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RESEARCH ARTICLE

Nanosuspension formulation to improve the dissolution rate of Clonazepam

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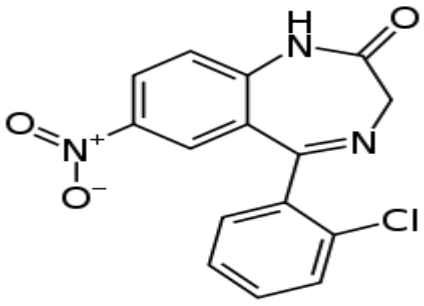
Abstract

Many FDA approved drugs currently available in the market have limitations in crossing the blood brain barrier (BBB) owing to its complicated vasculature posed by the presence of specialized cells One of the most challenging problems, if not the most challenging, in drug development is not to develop drugs to treat diseases of the central nervous system (CNS), but to manage to distribute them to the CNS across the blood–brain barrier. The development of BBB targeting technologies is a very active field of research and development. One goal is to develop chemically modified derivatives of CNS drug (clonazepam) chemically modified nanoparticulate of drugs, capable of crossing biological barriers, in particular the BBB. Nanocarrier drug delivery involves targeting CNS drugs enclosed in a particular PVP polymer. Drug nanoparticles have been shown to improve bioavailability and enhance drug exposure for oral and parenteral dosage forms. Nanoparticles of clonazepam were prepared by many methods.

INTRODUCTION

Clonazepam (CLZ) belongs to a class of anticonvulsants that enhances gamma-aminobutyric acid (GABA) receptor responses. Anticonvulsants used for several types of seizures, including myotonic or atonics seizures, photosensitive epilepsy, and absence seizures. CLZ exerts its action by binding to the benzodiazepine site of the GABA receptors, which causes an enhancement of the electric effect of GABA binding on neurons resulting in an increased influx of chloride ions into the neurons. This results in an inhibition of synaptic transmission across the central nervous system [1-8].

Structure -



Solubility problems pose a major challenge for the pharmaceutical industry as concerns the development of new pharmaceutical products. Studies of poorly soluble drugs have demonstrated that a particle size

reduction can lead to an increase in dissolution rate and higher bioavailability. During the last ten years, nanoparticle engineering processes have been developed and reported for pharmaceutical applications. In addition to overcoming issues of solubility, nanosuspensions (NSs) allow a higher mass per volume drug loading in comparison with drug solutions [9-15]. The aims of our study were to investigate the feasibility of nanosuspension preparation, to study the effects of different preparation methods and added stabilizers on the formulated nanosuspensions. Furthermore, the prepared (NSs) were transformed into dry powdered products, either by freeze-drying or by spray-drying, and investigated the rate of dissolution of dried samples [16-18]. Our model drug was clonazepam (CLZ) a anticonvulsant drug. According to the biopharmaceutical classification system, MEL is a Class II drug, since it is poorly water-soluble and well permeable. Therefore, increase in dissolution rate will result in increased biological availability [19].

MATERIALS AND METHODS:-

Materials-

The drug clonazepam was from INTAS PHARM Ltd., (Gujarat, India). Lutrol F68 (poloxamer 188) and polyvinylpyrrolidone (PVP) K25 were from BASF (Germany), Tween 80 (polysorbate 80), benzyl alcohol from Fluka (Switzerland), and ethyl acetate from Merck (Germany). Water was purified by reverse osmosis.

Sample preparation-

CLZ nanosuspensions were prepared from emulsions containing partially water-miscible organic solvent: ethyl acetate or benzyl alcohol. The drug (20 mg) was dissolved in 20 ml of ethyl acetate, poured under stirring at 8000 rpm with Ultra Turrax T 25 (Janke & Kunkel, IKA Labortechnik, Germany) into 140 ml 0.5% aqueous solution of Tween 80 followed by high pressure homogenization (APV-2000, Invensys, Denmark) at pressure of 800 bar for 5 min, diluted with 160 ml of water and further homogenized for 5 min. CLZ (20 mg) dissolved in 9 ml of benzyl alcohol was poured into 64 ml 0.5% poloxamer 188 aqueous solution, and sonicated for 3 min (amplitude 30%, 500 W Model, Cole-Palmer Instrument Co., UK Ltd.). Emulsion was diluted with 200 ml of water and further sonicated for 3 min. Reference samples (REF) of same composition were prepared using magnetic stirrer (Table I). NSs were transformed into dry product either by spray-drying (SPD)(Mini Spray Dryer B-290, Buchi, Switzerland) or by liophylization (LIO)(Crist Beta 1-8 K, Germany). Trehalose (6g per sample) was used as a redispersant or lyoprotectant.

Sample characterization-

Particle size and size distribution of nanosuspensions and reference samples was determined using Zetasizer 3000 (Malvern Instruments, Worcestershire, UK) and Mastersizer (Malvern Instruments, Worcestershire, UK). The particle *morphology* was determined by scanning electron microscopy (SEM; SUPRA 35 VP, Carl Zeiss). Drug content and *in vitro dissolution* rate of CLZ were determined using the dissolution apparatus (Erweka DT 6, Germany). The rotation speed of the paddles was 100 rpm. 900 ml of phosphate buffer solution with pH of 7.4 0.1 (Ph. Eur. 6) at 37 ± 0.5 °C was used as a dissolution medium.

RESULTS AND DISCUSSION:-

Table 1: The process-parameters of sample preparation

Sample	Organic solvent	Stabilizer	procedure Homogenization	Drying method
SPD-NS	ethyl Tween	80 acetate	HPH	spray drying
SPD-REF	-	80 acetate	Magnetic stirrer	spray drying
LIO-NS	Benzyl alcohol	Poloxamer 188	HIUS	lyophilization
LIO- REF	-	Poloxamer 188	Magnetic stirrer	lyophilization

Influence of organic solvents and stabilizers-

The choice of organic solvent for NS preparation is crucial factor influencing final particle size and was based on preliminary experiments. Ethyl acetate has higher water miscibility compared to benzyl alcohol, however

benzyl alcohol is better solvent for CLZ. The results of tested different stabilizers in various concentrations showed that. Tween 80 and Poloxamer 188 in increasing concentrations yielded smaller particle size and polydispersity index, whereas PVP K-25 did not exert such an effect. The smallest particle size (~290 nm) in nanosuspensions was achieved using 0.5% Tween 80 or poloxamer 188 as stabilizer and benzyl alcohol as an organic solvent. Therefore this composition was chosen for further research work. Table II presents mean particle size of CLZ samples, showing that the raw drug and reference samples have average particle size (d50) in micrometer range, whereas particle size of both NSs is approximately houndred times smaller.

Table 2: Particle size distribution after dispersion of pure CLZ or CLZ in different dried samples in water

Sample	d (µm)	d (µm)	d (µm)
	10%	20%	30%
MEL	24.80	85.39	237.92
SPD-NS	0.140	0.460	2.71
SPD-RER	5.62	42	50
LIO-NS	0.168	0.530	3.6
LIO-RER	22.83	59.17	88.87

From these results we can conclude that using Ultra Turrax alone is not enough to prepare NS from drug dispersion. The SEM pictures revealed a significantly morphologycal difference between the dried products.

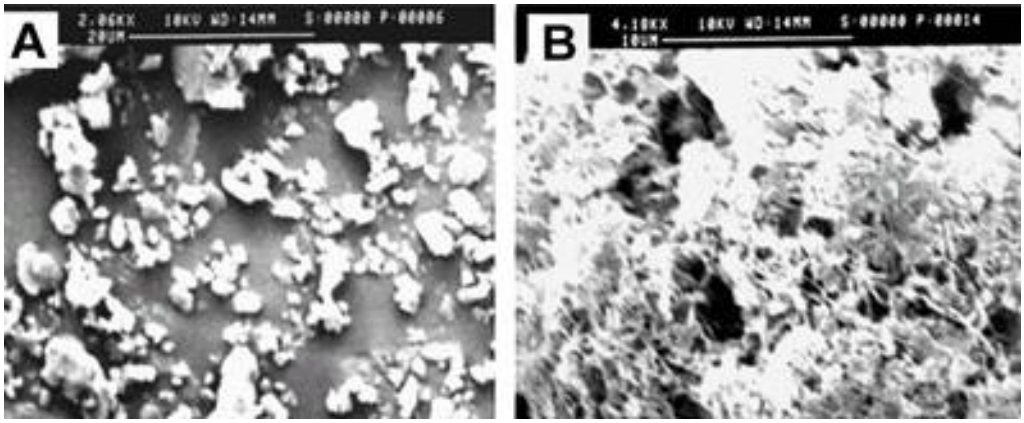


Figure 1: SEM Image of Clonazepam

CONCLUSIONS:-

In conclusion, there is a statistical significant difference between the dissolution rate for pure CLZ in 85nm size and for CLZ in nanosized particles. Scanning Electron Microscopy (SEM) to examine the surface topography morphology of fractured of sectioned surface,to analyze the surface of polymeric drug delivery system that can provide important information about the SEM analysis. The result for scanning microscope are shown in the image fig.-1.When solvents for preparation of nanosuspensions are compared the size of produced nanoparticles is similar. The improved dissolution rate of CLZ could improve its analgetic effect in the therapy. Targeting drugs to the brain by crossing the blood–brain barrier (BBB) has been a challenge. In this pursuit, many attempts have been made to develop novel drug delivery systems. BBB is formed by the tight endothelial cell junctions of the capillaries within the brain, which limits the ability of many drugs to penetrate through the brain tissue in order to enter the central nervous system (CNS). It is known that many regulators of the brain functions such as cytokines, transferrin, enkephalins, endorphins or delta sleep inducing peptides pass through BBB from the vessels into brain.

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