WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 14, 941-949. Research Article ISSN 2277– 7105

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF POORLY WATER SOLUBLE DRUG LANSOPRAZOLE

Keval Khatik*, Rahul Sharma and Dr. Jagdish Chandra Rathi

NRI institute of Pharmaceutical Sciences, Bhopal.

Article Received on
27 Sept. 2021,

Revised on 18 October 2021,
Accepted on 07 Nov. 2021

DOI: 10.20959/wjpr202114-22261

***Corresponding Author**
Keval Khatik
NRI institute of Pharmaceutical Sciences, Bhopal.

ABSTRACT

Lansoprazole (LSZ) is a substituted benzimidazole and selectively inhibits the H^+/K^+-ATPase of the parietal cell of the stomach. As a representative proton pump inhibitor, LSP has been clinically used in the therapy of gastric and duodenal ulcerative disease with a superior or equivalent clinical efficacy to H_2 receptor antagonist. However, the bioavailability of LSP was not consistent with wide intersubject variation, which is ascribed to the variation in the genotype of CYP2C19, possible degradation by the gastric acid, and limited water solubility Low aqueous solubility is a major problem faced during formulation development of new drug molecules. Lansoprazole (LPZ) is an anti ulcer agent and is a good example of the problems associated with low aqueous solubility. Lansoprazole is practically insoluble in water. Hence, purpose of this research was to enhance the solubility of Lansoprazole by using the concept of solid dispersion. The present investigations showed that solubility of Lansoprazole was markedly increased by its solid dispersion using PVP K30 as carrier. The formulation SDF8 containing (1:4) shows highest dissolution rate. Hence the solid dispersion a way is useful technique in providing fastest onset of action of Lansoprazole as well as enhanced dissolution rate.

KEYWORDS: Lansoprazole, Solubility enhancement, Solid dispersion, PVP K30.

INTRODUCTION

Throughout the past decade, in the development and commercialization of new pharmaceutical products, the formulation and delivery of Active Pharmaceutical Ingredients (APIs) have played a crucial role. To improve bioavailability, stability and convenience to the patient, is the major objective of formulation chemistry.[1] Bioavailability means the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical

form and becomes available at the site of action.[2] The bioavailability of an orally administered drug depends on its solubility in aqueous media over the pH range of 1.0–7.5 and the rate of mass transfer across biological membranes.[3] In the oral bioavailability of poorly water soluble compounds, the insufficient dissolution rate is the limiting factor.[3] Some new technologies have been recently developed to improve aqueous solubility of APIs. These methods are based on the use of compressed gases, supercritical fluids, and anti-solvent.[4]

The critical requirement for a poorly water-soluble drug for absorption to be possible from the gastrointestinal (GI) tract is, achieving a solution of drug in the GI fluid Horter and Dressman, 1997 defined a poorly water-soluble drug as the one whose dissolution in the GI fluid under ordinary conditions takes a longer time than its transition through the absorption sites in the GI tract. To increase dissolution rates of drugs, salt formation, particle size reduction etc., have commonly been used but achieving desired bioavailability enhancement may not always be possible due to some practical limitations with these techniques.[5] Solid dispersion systems have shown promising results in increasing bioavailability of poorly water-soluble drugs in which the drug is dispersed in solid water-soluble matrices either molecularly or as fine particles.[6]

The dispersion method allows the preparation of physically modified forms of the drug that are much more rapidly soluble in water than the pure compound. The most commonly used hydrophilic carriers for solid dispersions include polyvinyl pyrrolidone, polyethylene glycols, and plasdone-S630. Surfactants may also be used in the formation of solid dispersions. Surfactants like Tween-80, Myrj-52, and Pluronic-F68 and sodium lauryl sulfate are used. Chiou and Riegelman, (1969)[7] recommended polyethylene glycol, a water-soluble polymer, as an excellent universalcarrier for improving the dissolution rate and oral absorption of water-insoluble drugs.

The oral route of drug administration is the most common and preferred method of delivery. However, several orally administered drugs have a reduced bioavailability due to poor water solubility. In biopharmaceutical classification system drugs with low aqueous solubility, slow dissolution rate, high dose, and high membrane permeability are categorized as Class II drug. To overcome low bioavailability, many of the modern oral drug delivery systems emphasize on formulation strategies such as alteration of solvent composition, carrier systems as well as

chemical and physical modifications. Solid dispersion of drug in a water soluble polymer has been shown to be one of the most promising strategy to improve solubility.

Increasing the Bioavailability of a poorly soluble drug is a challenging aspect of drug development. Because of the poor aqueous solubility the drug possess dissolution problems due to which the in vivo absorption of the drug is reduced and thus the bioavailability is reduced, making the drug inappropriate for oral consumption and therefore solubility enhancement become necessary for such drug candidate. Solid dispersion is a most simple and efficient technique for increasing the aqueous solubility of a drug. So our aim of the study is formulation, development and evaluation of solid dispersion of Lansoprazole.

MATERIAL AND METHODS

Preparation of sold dispersion using PEG 8000, PVP K 30 and SLS

PEG 8000, PVP K 30 and SLS solid dispersion were used to prepare at weight ratios of 1:1, 1:2, 1:4 and 1:4 using three different preparation methods, physical trituration, kneading and solvent evaporation.[8]

Table 1: Preparation of solid dispersion complexes.

S. No.	Inclusion complexes		
	Drug: PEG 8000	Drug: PVP K30	Drug: SLS
1.	1:1	1:1	1:1
2.	1:2	1:2	1:2
3.	1:3	1:3	1:3
4.	1:4	1:4	1:4

Method of preparation of inclusion complexes

Physical trituration method

In the physical trituration method, drug and PEG 8000, PVP K 30 and SLS were weighed, sieved and mixed evenly by slowly adding drug into EG 8000, PVP K 30 and SLS separately in a mortar with light trituration. The mixture was continuously mixed for an hour (magnetic stirrer, Fisher, UK) until a homogeneous mixture was obtained. The mixtures were passed through a #65 mesh sieve (0.211 mm) and kept in a closed container.[9]

Kneading method

In the kneading method, PEG 8000, PVP K 30 and SLS in a mortar was wetted with sufficient amount of water (10% w/w) to obtain a paste and drug was slowly added into the paste. Kneading was performed manually for an hour and suitable amount of water was

added from time to time to maintain the consistency of the paste. The mixture was dried overnight for 24 hr in an oven (Electronic India) at 50°C. The dried complex was ground using mortar and pestle. After sieving through a #65 mesh sieve, the complex was kept in a closed container.[10]

Solvent evaporation method

In the solvent evaporation method, drug was dissolved in 25 mL of methanol, while PEG 8000, PVP K 30 and SLS were dissolved in 50 mL of distilled water. The two solutions were mixed together and stirred for 1 hr (Magnetic stirrer, Electronic India) methanol was evaporated off by heating at 40°C under constant stirring. Water was then removed under reduced pressure using rotary evaporator. The mixture was placed overnight for 24 hr in an oven at 40°C to remove the residual solvent. The inclusion complex was ground using mortar and pestle. After sieving through a #65 mesh sieve, the inclusion complex was kept in a closed container.[11]

Solubility studies

Solubility study was performed by adding an excess amount of solid dispersions in 50 mL of distilled water. The flasks were vortex-mixed for 3 min and agitated at 120 rounds per minute in a water bath maintained at 30°C for 72 hours. Samples of 3 mL were withdrawn and filtered through a 0.45 µm nylon membrane filter. Filtrate (0.1ml) was diluted appropriately and measured spectrophotometrically (Labindia 3000+) at 296nm. Each measurement was repeated three times.

Evaluation of dispersion granules of optimized formulation SDF8[12]

Percentage drug content

For the determination of Lansoprazole content, dispersion granules equivalent to 10 mg of drug, were weighed and extracted with 10 ml of methanol by mechanical mixing for 5min followed by centrifugation at 10,000 rpm for 5 min on a centrifuge. The supernant was filtered through 0.45µ membrane filter, and the filtered solutions were suitably diluted and analyzed for Lansoprazole at 296nm using a validated UV spectrophotometric method.

Evaluation of Flow properties

Angle of repose (θ): The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\tan \theta = h/r$$
$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, h is the height, r is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definit height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Packing}}$$

Carr's Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index (Ansel *et al.*, 1999), calculated by using following formula:-

$$\text{Carr's Index \%} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

Housner's ratio = Tapped bulk density/loose Bulk density

Dissolution rate studies of optimized solid dispersion SDF8

The prepared tablets were evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 75 rpm maintained at

37±0.2°C. A solid dispersion equivalent to 10mg placed in dissolution media (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml 0.1 N HCl. The samples withdrawn were assayed spectrophotometrically at 296nm using UV visible spectrophotometer. The release of drug was calculated with the help of standard curve of Lansoprazole.

RESULTS AND DISCUSSION

The drug solution was scan on UV-spectrophotometer at 200-400 nm in Wavelength range to determine the maximum absorbance (λ_{max}) and it was found at 296nm. The calibration curve was prepared in 0.1 N HCl. The regression coefficient (R^2) was 0.999 which was shows the linearity of curve. The line of equation for the standard curve was y = 0.018x + 0.012. Solid dispersion is a most simple and efficient technique for increasing the aqueous solubility of a drug. PEG 8000, PVP K 30 and SLS solid dispersion were used to prepare at weight ratios of 1:1, 1:2, 1:3 and 1:4, using three different preparation methods, physical trituration, kneading and solvent evaporation.

When the regression coefficient values of were compared, it was observed that ‘r’ values of First order was maximum i.e. 0.917 hence indicating drug release from formulations was found to follow first order kinetics. The present investigations showed that solubility of Lansoprazole was markedly increased by its solid dispersion using PVP K30 as carrier. The formulation SDF8 containing (1:4) shows highest dissolution rate. Hence the solid dispersion a way is useful technique in providing fastest onset of action of Lansoprazole as well as enhanced dissolution rate.

Table 1: Preparation of solid dispersion complexes.

S. No.	Inclusion complexes		
	Drug: PEG 8000	Drug: PVP K30	Drug: SLS
1.	1:1	1:1	1:1
2.	1:2	1:2	1:2
3.	1:3	1:3	1:3
4.	1:4	1:4	1:4

Table 2: Solubility of different solid dispersion complexes.

F. code	Complex	Solubility (mg/ml)		
		Physical method	Kneading method	Solvent evaporation method
	Pure drug	0.25 mg/ml		
SDF1	Drug: PEG 8000 (1:1)	0.35	0.45	0.65
SDF2	Drug: PEG 8000 (1:2)	0.48	0.65	0.75
FSD3	Drug: PEG 8000 (1:3)	0.52	0.74	0.82
SDF4	Drug: PEG 8000 1:4)	0.59	0.85	0.95
SDF5	Drug: PVP K 30 (1:1)	0.74	0.82	0.60
SDF6	Drug: PVP K 30 (1:2)	0.98	0.95	1.15
SDF7	Drug: PVP K 30 (1:3)	1.05	1.02	1.20
SDF8	Drug: PVP K 30 (1:4)	1.15	1.11	1.45
SDF9	Drug: SLS (1:1)	0.85	0.95	1.05
SDF10	Drug: SLS (1:2)	1.12	1.05	1.15
SDF11	Drug: SLS (1:3)	1.45	1.25	1.25
SDF12	Drug: SLS (1:4)	1.25	1.20	1.05

Table 3: Results of drug content.

Formulation	Label claim (mg)	Amount found (mg)	Label claim (%) Mean ± S.D.	% RSD
SDF8 Drug: PVP K 30 (1:4)	10	9.98	99.80 ±0.12	0.041

*Average of three determination

Table 4: *In-vitro* drug release data for optimized formulation SDF8.

Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
30	5.477	1.477	11.45	1.059	88.55	1.947
60	7.746	1.778	24.45	1.388	75.55	1.878
120	10.954	2.079	35.47	1.550	64.53	1.810
240	15.492	2.380	46.65	1.669	53.35	1.727

Table 5: Regression analysis data.

Batch	Zero Order	First Order
	r^2	
SDF8	0.901	0.942

CONCLUSION

Low aqueous solubility is a major problem faced during formulation development of new drug molecules. Lansoprazole (LPZ) is an anti ulcer agent and is a good example of the problems associated with low aqueous solubility. Lansoprazole is practically insoluble in

water. Hence, purpose of this research was to enhance the solubility of Lansoprazole by using the concept of solid dispersion. The present investigations showed that solubility of Lansoprazole was markedly increased by its solid dispersion using PVP K30 as carrier. The formulation SDF8 containing (1:4) shows highest dissolution rate. Hence the solid dispersion a way is useful technique in providing fastest onset of action of Lansoprazole as well as enhanced dissolution rate.

REFERENCES

1. Majerik V., Horvath G., Charbit G., Badens E., Szokonya L., Bosc N., Teillaud E. Novel particle engineering techniques in drug delivery: review of formulations using supercritical fluids and liquefied gases, Hun. J. Ind. Chem., 2004; 32: 41–56.
2. Vemavarapu C., Mollan M.J., Lodaya M., Needhamb T.E. Design and process aspects of laboratory scale SCF particle formation systems, Int. J. Pharm., 2005; 292: 1–16.
3. Charbit G., Badens E., Boutin O. Supercritical Fluid Technology for Drug Product Development, Drugs and Pharmaceutical Sciences, Marcel Dekker Inc., New York, 2004; 138.
4. Rogers T.L., Johnston K.P., Williams R.O. III Solution-based particle formation of pharmaceutical powders by supercritical or compressed fluid CO2 and cryogenic spray-freezing technologies, Drug Dev. Ind. Pharm., 2001; 27(10): 1003–1015.
5. Jung J., Perrut M. Particle design using supercritical fluids: literature and patent survey, J. Supercrit. Fluids, 2001; 20: 179–219.
6. Serajuddin, A.T.M. Solid dispersion of poorly water-soluble drugs: earlypromises, subsequent problems and recent breakthroughs. J. Pharm. Sci., 1999; 88: 1058–1066.
7. Chiou W., Riegelman S. Preparation and Dissolution Characteristics of Several Fast Release Solid Dispersion of Griseofulvin. J. Pharm. Sci., 1969; 58: 1505.
8. Vudathala Gopi K, Rogers James J Pharm Sci., 1992; 81(12): 1166-1169.
9. Biswas Manju, Akogyeram Clement O, Scott Kenneth R, Potti Gopal K, Gallelli Joseph F, Habib Muhammad J J Control Release, 1993; 23: 239-245.
10. Yamamura Shigeo, Rogers James Int J Pharm 1996; 130: 65- 73.
11. Mirza Sabiruddin, Miroshnyk Inna, Habib Muhammad J, Brausch James F, Hussain Muhammad D Enhanced Dissolution and Oral Bioavailability of Piroxicam Formulations: Modu Nagar P, Singh K, Chauhan I, Verma M, Yasir M, et al. J Appl Pharm Sci., 2011; 1: 35-45.

12. Kumar SV, Gavaskar B, Sharan G, Rao YM. Int J Pharmacy Pharm Sci., 2010; 2: 29-33. Committee for Medicinal Products for Human Use, European Medicines Agency EMEA (2006) Reflection paper: formulation of choice for the pediatric population.
13. Tolman KG, Sanders SW, Buchi KN, Karol MD, Jennings DE, Ringham GL: J Clin Gastroenterol, 1997; 24: 65–70.