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ENHANCEMENT OF SOLUBILITY & DISSOLUTION RATE OF LAMOTRIGINE BY KNEADING METHOD

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Abstract

Lamotrigine is poorly soluble drug exhibiting poor dissolution pattern. Lamotrigine, PVP K90 , skim milk solid dispersion were prepared with view to study influence of polymer on solubility & dissolution of these poorly soluble drug lamotrigine. Solid dispersion of lamotrigine were prepared using different ratios of PVP K90 & skim milk as carrier by kneading method . They were evaluated for percentage yield , drug content , FT-IR spectral studies , solubility & in-vitro dissolution. The solubility profile indicated that there is increase in solubility of lamotrigine when polymer concentration increases. The solid dispersion complex of drug (1:5 ratio) was giving better dissolution profile as compare to pure drug & other solid dispersion. This in turn can improve the solubility. FT-IR shows the compatibility of drug & carrier.

Key Word- solid dispersion, Kneading method, solubility

Introduction [1,2]

The term seizure refers to a transient alteration of behavior due to the disordered, synchronous & rhythmic firing of pupations of brain neurons. The term epilepsy refers to a disorder of brain function characterized by the periodic & unpredictable occurrence of seizures.

The epilepsies are common & frequently devastating disorders, affecting approximately 2.5 million people in the United States alone. Epileptic seizures often caused by transient impairment of consciousness, leaving the individual at risk of bodily harm and often interfering with education & employment.

Lamotrigine is a phenyltriazine derivative initially developed as an antifolate agent based upon the incorrect idea that reducing folate would effectively combact seizures. Structure activity studies indicate that its

effectiveness as an anti seizure drug is unrelated to its antifolate properties. It was approved by the food & drug administration in 1994. Solid dispersions can be defined as molecular or amorphous mixtures of poorly water soluble drugs in hydrophilic carriers in which the polymer properties play an important role in the drug dissolution profile. It has been estimated that 40% of new chemical entities being discovered are poorly water – soluble. With recent advances in screening methods for identifying potential drug candidates, an increasing number of poorly water soluble drugs have been identified as potential therapeutic agents. Unfortunately, these drugs have poor bioavailability due to their poor solubility. This has limited the commercial potential of these drugs. The solid dispersion technique is one of the most efficacious to improve the bioavailability of drugs with low water solubility.

Among the important factors increasing the solubility of drugs in solid dispersions, particle size reduction, reduced agglomeration, improved wet ability and solubility, or dispersion of the drug as micro – fine crystals, amorphous materials or in a molecular form must be mentioned. These formulations offer many advantages over others and the most relevant are the lower cost of the adjuvant and the feasible industrial application. Solid dispersion in an inert carrier or matrix of solid state prepared mainly by the kneading method. The melting method involves heating a physical mixture of an active agent and a carrier until melted, followed by rapidly solidifying under vigorous mixing, resulting in super saturation of the drug by instantaneous solidification.

On the other hand, the solvent evaporation method involves dissolving a physical mixture of two or more chemicals in a common solvent, followed by evaporation of the solvent. The proper selection of solvent and its removal rate are crucial in determining the quality of the final dispersion. The release mechanism of drug from a variety of solid dispersions depends on the physical properties of carriers as well as drug substances and preparation methods. Lamotrigine is anticonvulsant agent that can be incorporated into several pharmaceutical forms. The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of Lamotrigine by preparing Solid dispersion with various water soluble polymers such as PVP K90 and Skim milk. The prepared Solid dispersions were evaluated for % practical yield, drug content, in - vitro dissolution rate studies and interactions between the drug and polymer using IR spectral studies.

Material and method-[3]

Materials: Lamotrigine (manufactured by Lupin pharmaceuticals), PVP K90, skim milk. All other materials used were of pharmaceutical or analytical grade.

Preparation of solid dispersion by kneading method:

The SDs of lamotrigine with PVPK 90 (A) containing three different weight ratios (1:1, 1:3, 1:5) (lamotrigine: PVPK 90) and denoted as SD1, SD2 and SD3 respectively, were prepared by kneading method. In kneading method, a required amount of PVP K 90 was taken in a glass mortar along with 10% lactose. A required amount of lamotrigine was added to mortar and kneaded thoroughly with a glass rod by using ethanol. The mixture was kept for drying in a desiccator. The hardened mixture was powdered in a mortar, sieved through a 100-mesh screen, and stored in screw-cap vial at room temperature until further use & follow same procedure for SD of lamotrigine with skim milk(B).

Table 1: Formulation plan of Lamotrigine solid dispersions

Drug	Lamotrigine	Lamotrigine
Carrier	Pvp K 90 (A)	Skim milk (B)
SD 1	1:1	1:1
SD 2	1:3	1:3
SD 3	1:5	1:5

% Practical Yield: [4,5]

Percentage practical yield is calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

$$PY(\%) = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + carrier)}} \times 100$$

Drug content: [6,5]

10 mg of solid dispersions were weighed accurately and dissolved in 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 270nm by UV spectrophotometer. Each sample analyzed. Actual drug content was calculated for all batches using the equation as follows:

$$\text{Drug content \%} = \frac{\text{Tact}}{\text{Tss}} \times 100$$

$$\text{Actual Lamotrigine content in weight} = \frac{\text{Quantity of solid dispersion}}{\text{Theoretical amount of Lamotrigine in solid dispersion}} \times 100$$

In Vitro dissolution study: [7,5]

Dissolution studies were performed assuring sink condition according to the paddle method (USP) using USP XXIII apparatus type-II (electrolab TDTO9T). The dissolution medium was 900 ml 0.1N HCl kept at 37°C ± 0.5°C. The solid dispersions containing 100 mg of Lamotrigine was taken in a muslin cloth and tied to the rotating paddle kept in the basket of dissolution apparatus, the paddle was rotated at 50 rpm. Samples of 5 ml were withdrawn at specified time intervals and analyzed spectrophotometrically at 270nm using Shimadzu - 1800 UV-visible spectrophotometer. The samples withdrawn were replaced by fresh buffer solution. Each preparation was tested and then mean values were calculated.

Result & Discussion

Solid dispersions of Lamotrigine were prepared by different methods using carriers like PVP K 90 and Skim milk. In the present work, total 6 formulations were prepared and their complete composition is shown in Table -2. All the Solid dispersions prepared were found to be fine and free flowing powders.

Table 2: Result of percentage yield, & Drug content of solid dispersion of Lamotrigine.

Sr no	Formulation code	%practical Yeild	Drug content	%drug release in 60 min
1	SD-A1	81.00%	75.68%	84.69%
2	SD-A2	87.07%	83.86%	89.51%
3	SD-A3	95.33%	89.74%	97.55%
4	SD-B1	61.00%	66.56%	74.99%
5	SD-B2	75.50%	79.11%	76.5%
6	SD-B3	80.66%	82.75%	93.24%

Percent practical yield: The results of percent practical yield studies are shown in Table No. 2. The % Practical yield of the prepared solid dispersions was found to be in the

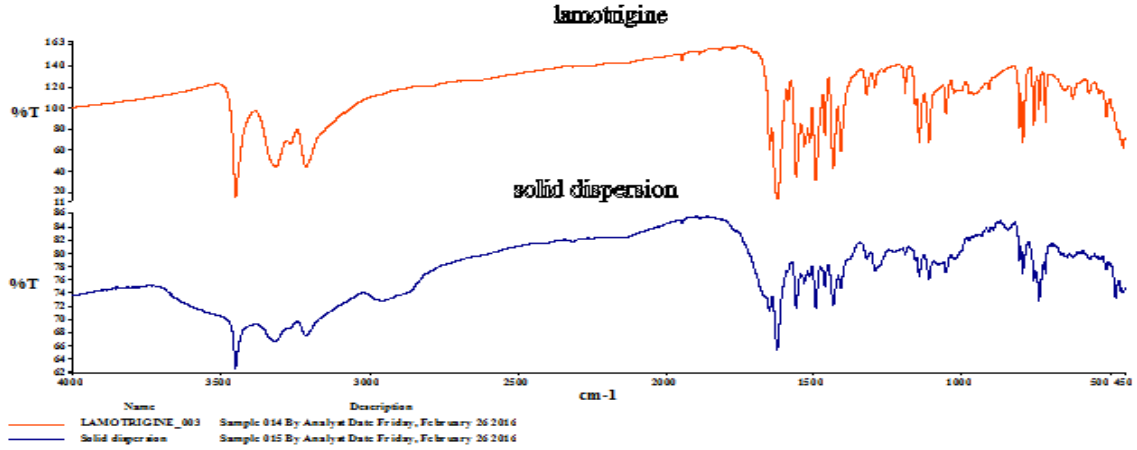
range of 61.00 - 95.33% The maximum yield was found 95.33 % in SD- A3 formulation.

Drug content: The actual drug content of all the 6 formulations are shown in Table No. 2. The drug content of the prepared Solid dispersions were in the range of 66.56-89.74% indicating the application of the present methods for the preparation of Solid dispersions with high content uniformity. The maximum % drug content was found 89.74% in SDA3 formulation.

In vitro dissolution study: Solid dispersion prepared by kneading method shows improved dissolution at the end of 60 min which is 97.55%. The ratio Drug: PVP K90 (1:5) showed better in vitro release when compared with that of pure drug which is 28.78 % at the end of 60min. The solid dispersion prepared by kneading method and showed 1.5 fold increase in dissolution. This is due to increased wet ability and dispersibility of drug by the carrier. Hydrophilic carrier will help to improve wetting property and reduce the interfacial tension between hydrophobic drug and dissolution medium. The increase in dissolution rate was in the order of Drug:PVPK90 > Drug: skim milk.

Infrared spectroscopy (IR): IR spectroscopic studies were conducted to determine possible drug: carrier interactions. IR spectra of pure drug Lamotrigine, and optimized Solid dispersion of Lamotrigine were obtained which shows all the characteristic peaks of Lamotrigine and carrier was present in the Solid dispersion, thus indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion. The result of IR study shown in Figure No: 1 .

Fig. 1: IR Spectra of Pure Lamotrigine and Solid dispersion.



Conclusion: The objective of the present study was to improve the solubility and dissolution behavior of the poorly soluble drug, Lamotrigine by solid dispersion technique using PVP K 90 & skim milk as carrier. Solid dispersion of Lamotrigine prepared by a Kneading method showed significantly higher drug solubility in comparison with pure drug. FTIR studie showed no evidence of interaction between the drug and carrier. Out of the 6 prepared formulation SD- A3 showed marked increase in the solubility as well as the dissolution when compared to pure drug. Thus it can be concluded that the solubility of the poorly soluble drug, Lamotrigine can be improved markedly by using solid dispersion technique and the carrier PVP K90 has increased the dissolution of the drug without any interaction.

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References

1. Goodman & Gilmans the pharmacological basis of Therapeutics 10th edition page no-521.
2. Goodman & Gilmans the pharmacological basis of Therapeutics 10th edition page no-539.
3. S.S. Mohanty, S. Biswal, et al. Enhancement of Dissolution Rate of glimepiride using Solid Dispersion with Polyvinylpyrrolidone K90, ijper; 2010; 44(I): 71-77.
4. Sachin R Patil, Rani Kumar, Patil MB, Mahesh S Paschapur and Malleswara Rao VSN. ; Enhancement of Dissolution rate of aceclofenac by solid dispersion technique; Int. J. Pharma Tech Res; 2009; 1(4): 1198-1204.
5. Kothawade S. N. et al; Formulation and Characterization of Telmisatan Solid Dispersions; International Journal o f Pharm Tech Research; 2010; 2(1): 341-347.
6. Venkates Kumar K, Arunkumar N, Verma PRP, Rani C.; Preparation and In-vitro characterization of valsartan solid dispersions using skimmed milk powder as carrier; Int . J. Pharma Tech Res; 2009; 1(3): 431-437.
7. Norbert Rasenack and Bernd W Miiller.; Dissolution Rate Enhancement by in Situ Micronization of poorly Water soluble Drugs; Pharmaceutical Research; 2002; 19(12); 1894-1900.