation in a water bath at 45ºc under reduced pressure. The resulting residue was then transferred to glass desiccator and dried under vacuum to constant weight. The dried product was powdered and sifted through sieve # 100 and stored in a desiccator prior to use.

Drug Content Analysis

An ultra violet spectrophotometric method based on the measurement of absorbance at 254 nm in water containing 2%w/v Sodium lauryl Sulphate was developed and used for the estimation of CXB. The method obeyed Beer's law in the concentration range of 0-10µg/ml. When a Standard drug solution was assayed repeatedly (n=6).

***In- vitro* Dissolution Study**

The dissolution rate of Celecoxib as such and it's solid dispersions was studied using DISSO 2000, Lab India 8-Station Dissolution Rate test Apparatus with a paddle stirrer ,at 50 rpm and temperature of 37±1^0 C . The Dissolution rate was studied in 900ml of water containing 2% SLS, Sodium lauryl sulphate was added to the dissolution fluid to maintain sink condition. Celecoxib (100mg) or its SDs equivalent to 100mg of Celecoxib were used in each test. Samples of dissolution medium (5ml) were withdrawn through a filter (0.45 micron) at different time intervals, suitably diluted and assayed for Celecoxib by measuring absorbance at 254nm.The dissolution experiments were conducted in Triplicate.

Characterization of SDs

Solid dispersions were characterized by (IR) spectroscopy and differential scanning calorimetry (DSC) and the FTIR spectra of pure drug and their solid dispersions were obtained on a Perkin –Elmer 841 FTIR spectrophotometer equipped with a DTSG detector. By using KBr disc method. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4cm^{-1} .DSC curves of the CXB and SD$_S$ were obtained by differential scanning calorimeter (DSC 220C,SEIKO, Japan) at a heating rate of 10^{0}C/min from 50 to 300^{0}C.

Dissolution Efficiency (DE)

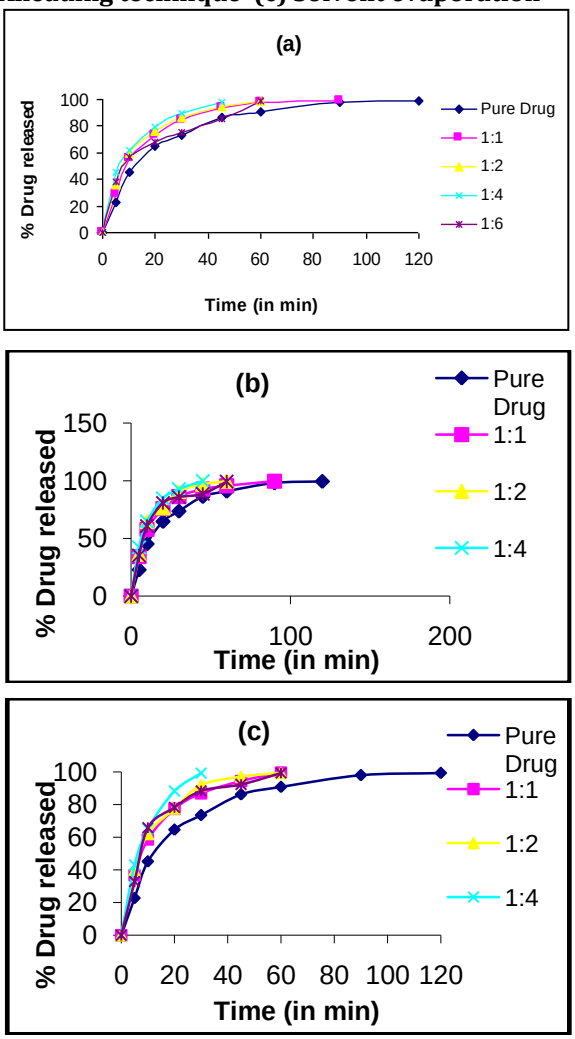
DE is a parameter for evaluation of in-vitro dissolution data. It is expressed as the area under dissolution curve up to a certain time 't' expressed as percentage of the area of the rectangle described by 100 percent dissolution at the same time.

$$DE = \left(\frac{\int_0^t y.dt}{y_{100}.t}\right)100$$

RESULTS AND DISCUSSION

All the Solid dispersions (SDs) were found to be free flowing under dry conditions. Low C.V (< 1.0%) values in percent drug content indicated uniformity of drug content in each batch of solid dispersions. The dissolution rate of Celecoxib as such and from various solid dispersions was studied in water containing 2 % SLS. Sodium Lauryl Sulphate was added in the dissolution medium to provide sink conditions. The dissolution profiles of various SDs are shown in Figure **1**.

Figure 1. Dissolution profiles of Celecoxib from PVP K30 Solid Mixtures prepared by (a) Physical mixing (b) Kneading technique (c) Solvent evaporation



The dissolution of Celecoxib was rapid and higher from all the SDs when compared to Celecoxib pure drug, i.e. the dissolution rates are in the order: SD> PM> Pure drug. The increased solubility of SDs was due to 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, wettability and prevention of aggregation of drug by carriers. There is a significant improvement in solubility and dissolution rtate of poorly soluble drugs by using different drug- polymer ratios and preparing SDs by different methods like PM, KM and SE. The dissolution rate of drug increased with increase in polymer concentration and it is dependent on the method of preparation.The dissolution parameters.Indicates that the solid dispersions prepared with Celecoxib by solvent evaporation method i.e. Celecoxib with PVP K30 1:4 drug-polymer ratio was found to be the best solid dispersion. The dissolution parameters were shown in Table **1**. Further increase in the concentration of the polymer shown decrease in the dissolution. This may be due to the high viscosity generated by the polymer in the microenvironment of drug polymer particles during dissolution, reducing the diffusion rate of the drug, thereby decreasing the dissolution efficiency.

The dissolution of Celecoxib as such and prepared solid dispersions followed First order kinetics (r>0.982). The dissolution rate constants (k_1) were calculated from the slopes of the first order linear plots of the dissolution data. Dissolution efficiency (DE_{20}) values based on the dissolution data were calculated according to Khan [21]. T_{50}

(Time taken for 50% dissolution) values were recorded from the dissolution profiles.

Table 1. Dissolution parameters of various Celecoxib solid dispersions prepared

Product	*Percent Dissolved in 10 (min)	*$T_{50\ (min)}$	*$DE_{20\ (\%)}$	*$K_{1\ (min-1)}$
CELECOXIB	-	> 60	20	-
CELECOXIB-PM				
1:1	55.47	9.10	43.86	0.0483
1:3	59.64	8.10	45.12	0.0658
1:6	61.68	7.40	50.14	0.0808
1:9	57.16	8.20	46.82	0.0438
CELECOXIB-KM				
1:1	57.85	8.10	45.12	0.0469
1:3	61.63	7.05	46.18	0.0601
1:6	64.83	7.10	53.12	0.0739
1:9	60.74	9.0	48.14	0.0483
CELECOXIB-SE				
1:1	58.72	8.40	45.12	0.0446
1:3	62.03	8.0	54.18	0.0564
1:6	65.14	6.0	58.14	0.2275
1:9	56.85	10.0	38.62	0.0414

$DP_{10=}$ Percent drug dissolved in 10 minutes, $T_{50=}$ Time taken for 50% dissolution, $DE_{20=}$ Dissolution efficiency at t=20 minutes, $K_{1\ (min-1)}$ =First order rate constant. (n=3)
* = Average of 3 determinations.

FTIR spectra of Celecoxib, PVP K30 pure form and solid dispersions of celecoxib: PVP K30 1:4 SE shown in Figure **2, 3** and **4.**

Figure 2. FTIR Spectra of PVP K 30

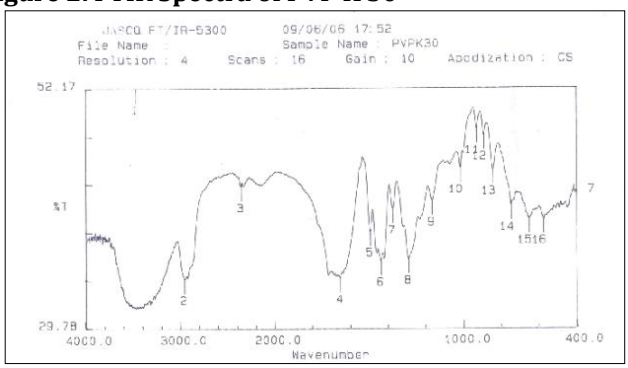


Figure 3. FTIR Spectra of Celecoxib

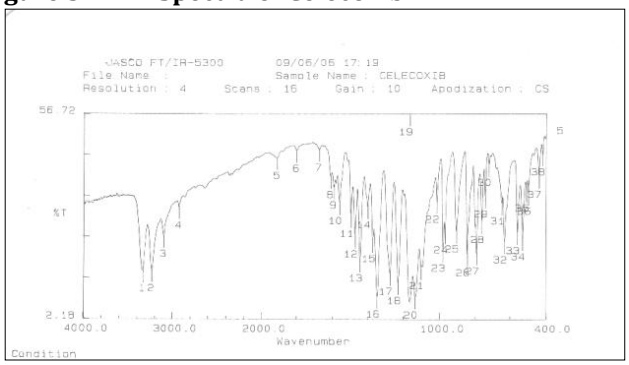
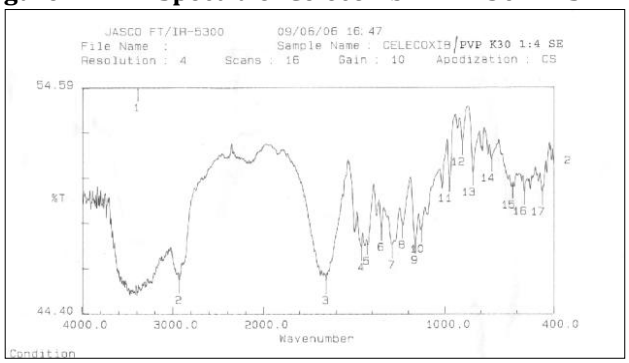
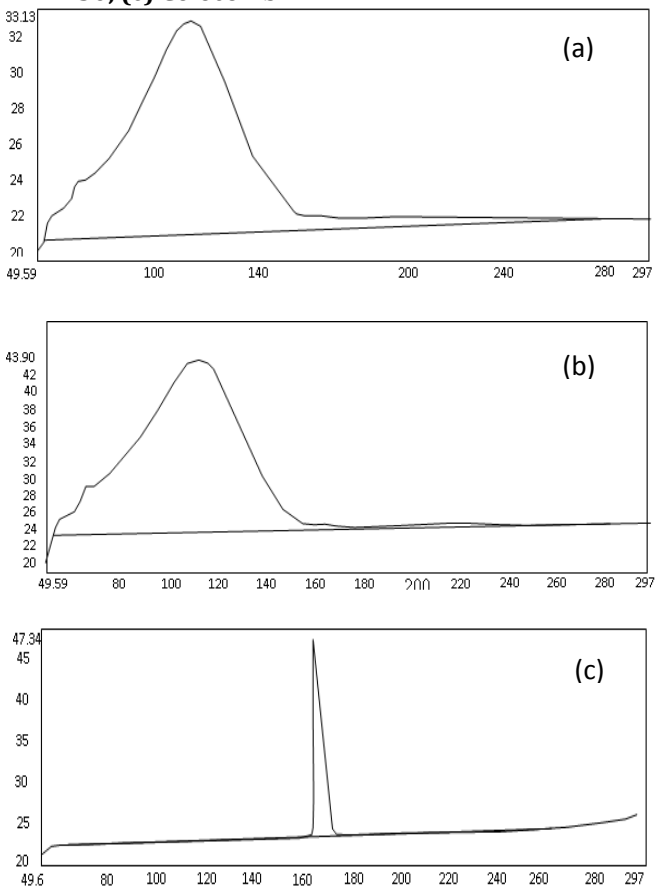


Figure 4. FTIR Spectra of Celecoxib:PVPK 30 1:4 SE



The IR spectroscopy was used to study the possible interaction between Celecoxib and carriers used in the solid dispersions, The FTIR spectra of SDs did not differ from that CXB and the principle of absorption bonds as in IR spectra of CXB, in particular the characteristic sulfonamide (SO_2 stretching) 116.5cm^{-1} was unchanged showing no interaction between drug and carrier.The DSC thermogram of CXB and PVP K30 and its SD_s are given in the Figure **5**.

Figure 5. DSC Thermograms of (a) CXB-PVP-1: 4-SE, (b) PVP K30, (c) Celecoxib



The DSC thermogram of CXB exhibits sharp meltimg endotherm of 166.36^{0}c corresponding to its melting point. The carrier PVP K30 exhibited endothermic peak of 115.85^{0}c respectively corresponding to dehydration. The thermogram of CXB: PVPK30 1:4 SE showed endothermic peak of 114^{o}c, the appearance of endothermic peaks at lower temp. For both SDs prepared with PVP K30 and indicated the possible formation of solid dispersion between the drug and the polymer there by reducing the respective melting points. SDs were stable and absence of any additional peaks indicated no interaction between the drug and the carrier.

CONCLUSION

From the above study, it was concluded that the solid dispersion technique has been shown as a successful approach to improve the dissolution rate of Celecoxib. The method and the amount of carrier played an important role in the enhancement of dissolution rate. The solvent evaporation technique would be used to develop fast release formulations of Celecoxib and other poorly soluble drugs.

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