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Original Article

A comparative study of dissolution profile of drug by enhancing aqueous solubility through Kneading method

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ABSTRACT: Solid dispersions (SDs) are resulted by dispersion of drug in biologically inert matrix. They can be used to increase the solubility of a drug with low aqueous solubility, thereby improving its oral bioavailability. Higher drug dissolution rates from a SD can be facilitated by optimizing the wetting characteristics of the compound surface, as well as increasing the interfacial area available for drug dissolution. Although the latter can be easily accomplished by, for example: decreasing the particle size of the drug powder but micronized powders may result in further complications as they occasionally tend to agglomerate. A more preferable solution would be to introduce the drug in the form of a molecular dispersion. The aim of present study was to enhance the dissolution rate of diclofenac a practically less water-soluble drug. The same was done by preparation of solid dispersions of the drug employing different ratios of established polymers. This was done by using polymers namely; hydrophilic polymer β-cyclodextrins, PVP and PEG. The kneading method was used to prepare solid dispersions in various ratios with polymer. The dissolution data was studied for all the three formulations. The data obtained was compared with that of physical mixtures containing drug, polymer and lactose in the same ratio as that of solid dispersions. The dissolution data showed that best release was obtained in formulation f1 containing beta –cyclodextrins, PVP and PEG as polymer. The comparative data showed 98% release at approximately 4 hours with polymer β –cyclodextrins, whereas, 90% and 88% release were obtained using PEG and PVP respectively in the same time frame.

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INTRODUCTION

Diclofenac sodium is the sodium salt form of diclofenac, a benzene acetic acid derivate and nonsteroidal anti-inflammatory drug (NSAIDs) with analgesic, antipyretic and anti-inflammatory activity. Diclofenac sodium is a non-selective reversible and competitive inhibitor of cyclooxygenase (COX), subsequently blocking the conversion of arachidonic acid into prostaglandin precursors. This leads to an inhibition of the formation of prostaglandins that are involved in pain, inflammation and fever. Solid Dispersions (SDs) are resulted by dispersion of drug in biologically inert matrix. They can be used to increase the solubility of a drug with low aqueous solubility, thereby improving its oral bioavailability. Higher drug dissolution rates from a SD can be facilitated by optimizing the wetting characteristics of the compound surface, as well as increasing the interfacial area available for drug dissolution. Although the latter can be easily accomplished by, for example, decreasing the particle size of the drug powder but micronized powders may result in further complications as they occasionally tend to agglomerate. A more preferable solution would be to introduce the drug in the form of a molecular dispersion. The formulation of poorly soluble compounds for oral delivery now presents one of the greatest and most frequent challenges to formulation scientists in the pharmaceutical industry. Several methods have been employed to improve the solubility of poorly water-soluble drugs. The mechanisms of enhancement of dissolution rate of SDs have been proposed by several investigators. A molecular

dispersion of the drug in polymeric carriers may lead to particle size reduction and surface area enhancement, which results in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during the dissolution process, and there is an improvement in drug solubility and wettability due to surrounding hydrophilic carriers. The method of preparation and type of the carrier used are important influences on the properties of SD [1, 5].

MATERIALS AND METHODS

The diclofenac sodium was obtained from Sigma Aldrich. Polyvinyl pyrrolidone (PVP) & Polyethylene glycol (PEG 400) was purchased from SDFCL and β-Cyclodextrin was obtained from sisco research laboratories and fine chemicals and all other chemicals solvents used were of analytical grade and supplied by the Pharmacy Department, Faculty of Pharmaceutics, of the Amity University Lucknow [6].

Preparation of solid dispersion

Solid dispersion was prepared by mixing accurately weighted of drug and polymer in ratio of 2:1:1 for 5 min using pestle and mortar. Same was done using of the three polymers. The solid dispersion was triturated using a small volume of ethanol and water (1:1) solution to convert into a thick paste, which was then kneaded for 30 min, and dried at 45°C in an oven. The dried mass was pulverized, passed through 30 mesh sieve size, stored in a desiccator (48 h), and passed through 60 mesh sieve size, then weighed, transferred to, airtight container, stored at 30°C [7, 8].

Preparation of physical mixture

Physical mixture was prepared by mixing of accurate weight of drug and polymer ratio and filled in gelatin capsules. [9]

Table 1: Composition of the prepared formulation

S. No,	Ingredients	Formulations			
		F1	F2	F3	F4
1	Diclofenac sodium	400 mg	400 mg	400 mg	400 mg
2	PVP	-	-	200mg	-
3	PEG	-	200mg	-	-
4	β- cyclodextrin	200mg	-	-	-
5	Lactose	200mg	200mg	200mg	200mg

In-vitro drug release profile

The dissolution studies were carried out in dissolution apparatus USP Type 1. The temperature and basket speed were maintained at 37.0±0.5°C at 75 rpm for 2 hrs. The dissolution medium consisted of 600 ml of pH (1.2) simulated gastric medium. At predetermined time, 5 ml samples were withdrawn filtered through 0.45µm Whatman filter paper, diluted suitably and analyzed spectrophotometrically at -278 nm (Model UV- 1700, UV- Visible spectrophotometer, Shimadzu, Kyoto, Japan). An equal volume of fresh dissolution medium maintained at the same temperature was added to maintain the sink conditions and calculated the percentage cumulative release [10,11].

RESULTS AND DISCUSSION

The present investigation was aimed to prepare solid dispersion of diclofenac sodium by kneading method using PVP, PEG-400 and β- Cyclodextrin. Methanol was employed as a common solvent to dissolve the polymers as well as drug.

Dissolution studies

Release of diclofenac sodium from solid dispersion formulation in acidic medium showed that the release rates of diclofenac sodium from solid dispersion were faster as compared with physical mixture. The significant drug particle size reduction achieved in solid dispersion contributes to this improved dissolution rate.

The data obtained was compared with that of physical mixtures containing drug, polymer and lactose in the same ratio as that of solid dispersions. The dissolution data showed that best release was obtained in formulation F1 containing β–cyclodextrins, PVP and PEG as polymer. The comparative data showed 98% release at approximately 4 hours with polymer β–cyclodextrins, whereas, 90% and 88% release were obtained using PEG and PVP respectively in the same time frame.

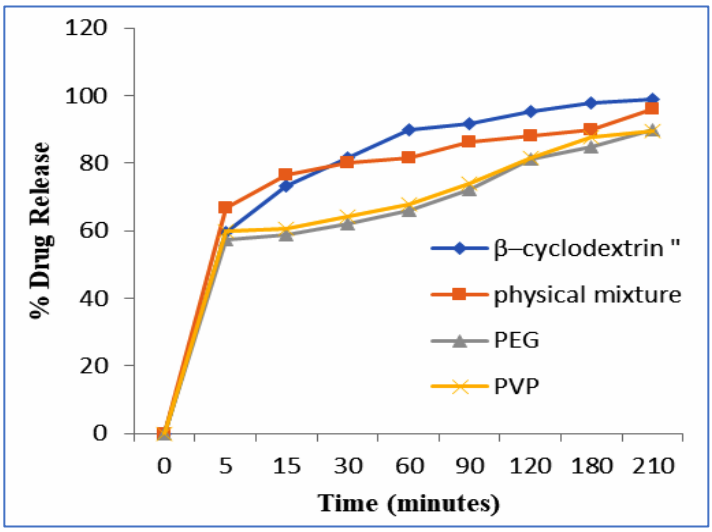

Figure 1: Comparative dissolution profile of SD of different polymer with physical mixture

CONCLUSION

Results demonstrate that among all three polymers, β-cyclodextrin when entrapped the drug through formulation of solid dispersion showed best increase in solubility and release kinetic profile. This can be correlated with the release profile as depicted in figure 1. Hence kneading method for solubility enhancement provide as cheaper and economical technique for increasing solubility of the drug.

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