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FORMULATION AND EVALUATION OF SOLID DISPERSIONS OF NIMESULIDE WITH SELECTED POLYETHYLENE GLYCOLS

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ABSTRACT

Nimesulide is a poorly soluble drug in aqueous media for better bioavailability the rate of dissolution should be enhanced so as to keep more drug in solution under sink conditions. The present work is aimed at enhancing the rate of dissolution of Nimesulide by preparing solid dispersions using PEG 4000 and PEG 6000 as carriers. uniform and homogenous solid dispersions of Nimesuilide with PEG 4000 and PEG 6000 were prepared in the ratio of 1:1 ,1:2,1:3,1:4 by fusion technique. the pure drug, powder blend and solid dispersion were subjected to dissolution studies using a buffer pH 8.5 and 1.2pH buffer containing 3% SLS disposition and all the released the drug within an accepted range. In the above study several fold increase in dissolution was observed with the solid dispersion of Nimesulide containing PEG 4000 as carriers compared to the pure drug and the physical mixtures. As the concentration of the carriers increased the cumulative amount of the released also gradually increased. The enhanced solubility is probably due to the solubilization effect of PEG at higher level and Similar results were observed with PEG 6000.

INTRODUCTION

Nimesulide is a poorly soluble drug in aqueous media. One of the techniques to increase the solubility of poorly soluble drugs is to prepare them into solid dispersions. We can define Solid dispersion as dispersion of one or more active ingredient in an inert carrier at solid state prepared by melting /fusion, solvent or melting solvent method. In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. Solid dispersion techniques can yield eutectic (non-molecular level mixing) or solid solution(molecular level mixing) products [1]. According to the Biopharmaceutical Classification System (BCS) drugs can be divided into four classes, depending on their solubility and permeability. Drug (nimesulide) Which belong to class II is characterized by low solubility and high permeability [2].Nimesulide (N-(4-nitro-2-phenoxyphenyl)-methane-sulphonamide) is a relatively non-steroidal anti-inflammatory drug with analgesic and antipyretic properties that does not induce gastrointestinal ulceration [3]. Drugs with a limited dissolution and adsorption might benefit from a reduction in particle size (table1), as well as from an increase in saturation solubility. Both principles form the prerequisite for the use of solid dispersions, a possible pharmaceutical strategy that can result in increased solubility and dissolution rate. This term refers to a dispersion of an active ingredient in an inert hydrophilic carrier in the solid state, prepared by melting (fusion) or

solvent method [4]. Poorly water-soluble compounds with dissolution rate-limited low oral bioavailability present one of the major challenges in pharmaceutical formulation development.

There are many ways to increase the aqueous solubility of such compounds, including micronization, salt formation, polymorphs, complexation, cosolvency, micronization, nanotechnology and formulation of the drug as a solid dispersion [5].Solid dispersion (SD) technique has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs[6].The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles therefore, based on their molecular arrangement six different types of solid dispersions can be distinguished [7]. Solid dispersions, in which the drug may be present in the amorphous state, offer an attractive means of increasing the solubility and therefore, potentially increase the oral bioavailability of these problem compounds[8].In various studies the designation of solid dispersions is based on the method of preparation[9].Many case studies showed accelerated dissolution of hydrophobic compounds using solid dispersions but mechanisms are rarely discussed[10].Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules [11]. The commercial use of such systems has been limited primarily because of manufacturing problems with solid dispersion systems may be overcome by using surface active and self-emulsifying carriers. The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers [12]. Recently, surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating their solubility [13]. The influence of drug load and method of preparation on dissolution behavior and stability of solid dispersions can only be understood and predicted when the relation between these characteristics and the mode of incorporation is known[14]. Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high[15].

Objective: Nimesulide is a poorly soluble drug in aqueous media.For better bioavailability the rate of dissolution should be enhanced so as to keep more drug in solution under sink conditions.The present work is aimed at enhancing the rate of dissolution of nimesulide by preparing solid dispersions with PEG 4000 and PEG 6000

METHODOLOGY:

Solid dispersion of Nimesulide: PEG4000 were prepared in different ratios of 1:1, 1:2, 1:3, 1:4 and 1:5. Nimesulide is to PEG6000 in the ratio of 1:1, 1:2, 1:3, 1:4 .Solid dispersions were prepared by fusion method .The pure drug, the physical mixtures and solid dispersions were evaluated for the dissolution rate in pH 8.4 buffer and pH 1.2 buffer containing 3% SLS the absorbance was measured at 397 nm for pH 8.4 buffer and at 293 nm for Ph 1.2 buffer using U.V visible spectrophotometer.

RESULTS AND DISCUSSION:

Various formulations of Nimesulide solid dispersions with PEG 4000 and PEG 6000 in the proportion of 1:1, 1:2, 1:3, 1:4 (50%, 33.33%, 66.66%, 80% of carrier mass) were prepared respectively and the rate of dissolution of the above dispersions were studied. The dispersions were yellowish in color and free flowing in nature. In case of the pure drug, the cumulative percentage amount of the drug dissolved was 39.73% in pH 1.2 buffer containing 3% sodium lauryl sulphate (SLS), about 68% in pH 8.4 buffer which shows that Nimesulide is more soluble in pH 8.4 buffer than in pH 1.2 buffer containing 3% SLS. Several fold increase in the rate of dissolution was absorbed from Nimesulide solid dispersions with PEG 4000 and PEG 6000 as carriers. The rate of dissolution of Nimesulide was increased gradually as the concentration of the carrier increased from 50% to 80%. In case of 1:1 ratio of drug : PEG 4000, physical mixture gave a marginal increase in ratio of dissolution and total cumulative amount of drug released when compared with pure drug.

Solid dispersions	Ratio	Percent of Nimesulide present + carrier
Nimesulide: PEG4000	1:1	98.2+0.32
	1:2	97.4+0.22
	1:3	95.02+0.62
	1:4	99.8+0.52
Nimesulide: PEG6000	1:1	96.02+0.35
	1:2	94.5+0.24
	1:3	98.5+0.50
	1:4	99.0+0.78

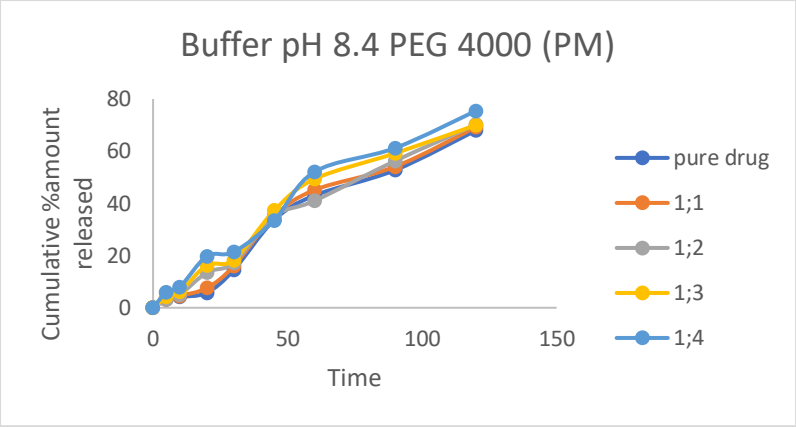

Fig 1: Dissolution of nimesulide from physical mixture of drug:PEG-4000 in pH8.4 buffer

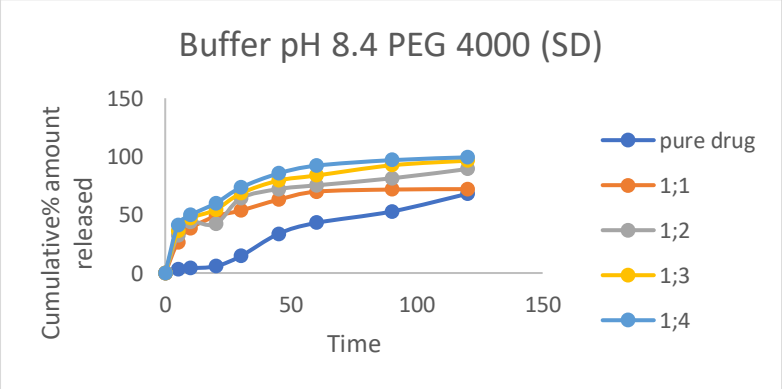

Fig 2: Dissolution of nimesulide solid dispersions of drug:PEG4000 in pH8.4 buffer

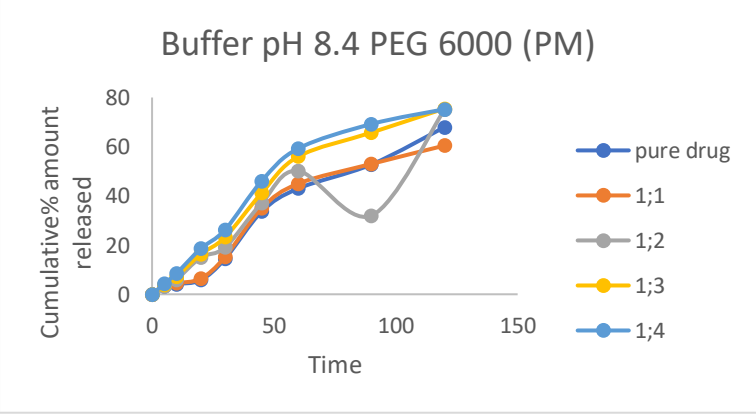

Fig 3: Dissolution of nimesulide from physical mixture of drug:PEG6000

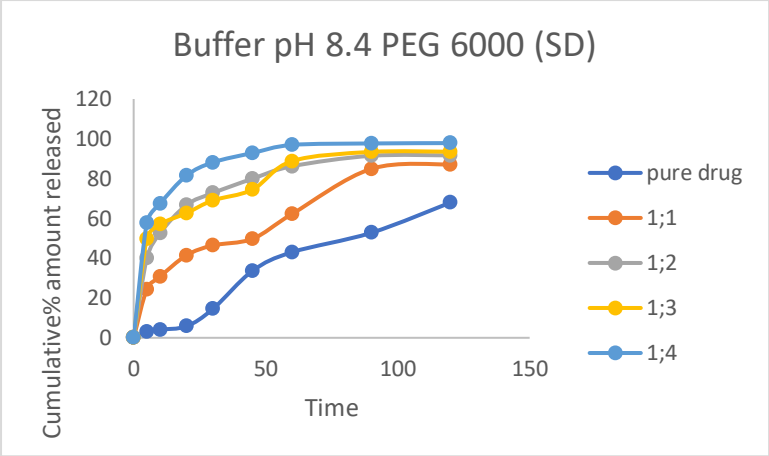

Fig 4.Dissolution rate of nimesulide from solid dispersions of drug: PEG6000 in pH8.4 buffer

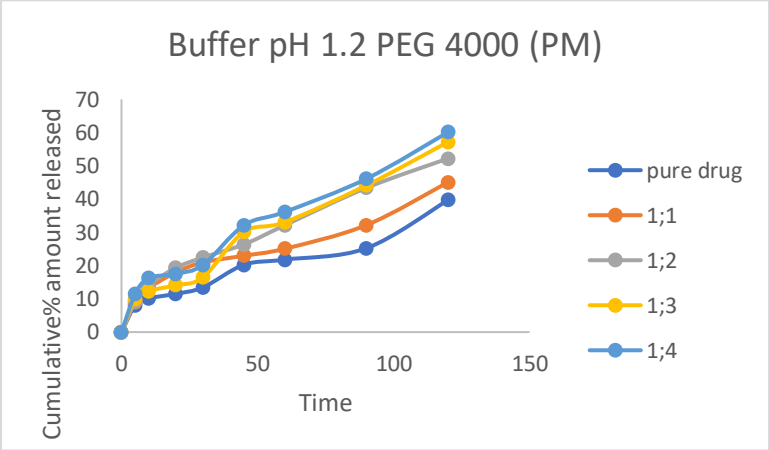

Fig 5- Dissolution rate of nimesulide from physical mixture of drug: PEG4000 in pH1.2 buffer

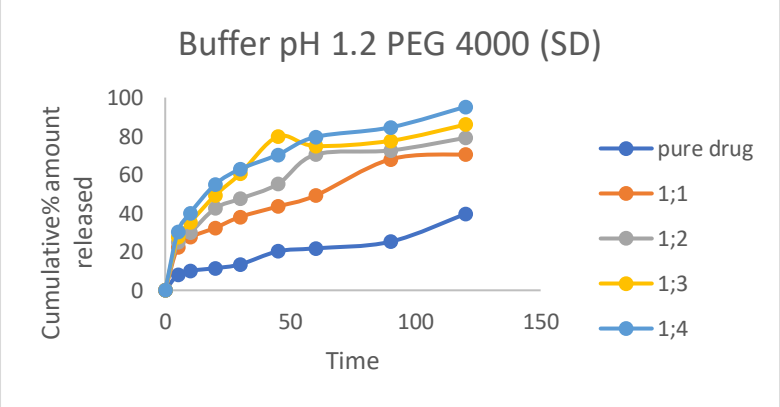

Fig 6- Dissolution rate of nimesulide from solid dispersions of drug: PEG4000 in pH1.2 buffer

Whereas the solid dispersions in the same ratio gave higher rates of dissolution, almost double that of pure drug or physical mixture in pH 1.2 containing 3% SLS. Similar results were obtained in case of 1:2, 1:3 and 1:4 proportions namely 99%. In case when the dissolution fluid was pH 8.4 buffers the increase in the rates of dissolution and cumulative amount released was marginal i.e.., the cumulative amount released in case of the pure drug was 68%, and in physical mixture and solid dispersions were 64.2% and 72% respectively for 1:1 mixtures. The above results show that the influence of the pH 8.4 buffer as a dissolution medium is more rather than the contribution due to the solid dispersions of the drug, where as when the

dissolution medium was pH 1.2 buffer the contribution of the solid dispersions towards the enhanced dissolution of the drug was more. The cumulative percentage amount released in case of physical mixture and solid dispersions was 52.2% and 79.11% in case of 1:2 mixture and 57.16% and 85.99% in case of 1:3 mixture, 60.11% and 95.23% in case of 1:4 mixture respectively. Hence there was gradual increase in the cumulative amount released as the content of PEG 4000 was increased from 50% to 80%. The enhanced solubility is probably due to solubilising effect of PEG at higher levels. In the case when pH 8.4 buffer was used as the dissolution medium there was increase of about 18 to 19% when proportion of PEG 4000 was increased from 50 to 80% while the cumulative percentage released for pure drug was 68%. From the above result pH of the dissolution medium and composition has profound influence on the cumulative percentage released. As the drug is acidic in nature it dissolved more in alkaline buffer i.e.., at pH 8.4 than in pH 1.2 buffer although containing 3% SLS. Similar results were observed when dispersions were prepared with PEG 6000 showing that the average weight of PEG has little influence on dissolution. The T_{50} values were half to 1/3rd for solid dispersions with PEG 4000 when compared with that of pure drug and physical mixture in pH1.2 buffer and pH 8.4 buffer. More or less similar results were obtained when PEG 6000 was used as carrier. These results clearly show that solid dispersions of Nimesulide and PEG 6000 and PEG 4000 sufficiently enhance the rates of dissolution as well as amounts of drug released.

CONCLUSION:

From the foregoing studies the following conclusions can be drawn.

1. Uniform and homogenous solid dispersions of Nimesulide with PEG 4000 and PEG 6000 could be prepared by fusion technique.
2. The dissolution rate and cumulative amount of Nimesulide dissolved was increased several fold in all the solid dispersions prepared.
3. The dissolution medium namely pH 8.4 buffer influenced more than pH 1.2 buffer as far as cumulative percentage amount dissolved is concerned.
4. Hence by proper choice of dispersing agents like PEG 4000 and PEG 6000 and proper proportion of drug: PEG an effective dosage form for enhancing dissolution rate of Nimesulide may be prepared.

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