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IMPROVEMENT OF SOLUBILITY OF BADLY WATER SOLUBLE DRUG (IBUPROFEN) BY USING SURFACTANTS AND CARRIERS

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ABSTRACT: Although there was a great interest in solid dispersion systems during the past four decades to increase dissolution rate and bioavailability of badly water-soluble drugs, their profitable use has been very limited, primarily because of manufacturing difficulties and stability problems. In this study solid solutions of drugs were generally produced by fusion method. The drug along with the excipients (surfactants and carriers) was heated first and then hardened by cooling to room temperatures. They were then pulverized, sieved, and encapsulated into hard gelatin capsules, then drug release was studied USP basket method at 50 rpm and controlling the temperature 37^0C. Ibuprofen is a non-steroidal anti-inflammatory drug commonly used to reduce fever, pain and stiffness. An attempt was taken to study the effect of surfactants and carriers in badly water soluble drug (Ibuprofen) by using solid solution method. In this trial Sodium Lauryl Sulfate, Poloxamer, Polyethylene Glycol (PEG)-6000, Tween 80 and Polyvinylpyrrolidone (PVP) K30 were used as solubilising agent. Ibuprofen is badly water soluble drug and distilled water was used as dissolution medium. The amount of drug was measured form the absorbance of UV spectrophotometer at 214nm. The release of drug was schemed in a choice of release pattern. The present study shows that PEG 6000, Sodium Lauryl Sulfate, Poloxamer, Tween 80 and PVP K30 enhanced the release profile of capsule ibuprofen. From this effort it is possible to increase the release of ibuprofen by using surfactants and carriers.

INTRODUCTION: Ibuprofen is a non-steroidal anti-inflammatory drug commonly used to reduce fever, pain and stiffness. An attempt was taken to study the effect of surfactants and carriers in badly water soluble drug (ibuprofen) by using solid solution method.

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The improvement of oral bioavailability of badly water soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization, and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs, there are practical limitations of these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not

be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co-solvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc.

The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability. In 1961, Sekiguchi and Obi developed a practical method whereby many of the limitations with the bioavailability improvement of badly water-soluble drugs just mentioned can be overcome. This method, which was later termed solid dispersion, involved the formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical mixtures. Sekiguchi and Obi 2 suggested that the drug was present in a eutectic mixture in a microcrystalline state.

Later, Goldberg et al. demonstrated that all the drug in a solid dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and 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 [1].

Badly water soluble drugs are the compounds which have less affinity to the water and they are always hydrophobic in nature. Poorly water-soluble drug candidates often emerge from contemporary drug discovery programs, and present formulators with considerable technical challenges. The absorption of such compounds when presented in the crystalline state to the gastrointestinal tract is typically dissolution rate-limited, and the drugs are typically BCS class II or class IV compounds. Class IV compounds, which have low membrane permeability as well as poor aqueous solubility, are often poor candidates for development, unless the dose is expected to be low.

The rate and extent of absorption of class II compounds is highly dependent on the performance of the formulated product. These drugs can be successfully formulated for oral administration, but care needs to be taken with formulation design to ensure consistent bioavailability. Drug substances are seldom administered alone, but rather as part of a formulation in combination with one or more non-medicinal agents that serve varied and specialized pharmaceutical function. The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all the drug substances and pharmaceutical ingredients to be used in fabricating the product. An important physical-chemical property of a drug substance is solubility, especially aqueous system solubility.

A drug must possess some aqueous solubility for therapeutic efficacy. However 35-40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility [2, 3]. The solubility/dissolution behavior of a drug is key determinant to its oral bioavailability, the latest frequency being the rate-limiting step to absorption of drugs from the gastrointestinal tract [3]. Consequently poor solubility results in low bioavailability, increase in the dosage, large inters and intra-subject variation and large variations in blood drug concentrations under fed versus fasted conditions.

Solid dispersion: Solid dispersion was firstly introduced to overcome the low bioavailability of lipophilic drugs by forming of eutectic mixtures of drugs with water-soluble carriers. Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state, prepared by melting (fusion), the addition of solvent, or the melt-solvent method, with a view to enhancing the oral bioavailability of poorly water-soluble drugs.

It has been demonstrated that the drug can be present in a eutectic mixture in a microcrystalline state, or molecularly dispersed in the matrix, thereby forming a solid solution. In either case, when the solid dispersion is exposed to aqueous media and the carrier dissolved, the drug is released as very fine, colloidal particles. Due to the greatly enhanced surface area obtained this way, the dissolution rate and the bioavailability of poorly water-soluble drugs are expected to be high. Dispersions have traditionally been formed by heating mixtures of the

drug and carrier to a molten state, followed by resolidification via cooling. Alternative methods involve dissolving the components in a mutual volatile solvent followed by evaporation or dissolving the drug in a solvent such as propylene glycol and adding that to the molten carrier. Different techniques have been exlploited to enhance the dissolution of poorly water soluble drugs among which solid dispersion technique, because of their simplicity and effectiveness have received considerable attentions and these encouraged me to work on this topic.

As early as in 1961, Sekiguchi and others [4, 5] developed the concept of solid dispersion to enhance absorption of poorly water-soluble drugs. It involved formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures, and once the carriers dissolved, the drug precipitated in a finely divided state in water. Later, Goldberg and others [6, 7] demonstrated that a certain fraction of the drug may also be molecularly dispersed in the matrix, forming solid solutions, while other investigators reported that the drug may be embedded in the matrix as amorphous materials.

On the basis of these considerations, Chiou and Riegelman defined solid dispersion as "the dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states" [8].

MATERIALS AND METHODS: Drugs and chemicals: Ibuprofen (Xamim, China), distilled water (University Laboratory), Polyvinylpyrrolidone PVP K30 (BASF, Germany), Polyethylene Glycol PEG 6000 (BASF, Germany), Poloxamer (BASF), Sodium lauryl sulphate (BASF, Germany), Tween 80 (BASF, Germany), Mineral oil (BDH) etc.

Preparation of Formulation: At first the active drug was taken into a vial. Then the excipients (carriers and surfactants) were added one by one with it, careful attention must be given to the drug-to-carrier ratio is necessary in the successful development of a formulation. When the solubility of a particular drug is relatively low, a high drug-to-carrier ratio is necessary to deliver it in a solubilised state, and, therefore, the dose has to be low if it is desired that the total dose is delivered as a single unit. After that the vial along with ingredients was melted with the help of liquid paraffin oil. Then the mixture was stirred in one direction with the help of glass rod. Then the melted mixture was made into solid mass. After that the solid mass was converted into powder form with the help of mortar and pestle. Then the power particles were passed through sieve of mesh size 40, (**Tables 1-4**).

Filling of Capsule Shell: After sieving the powder, 109 mg Equivalent weight of ibuprofen were taken in each 0 size capsule shell and filled the capsule carefully. Finally the capsules were sealed.

TABLE 1: FORMULATION OF IBU-TPS SERIES

Ingredients	Amount (mg)		
	IBU-TPS-F1	IBU-TPS-F2	IBU-TPS-F3
Ibuprofen	2500	2500	2500
Tween 80	100	200	250
Poloxamer	200	150	150
Sodium Lauryl Sulphate	200	150	100

TABLE-2: FORMULATION OF IBU-PS SERIES

Ingredients	Amount (mg)		
	IBU-PS –F1	IBU-PS –F2	IBU-PS –F3
Ibuprofen	2500	2500	2500
PVP K30	500	500	500
Sodium Lauryl Sulphate	-	100	200

TABLE 3: FORMULATION OF IBU-PT SERIES

Ingredients	Amount (mg)		
	IBU- PT-F1	IBU- PT-F2	IBU- PT-F3
Ibuprofen	2500	2500	2500
PEG 6000	100	200	300
Tween 80	200	200	20

TABLE 4: FORMULATION OF IBU-PPS SERIES

Ingredients	Amount (mg)	
	IBU-PPS-F1	IBU-PPS-F2
Ibuprofen	2500	2500
PEG 6000	100	200
PVP K30	200	100
Sodium Lauryl Sulphate	50	50

RESULT & DISCUSSION: Ibuprofen is a poorly soluble drug. It was not seemed to be soluble in normal condition, but it was soluble when heated in a steam bath for few minutes. The solubility and the dissolution of ibuprofen were very slow. But it was made soluble and brought into the dissolution first by the addition of surfactant such as Tween-80, SLS; and carriers PVP K30, PEG 6000, Poloxamer. Drug release kinetics was done by basket method using distilled water as dissolution medium at room temperature (37^{o}C) at 50 rpm speed. The sample was collected for 1 hour studies and percentage of drug release at different time interval was calculated from the UV absorbance reading.

The amount of drug was measured form the absorbance of UV spectrophotometer at 214nm. 5ml syringe was used to take 5ml sample from each sample basket and 5ml fresh distilled water was added after the sample was taken into each sample basket.

Sample was filtered and percent (%) release of ibuprofen was calculated from UV absorbance reading of sample. The formulation IBU-TPS-F1, IBU-TPS-F2, IBU-TPS-F3, IBU-PS-F1, IBU-PS-F2, IBU-PS-F3, IBU-PT-F1, IBU-PT-F2, IBU-PT-F3, IBU-PPS-F1 and IBU-PPS-F2 showed about 93.6%, 90.97297%, 92.52973%, 94.08649%, 95.74054%, 95.15676%, 94.96216%, 95.83784%, 96.61622%, 94.57297%, and 96.61622% release respectively within 1 hour.

Figure 1 and 2 shows comparative study of zero release curves; of different Ibuprofen formulations. The correlation coefficients values of the trend lines of the graphs showed that formulation IBU-TPS-F1; IBU-TPS-F2; IBU-TPS-F3; IBU-PS-F1; IBU-PS-F2; IBU-PS-F3; IBU-PT-F1; IBU-PT-F2; IBU-PT-F3; IBU-PPS-F1 and IBU-PPS-F2 best fits in Higuchian release pattern.

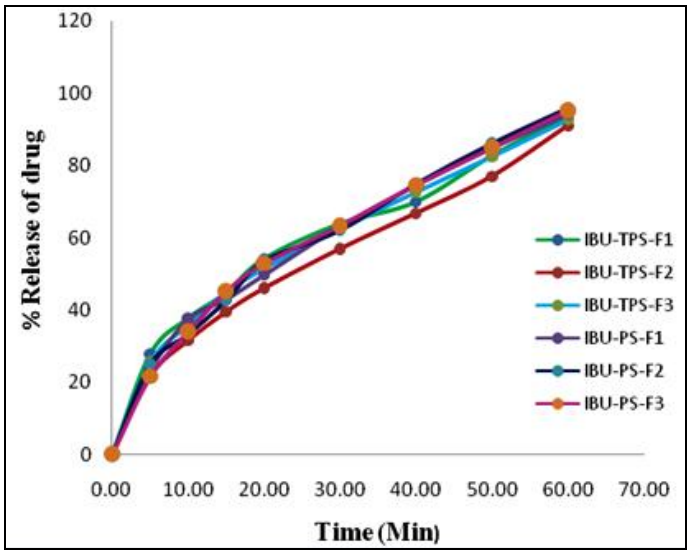

FIGURE 1: PERCENT RELEASE CURVE OF IBUPROFEN WITH DIFFERENT EXCIPIENTS FOR THE FORMULATIONS IBU-TPS-F1, IBU-TPS-F2, IBU-TPS-F3, IBU-PS-F1, IBU-PS-F2 AND IBU-PS-F3

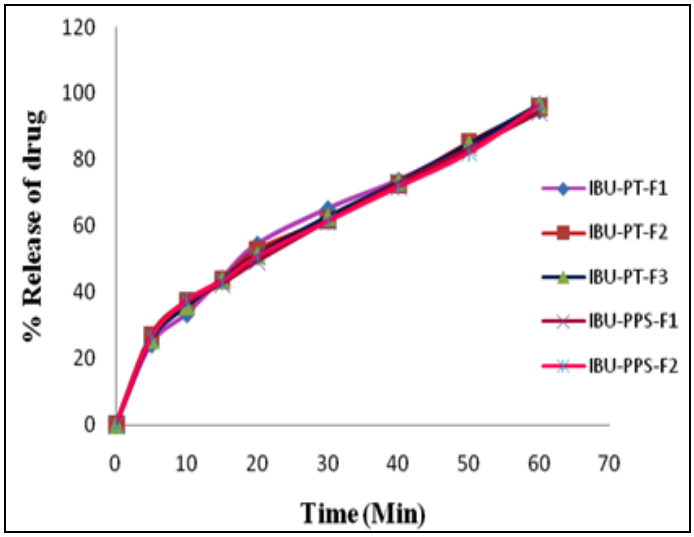

FIGURE 2: PERCENT RELEASE CURVE OF IBUPROFEN WITH DIFFERENT EXCIPIENTS FOR THE FORMULATIONS IBU-PT-F1, IBU-PT-F2, IBU-PT-F3, IBU-PPS-F1 AND IBU-PPS-F2

However, it is very difficult at this stage to explain in details the actual mechanism of release since, the polymer degradation starts during the dissolution period. The values of the correlation coefficients are shown in the **table 5**.

TABLE 5: CORRELATION COEFFICIENT (R^2) VALUE OF THE FORMULATIONS

Formulations	Zero order plot	Higuchi plot	Hixson Crowell plot	First order plot
IBU-TPS-F1	0.915	0.995	0.538	0.150
IBU-TPS-F2	0.953	0.990	0.590	0.006
IBU-TPS-F3	0.928	0.999	0.556	0.003
IBU-PS-F1	0.939	0.996	0.575	0.001
IBU-PS-F2	0.944	0.995	0.582	0.028
IBU-PS-F3	0.938	0.996	0.585	0.021
IBU-PT-F1	0.932	0.996	0.572	0.017
IBU-PT-F2	0.934	0.995	0.558	0.024
IBU-PT-F3	0.942	0.995	0.571	0.034
IBU-PPS-F1	0.939	0.995	0.563	0.013
IBU-PPS-F2	0.938	0.993	0.562	0.028

The release rate of Ibuprofen was also calculated from the trend lines of the graphs for formulation IBU-TPS-F1; IBU-TPS-F2; IBU-TPS-F3; IBU-PS-F1; IBU-PS-F2; IBU-PS-F3; IBU-PT-F1; IBU-PT-F2; IBU-PT-F3; IBU-PPS-F1; and IBU-PPS-F2. The values are shown in the table 5. This Study is not sufficient to realize the actual release pattern for above formulations, so more study is required to get effective result. However here the dissolution process can be described by two distinct processes. Once the solid dispersion has exposed to aqueous media and the carrier dissolved in the aqueous medium, 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. The enhancing efficacy of the dissolution rates was also pronounced in cases with hydrophilic surfactants, such as Polysorbate 80 and Sodium Lauryl Sulfate.

It is well known that hydrophilic surfactants in the SDs could play a key role as solubilizers and wetting agents for poorly water soluble drugs. Finally it can be concluded that dissolution rate of Ibuprofen was increased by the use of surfactants which is due to the wettability and spreadability of the precipitated drug by reducing aggregations in the readily soluble state. So it can be considered that the vehicles acted here as dispersing or emulsifying agents for the liberated drug, thus preventing the formation of any water-insoluble surface layers.

Although the liberated drug remained un-dissolved in the dissolution medium when its concentration exceeded its saturation solubility, it was dispersed or emulsified in a finely divided state because of surface activity of the dissolved vehicle.

CONCLUSION: The enhancement of oral bioavailability of badly water soluble drugs remains one of the most challenging aspects of drug perfection. Various scientists achieved a complete dissolution of drug from solid dispersions by using surface active or self-emulsifying carriers. The vehicles acted as dispersing or emulsifying agents for the liberated drug, thus preventing the formation of any water-insoluble surface layers.

Although the liberated drug remained un-dissolved in the dissolution medium when its concentration exceeded its saturation solubility, it was dispersed or emulsified in a finely divided state because of surface activity of the dissolved vehicle. The high surface area of a drug produced in this way would facilitate its dissolution in the dissolution medium. However, further studies have to be conducted in this aspect to produce a successful drug delivery system.

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