Solubility and Bioavailability Enhancement of Poorly Water-Soluble Drug Using Solid Dispersion Solubility Techniques

Prashant Sharma[1*], Dharmendra Singh Rajput[2], Naveen Gupta[3]

[1.] Patel College of Pharmacy, Madhyanchal Professional University, Bhopal, M.P.
Email Id: ps234992@gmail.com
[2.] Professor, Patel College of Pharmacy, Madhyanchal Professional University, Bhopal, M.P.
Email Id: dr.dsr141@gmail.com
[3.] Professor, Patel College of Pharmacy, Madhyanchal Professional University, Bhopal, M.P.
Email Id: naveenmpharm@gmail.com
*Corresponding Author: Prashant Sharma, Department of Pharmaceutics, Patel College of Pharmacy, Madhyanchal Professional University, Bhopal, M.P. ps234992@gmail.com

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Abstract

Poor aqueous solubility remains one of the major challenges in oral drug delivery, often resulting in low dissolution rates and poor bioavailability. Oxaprozin, a non-steroidal anti-inflammatory drug (NSAID), is classified as a poorly water-soluble drug, which limits its therapeutic effectiveness following oral administration. The present study aims to enhance the solubility, dissolution rate, and bioavailability of oxaprozin by employing the solid dispersion technique. Solid dispersions of oxaprozin were prepared using hydrophilic carriers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), or other suitable polymers by solvent evaporation, fusion, or spray-drying methods. The prepared formulations were evaluated for drug content, saturation solubility and in vitro dissolution.The results demonstrated a significant improvement in the aqueous solubility and dissolution profile of oxaprozin compared to the pure drug, primarily due to reduced crystallinity, improved wettability, and molecular dispersion of the drug within the polymeric matrix. Enhanced dissolution is expected to improve the oral bioavailability of oxaprozin, leading to better therapeutic efficacy and patient compliance. This study highlights solid dispersion as an effective and promising strategy for overcoming the limitations associated with poorly water-soluble drugs and provides a potential approach for improving the pharmaceutical performance of oxaprozin.

Keywords: Pharmacokinetics, Oxaprozin, Bioavailability, Solid Dispersions, Dissolution, Hydrophilic Carriers.

Introduction

Pharmacokinetics has now become an integral part of drug development, particularly in determining the biological properties of drugs. Pharmacokinetics refers to the application of kinetics to drugs and toxicants. Therefore, this term brings the passage of time and the fate of the drug in the body. This general definition broadly includes absorption, distribution, metabolism, and excretion. A very important property of non-intravenous dosage forms is their ability to deliver active ingredients into the bloodstream and elicit a pharmacological response. This property of a dosage form has historically been defined as bioavailability. Bioavailability reflects two important properties: rate of absorption and degree of absorption. In principle, these two properties of non-intravenous dosage forms are important in determining the dose response of a drug.[1]

Because bioavailability depends on the rate and extent of drug absorption, drugs with poor bioavailability are those that have low aqueous solubility and/or slow dissolution rates in body fluids, low stability of the drug at physiological pH, insufficient partition coefficients, poor permeability across biological membranes, and significant first-pass metabolism.[2]

Solubility is one of the important parameters to achieve the desired concentration of a drug in systemic circulation for pharmacological reactions. Drugs that are inherently less water soluble have limited solubility in the gastrointestinal contents, resulting in slower release rates. The rate of dissolution often determines the rate of absorption of the drug. The problem with drugs that are poorly soluble in water is that they dissolve faster. This increases absorption and bioavailability. Methods are constantly being introduced to create formulations aimed at improving the solubility of poorly soluble substances. Oral route of drug administration remains preferred due to its convenience, good patient compliance, and low drug manufacturing costs. In order for a drug to be absorbed into the systemic circulation after oral administration, it must be dissolved in gastric fluid. Active pharmaceutical ingredients in solid dosage forms must be dissolved before they can be absorbed from the gastrointestinal tract. For hydrophobic drugs, the dissolution process acts as a rate-controlling step that determines the rate and extent of absorption. Therefore, many hydrophobic drugs exhibit uneven and incomplete absorption from the gastrointestinal tract. Therefore, one of the major challenges in drug development today is low solubility, with approximately 40% of newly developed drugs being poorly soluble or insoluble in water. Furthermore, up to 50% of orally administered drug compounds suffer from formulation problems related to low solubility and high lipophilicity.[3,4]

The therapeutic efficacy of a drug depends on its bioavailability and ultimately the solubility of the drug molecule. Solubility is one of the important parameters for achieving the desired concentration of pharmacologically responsive drugs in the systemic circulation. Poorly soluble drugs have poor absorption and bioavailability, so it is important to improve their solubility and dissolution rate. Solubility is a key determinant of drug release and therefore plays an important role in drug bioavailability[5]. In fact, only solubilized drug molecules are absorbed into the cell membrane and reach the site of drug action (e.g., the vasculature). The drug to be absorbed must be present as an aqueous solution at the site of absorption.[5,6]

Solubility is one of the very important parameters to achieve the drug concentration in the blood required to exhibit a pharmacological response. Drugs that are poorly soluble in water pose many challenges in the development of pharmacological dosage forms for oral delivery systems due to their low bioavailability. The process of solubilization involves breaking intermolecular or ionic bonds within the solute, separating solvent molecules to create space for the solute within the solvent, and interactions between solvent and solute molecules or ions.[7,8]

Solid dispersion

In the pharmaceutical sciences, solid dispersion refers to a system in which one or more active pharmaceutical ingredients (APIs) are uniformly distributed within an inert carrier or matrix in a solid state. This strategy is widely employed to enhance the dissolution rate and bioavailability of drugs characterized by poor aqueous solubility. The carriers selected must be physiologically inert and can be either readily soluble in water for rapid drug release or water-insoluble for controlled dissolution profiles. To facilitate an accelerated dissolution rate, the hydrophobic drug is molecularly dispersed within a rapidly water-soluble inert carrier, resulting in a solid dispersion. Achieving a molecular-level dispersion ensures the formation of a homogeneous solid phase. Upon exposure to gastric fluids, the water-soluble carrier dissolves quickly, causing an immediate liberation of the drug at the molecular scale, which consequently improves its dissolution behavior and bioavailability.[9,10]

Methods of preparation of Solid dispersions

i) Fusion (Melt) Method: Accurately weighed amounts of carrier(s) are placed in an aluminum pan on a hot plate and melted, with constant stirring at a temperature of about 60°C. An accurately weighed amount of active drug is incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture is heated until a clear homogeneous melt is obtained. The pan is then removed from the hot plate and allowed to cool at room temperature.[11]

ii) Solvent Evaporation Method: Accurately weighed amounts of active drug and carrier(s) are dissolved in minimum quantities of solvent in a vessel. The solvent is removed using a rotary evaporator or water bath. The resultant solid dispersion is transferred to an aluminum pan and allowed to dry in a hot air oven.[12,13]

iii) Dropping Method: A solid dispersion of a melted drug-carrier mixture is pippeted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate, it solidifies to a spherical shape.[14,15]

Adantages of solid dispersion

i) Particles with reduced size: Molecular dispersions represent the last state on particle size reduction and after carrier dissolution, the drug is molecularly dispersed in dissolution medium. Solid dispersion apply this principle to drug release by creating a mixture of poorly water soluble drug and highly soluble carriers. A high surface area is formed resulting in an increased dissolution rate and improved bioavailability.[16]

ii) Particles with improved bioavailability: The drug solubility enhancement is strongly related to the drug wettability improvement verified in solid dispersions. Carriers with or without surface activity improved wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co solvent effect.

iii)Particles with higher porosity: Particles in solid dispersion have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties of the instance; the solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore result in a higher dissolution rate. The increase in porosity of solid dispersion particles fastens the drug release profile.

iv) Drugs in amorphous state: The enhancement of drug release can usually be achieved using the drug in its amorphous form, because no energy is needed to break up the crystal lattice during the dissolution process. In solid dispersions drugs are presented as supersaturated solutions after system dissolution and it is assumed that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the stable crystal form. Surface solid dispersion is a technique which provides deposition of the drug on the surface of certain materials that can alter the dissolution characteristics of the drug. Deposition of the drug on an inert carrier causes a reduction in the particle size of the product thus provides a faster dissolution rate. Various hydrophilic excipients with high surface area can be utilized for deposition of the drug on their surfaces. Surface modifications and solid dispersion formulations using hydrophilic excipients can significantly alter the dissolution behavior of hydrophobic drug materials.[17]

Methodology

Formulation, characterization and optimization of of solid dispersion (SD)

Solubility of oxaprozin in different ratio of kneaded solid dispersion mixtures was assessed by dissolving 5 mg/ml of each sample and solvent in distilled water prepared from mechanical method. Polymer was diluted in glass mortar with solvent, methanol to give a homogeneous paste. The drug was then integrated into the paste, by slowly adding various concentrations of drugs to the paste and triturating for 1 hr. The water content was empirically adjusted during this process to guarantee the consistency of paste remains uniform. This paste was vacuum dried for 24hrs. Dried powder was passed through CGS sieve and placed in desiccator until further assessment. Solid dispersions was prepared by PEG 6000 and HPMC K100M in order to finding the appropriate polymer for getting Solid dispersion.[19]

Optimization by factorial design

A 3^2 full factorial design in which we selected the X1 and X2 as the two independent variables. This is appropriate for exploring the response surfaces of the quadratic and creating a second-order polynomial, od enabling to perform optimization. The levels of the two factors were chosen according to preliminary studies conducted prior to the execution of experimental design. Elsewhere, all formulation and processing variable were maintained stable during the study. Statistical software package, Design expert 10.0.3.1 (Stat – Ease; trial) was used for the optimization of SD. All the above formulations were prepared and subjected for different evaluated parameters. The data was entered on a design expert software and polynomial equation is derived. Responses (dependent variables) Investigated Y1, Y2 and Y3.[20]

Optimization of solid dispersion

In this work, a factorial design was chosen for the optimization of Solid dispersion (SD) because it allows to define in as less experiments as possible, which factors influence the response surface. The independent variables were the amount of PEG 6000 (X1) and the amount of methanol (X2). Three Response Variables were investigated as dissolution at 60th min (%) (Y1), Drug content (Y2) and Solubility enhancement ratio (Y3). While nine formulations were developed based on the factorial design. The designs were from F1 to F9. The output obtained from the design matrix was evaluated statistically by using Design expert 10 statistical software trial package, Stat - Ease 10.0.3.1.[21]

Table 1 : List of factors and responses with their levels and constraints

Factors	**Levels used**		
	-1	**0**	**+1**
X1= Amount of PEG 6000 (gm.)	2	3	4
X2= Amount of methanol (ml)	3	4	5
Responses	Constraints		
Y1= Dissolution at 60^{th} minute	83.33% - 95.89%		
Y2= Drug content	72.78% - 95.21%		
Y3= Solubility enhancement ratio	6-15		

Characterization of optimized Solid dispersion

i) Percentage drug release

All the optimized formulations were subjected to dissolution studies using USP dissolution apparatus type I for 900 ml 0.1N HCl at 50 rpm and 37 ±0.5 0C with withdrawal of samples at proper time intervals (0,10,15,30,45 &60 minutes) and replacement of equivalent volume of plain dissolution medium. The samples were extracted, filtered and diluted. UV-visible Spectrophotometer – Absorbance of forming solution at 282nm - The dissolution rate of oxaprozin pure drug,optimized SD and marketed available tablet was also compared.[22]

ii) Solubility Analysis

The saturation solubility measurements were done after the formation of optimized formulations to evaluate drug solubility increase. Then, known excess of optimized formulations were introduced into 10 ml distilled water. The samples were placed in a rotary flask shaker and kept on shaking at room temperature for 24 h. The samples were subsequently passed through No. 41 whatman filter paper and the filtrate was appropriately diluted and spectrophotometrically seeded. [23,24]

Pharmacokinetic studies

In order to use RP-HPLC for estimation of Oxaprozin in rat plasma, an already reported bio-analytical method has been used which is simple and accurate. Liquid-liquid extraction, solid phase extraction and protein precipitation, methods are commonly used bio-analytical method sample preparation techniques. In the present study, protein precipitation method was used. It is the method in which miscible organic solvent such as acetonitrile, acetone or methanol are added to biological sample resulting in precipitation of proteins. It is a fast and simple method for extraction procedure of both hydrophilic and hydrophobic compounds from biological

samples . Wistar albino rats of either sex weighing 250±10 g used. The procedure followed was standard during the experiment period and mouse were hold under normal environment condition of 12 h light dark cycle with temperature of 25±2° C, relative humidity maintained at 50±10 %RH for housing of animals. Animals were given ad libitum standard commercial diet and tap water. The rats were kept fasted overnight with water provided ad libitum on the day before experiment. Collection of zero hour blood sample (femoral artery; administered). Oxaprozin and its optimized formulation were administered orally as a suspension in distilled water with 0.5 %w/v sodium carboxymethyl cellulose, to suspend the test compounds at the dose of 50 mg/ kg. Each formulation was administered orally, and blood samples were taken from the femoral artery at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8 and 12 h after administration.[25]

Result

Optimization by factorial design of solid dispersion

Solid dispersions with different ratios were prepared and variables like amount of PEG 6000 and amount of methanol were optimized for the best formulation.

Table 2: Formulation of Solid dispersions

Runs	Formulation	Oxaprozin(gm.)	PEG 6000 (gm.)	methanol (ml)
1	**SDF1**	1	2	3
2	**SDF2**	1	2	4
3	**SDF3**	1	2	5
4	**SDF4**	1	3	4
5	**SDF5**	1	3	3
6	**SDF6**	1	3	5
7	**SDF7**	1	4	5
8	**SDF8**	1	4	4
9	**SDF9**	1	4	3

Optimization of solid dispersion

The experiment runs with independent variables and the observed responses for the nine Solid dispersions formulations were shown in the table .

Table 3: The factors and responses for nine Solid dispersions formulations

Formulation	Factor 1	Factor 2	Response 1	Response 2	Response 3
	X1 PEG 6000	X2 methanol	Dissolution at 60th minute	Drug content	Solubility enhancement ratio
SDF1	2	3	83.33	72.78	06
SDF2	2	4	84.41	78.10	08
SDF3	2	5	83.36	77.10	07
SDF4	3	4	88.63	88.88	11
SDF5	3	3	86.50	84.00	09
SDF6	3	5	87.59	87.01	10
SDF7	4	5	93.82	93.20	12
SDF8	4	4	95.89	95.21	15
SDF9	4	3	94.85	94.06	14

After generating the polynomial equation relating to the dependent and independent variables, They optimized the formulation according to how it reacted with responses. The ranges of the responses were constrained to obtain the cumulative percent release at 60th minute in between 83.33%- 95.89%, drug content in between 72.78% - 95.21% and solubility enhancement ratio in a range of 6-15. Optimal values of the variables were identified using a desirability function based optimization via numerical analysis. Thus, another batch of spherical agglomerates with the desired formulation factors was prepared to demonstrate that our optimization procedure worked as expected.

Development of the optimum solid dispersion batch

The software generated a solution for achieving maximum percentage drug release, percent drug content and solubility enhancement ratio of the SD formulations from these statistical evaluations. The formula selected for the further studies were listed along with % drug release, drug content and solubility enhancement ratio.

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Table 4: Formula for optimum SD batch based on statistical evaluations

Number	Amount of PEG 6000 (gm.)	Amount of methanol (ml)	Dissolution at 60^{th} min (%)	Drug content (%)	Solubility enhancement ratio
1	4	3.825	95.788	95.915	14.858

Evaluation of optimized solid dispersion

Table 2: Evaluation of the optimized SD formulation for Percentage yield, Drug content, Dissolution at 60th min, Solubility analysis, FTIR, SEM, Powder X-ray diffraction,. Yeild percentage of all the formulations were above 90%. All of the formulations showed a substantial percentage yield which demonstrate reproducibility also in technique for larger optimized SD formulations preparation. The optimized percentage drug content of SD formulations was determined to be higher. The solubility profiles of the optimized SD formulations were higher than that of the pure drug.

Table 5: Evaluation of optimized SD formulations

Formulation	Percentage yield (%)	Drug content (%)	Solubility (mg/ml)	Solubility enhancement ratio
Optimized SD	96.64±0.38	95.81±0.22	0.135	15

i) Percentage drug release of optimized SD

Table 6: Percentage drug release of optimized SD formulation

Time (min)	Percentage(%) drug release
	Optimized SD
0	0
10	33.41±0.42
15	54.21±0.63
30	73.96±0.37
45	81.30±0.18
60	95.89±0.25

ii) Comparison of dissolution profile of optimized solid dispersion

Table 7: Comparison of dissolution profile of optimized solid dispersion

Time (min)	(%CDR)		
	Optimized SD	Pure drug	Marketed
0	0.0	0.0	0.0
10	33.41±0.23	9.61±0.34	51.43±0.28
15	53.17±0.16	13.77±0.14	63.97±0.35
30	75.00±0.57	16.90±0.68	71.28±0.68
45	83.26±0.34	21.05±0.25	75.85±0.43
60	93.82±0.49	24.19±0.73	79.15±0.27

Pharmacokinetic study of optimized solid dispersion

Table 8: Mean plasma drug concentrations data

S.No.	Time (h)	Mean plasma drug concentration (ng/ml	
		Reference	Test formulation
1	0.25	273.16±29.31	509.51±41.08
2	0.5	364.82±35.14	1126.34±103.27
3	0.75	439.71±45.19	703.85±51.69
4	1	237.45±20.75	384.19±31.74
5	2	201.07±16.83	310.47±26.10
6	4	151.38±19.55	226.9±19.34
7	6	132.09±14.68	163.27±12.88
8	8	78.36±10.17	89.31±20.67
9	12	56.85±7.62	63.48±11.35

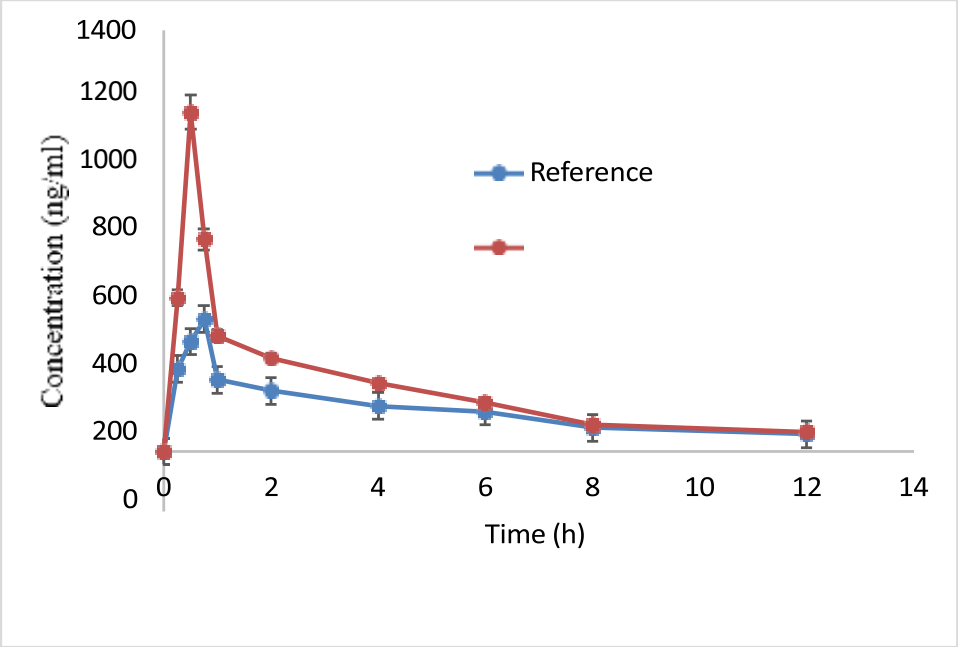

Figure 1: Mean plasma drug concentration *vs.* time curves

Table 9 : Pharmacokinetic parameters

Pharmacokinetic parameter	Pure drug (Reference)	Optimized solid dispersion of Oxaprozin(Test)
Tmax (h)	0.75	0.5
Cmax (ng/ml)	439.71±53.28	1126.34±163.18
AUC0-t (ng.h.ml^{-1})	1635.15±186.42	2465.98±332.57
AUC0-∞ (ng.h.ml^{-1})	3266.85±256.91	4178.61±389.24

Conclusion

Solid dispersion is one of the most widely used techniques to improve the solubility and dissolution rate of poorly water-soluble drugs such as oxaprozin. In this approach, oxaprozin is molecularly dispersed or finely distributed within a hydrophilic carrier such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), or Soluplus. The hydrophilic carrier enhances drug wettability, reduces particle size, and often converts the crystalline drug into an amorphous form, resulting in significantly faster dissolution. Improved dissolution leads to enhanced gastrointestinal absorption and greater oral bioavailability. Solid dispersion is relatively simple to prepare, cost-effective, and suitable for large-scale pharmaceutical manufacturing, although long-term physical stability due to drug recrystallization remains a potential challenge.

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