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Design and development of a novel formulation of Ganaxolone for treatment of seizure

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ABSTRACT
The risk of premature death in people with epilepsy is up to three times higher than for the general population. Each year, more than 1 in 1,000 people with epilepsy die from SUDEP [8]. dosage forms having Nano Particle have the advantage of better patient compliance[7]. Ganaxolone is a drug of choice for seizure . The fabricate Ganaxolone nano suspension to boost its rate of in vitro dissolution and eventually its oral bioavailability The optimized nanosuspension with particle size of 112±2.01 nm was fabricated using polycapro lactone as a polymer to give strength to Ganaxolone nanoparticle . The characterization was performed using Malvern zetasizer, SEM, TEM, DSC and P-XRD Finally, The quality of Nano suspension evaluated by parameter like Description assay , Related substances, pH. it was concluded that the F6 batch shows the best results, amongst all formulated batches.

Keywords: Nano Particle , Ganaxolone, seizure, Nano suspension

I. INTRODUCTION

The risk of premature death in people with epilepsy is up to three times higher than for the general population. Each year, more than 1 in 1,000 people with epilepsy die from SUDEP. dosage forms having Nano Particle have the advantage of better patient compliance. Ganaxolone is a drug of choice for seizure . The fabricate Ganaxolone nano suspension to boost its rate of in vitro dissolution and eventually its oral bioavailability The optimized nanosuspension with particle size of 112±2.01 nm was fabricated using polycapro lactone as a polymer to give strength to Ganaxolone nanoparticle . The characterization was performed using Malvern zetasizer, SEM, TEM, DSC and P-XRD Finally, The quality of Nano suspension evaluated by parameter like Description assay , Related substances, pH. it was concluded that the F6 batch shows the best results, amongst all formulated batches.

Enormous increase in electrical impulses occurs in one focal locus of the brain and/or the entire brain, leading to partial or generalized seizures, this condition is known as epilepsy. Epilepsy is a non-communicable central nervous system (CNS) disorder. Abnormal and drastic neuronal excitation may lead to physical and mental benign ailments and serious co-morbidities. More than 60 million people in the world are affected with this disorder. Despite the developments that happened in the treatment of this disorder, the quality of life of patients suffering from epilepsy remains poor. Drug resistance and recurrence of epilepsy after reduction of medication are the major hurdles in the treatment. Most anti-epileptic drugs are administered orally or intravenously.

Up to 40% of patients develop drug resistance at later stages of treatment resulting in uncontrolled seizures, a higher risk of brain damage and increased mortality rates. Patients experience emotional and behavioral changes, seizures, convulsions, muscular spasms, depression and, in some cases, unconsciousness.

Drug-resistant epilepsy is a formidable health issue. Drugs for epilepsy suffer from poor bioavailability and eventually become ineffective over the course of treatment due to drug resistance. Epilepsy treatment is often complicated due to the inability of available AEDs to cross the adjunctive blood brain barrier (BBB), which could be overcome through appropriate drug delivery systems. The ideal system would provide localized and controlled release of AEDs to targeted sites in the brain to help reduce drugassociated toxicities and enhance the efficacy of the drugs. Several strategies for the effective delivery of AEDs have been reported in the scientific literature.

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Nanotechnology-based systems appear to be a promising and innovative development. Several nanostructure drug delivery carriers have recently been reported as an effective CNS delivery systems to overcome the problem of AED elimination at the BBB and result in increased persistence of drugs [7]. Nanotechnology-based medicine (nano-medicine) refers to the surface property characterization and design of nano-carriers for various medicinal strategies. Therapeutic agents are embedded into or coated onto nano-carriers, small colloidal or compact structural platforms ranging in size from a 1 to 200 nm. These nano-platforms (NPs) readily interact with the cellular environment at the molecular level to produce the desired physiological response. Nanotechnology-based AEDs have recently garnered attention because of their ability to cross the BBB, improved selectivity and potential for sustained drug delivery to the brain. The size, molecular weight, co-polymer ratio, mechanism of erosion and surface charge are important factors when considering the effectiveness of NPs. For example, the size of the NPs is a very important determinant for its efficiency in crossing the BBB; NPs ranging from 35 to 64 nm easily access most neural tissues. Size-specific Nano Particless synthesis could be achieved through different preparation methods. As a result of the reduction in the sizes of nano particle, the nano-carrier system presents a large surface area that can carry large dosages of drugs, efficiently decrease the peripheral toxicity of drugs, and provide adequate delivery of drugs to their targets. The surface charge of Nanoparticles is also an important factor in determining their efficiency in brain targeting.

II. MATERIALS AND METHODS:

The list of materials procured from various sources have been enlisted in Table 1.

Table 1: List of materials procured

Materials	**Source**
Ganaxolone	Absin Bioscience Inc.
Polycaprolactone	Sigma-Aldrich Co. LLC.
Tween 80	Croda
Ethanol	Sigma-Aldrich Co. LLC.

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is first step in the rational development of dosage forms. Preformulation Study of Ganaxolone included various test like Organoleptic properties, Particle size, Crystallinity, Solubility and Drug, Excipient compatibility study.

The process for formulation of Ganaxolone was developed in a systematic way. Trials were taken by wet solvent evaporation process hydrophobic polymers and different concentration of ethanol. The particle size of nano suspension is improved due to the added ethanol that reduce particle size of particles, causing them to adhere to each polymer particle so that they can be formed into small particle called Nano particle. By this method, properties of the formulation components are modified to overcome their solubility and bioavailability deficiatiancy. Ganaxolone having a high dosage and low solubility and need to for Nano particle using solvent evaporation method to achieve desire particle size below 200 nano particle. In this process, the proportion of the ethanol required imparting adequate particle size and uniform particle size distribution.[11-14] The various steps of formulation trials F1 to F6 are given in Table 2.

Table 2: The various steps of formulation trials F1 to F10

S.No.	**Mfg Steps**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1.	**Dispensing**	√	√	√	√	√	√
2.	**Dry Mixing**	√	√	√	√	√	√
3.	**Solvent evaporation**	√	√	√	√	√	-

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Formulation of batches:
The various formulation steps are provided in Table 3.

Table 3: The various steps of formulation trials F1 to F10

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Size reduction		**Solvent evaporation**				
Ganaxolone In House	450	450	450	450	450	450
Polycaprolactone	100	100	100	100	100	100
Ethanol**	500	600	700	800	900	1000
Tween 80	50	50	50	50	50	50
Water*	500	500	500	500	500	500

III. RESULTS:

After the evaluation of all formulation the of **Ganaxolone Nano suspension** analytical parameter in Table 4, particle size of **Ganaxolone Nano suspension** Trial Batches are in Table 5

Table4: Particle size of all formulation from F1 to F6

Trial	**Description**	**pH**	**Assay**
F1	White uniform suspension	5.9	99.98%
F2	White uniform suspension	5.8	99.02%
F3	White uniform suspension	6.0	99.21%
F4	White uniform suspension	5.6	100.01%
F5	White uniform suspension	5.7	99.35%
F6	White uniform suspension	6.0	99.67%

Table5: Particle size of all formulation from F1 to F6

Trial	**PDI**	**Particle size**
F1	0.8	1834 nm
F2	0.9	1219nm
F3	0.5	831nm
F4	0.3	557nm
F5	0.2	341 nm
F6	0.2	123nm

Table6: Chemical Evaluation of Pacritinib Citrate SR Tablets Trial Batches

Trial	**% of drug loaded in polymer**	**% of Drug Retained in supernant solution**
F1	95.45%	4.31%
F2	95.67%	3.47%
F3	95.34%	4.81%
F4	94.49%	5.97%
F5	95.84%	5.63%
F6	97.93%	2.37%

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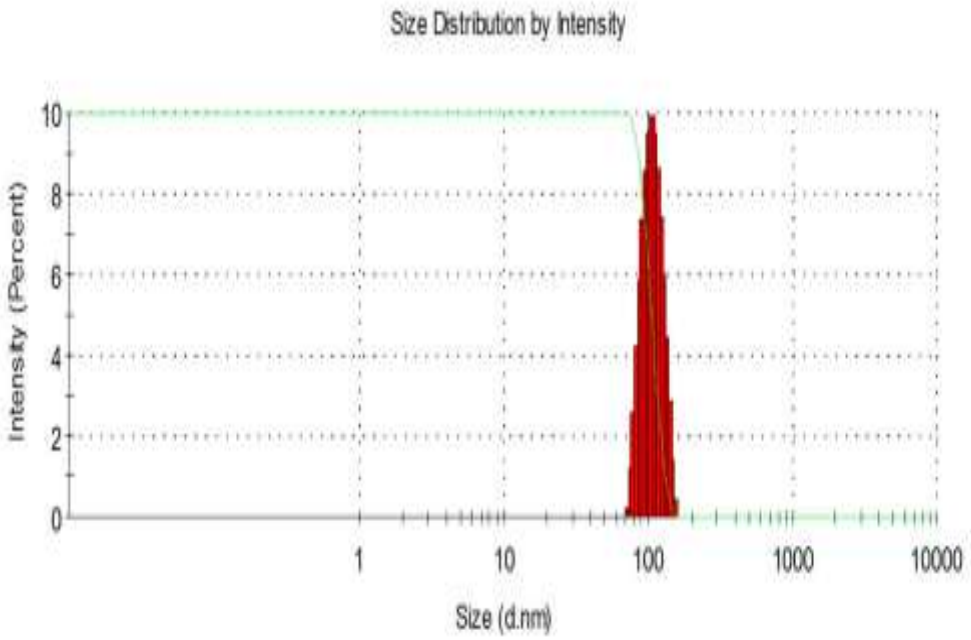
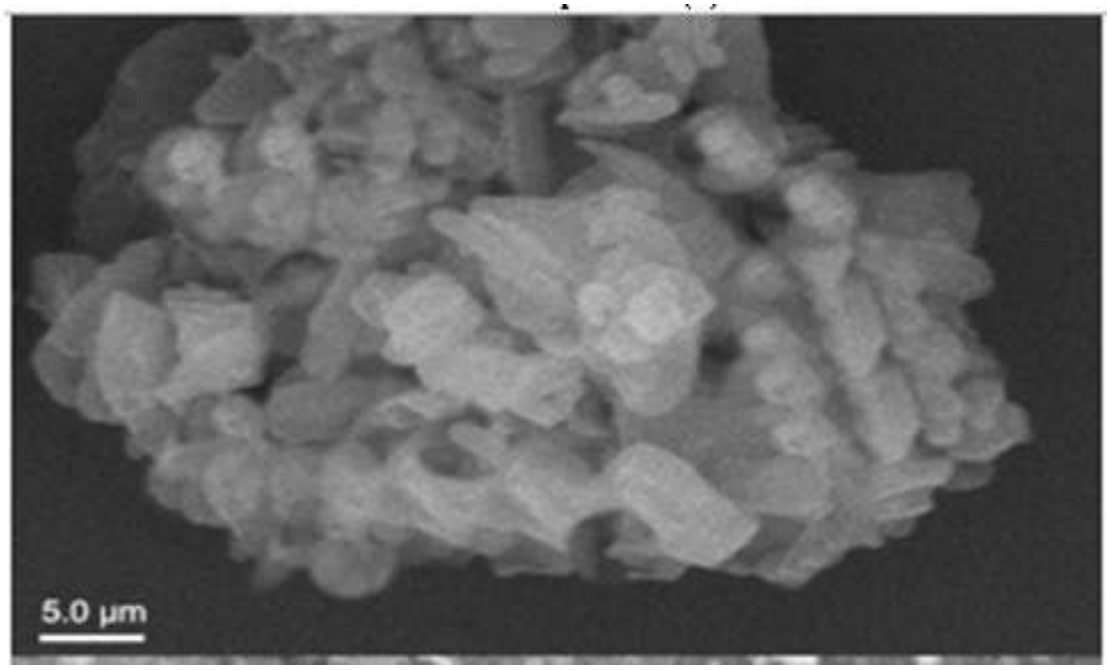
Fig 1: particle size of **Ganaxolone** nano suspension F6





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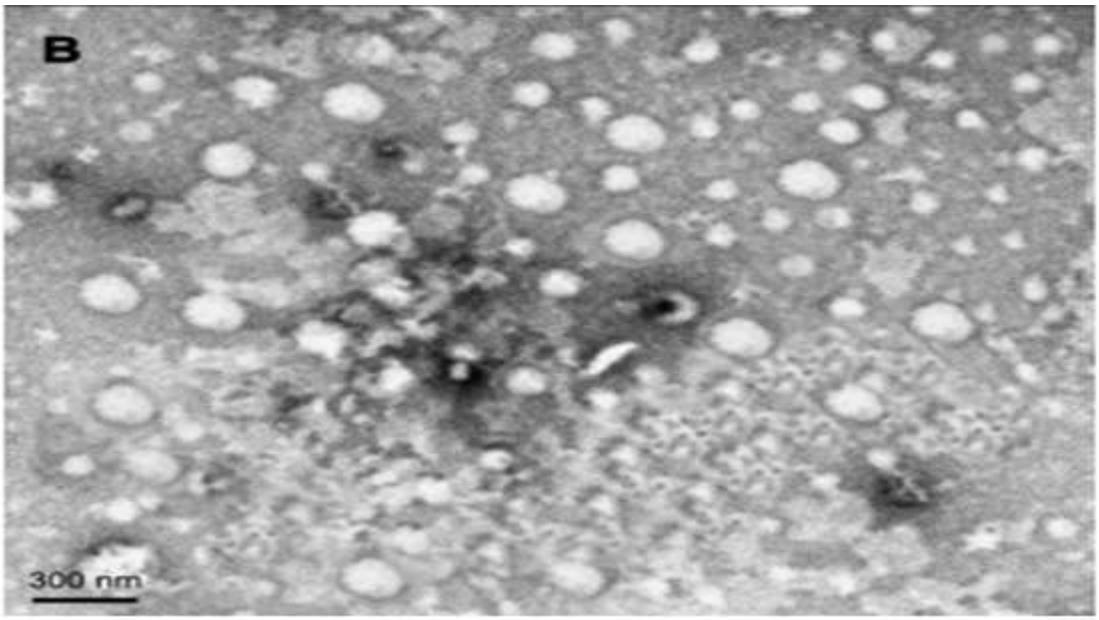

Fig 2 Scanning electron micrographs of raw drug (A); transmission electron micrographs of drug nanoparticles (B)

IV. DISCUSSIONS:

1. The results of physicochemical evaluation of Nano suspension are given in table no 4. The tablets of different batches were found satisfactory with respect to description, pH and assay
2. The homogeneity of different batches of suspension were found within the prescribed limits. Hence, the suspension containing drug, Polycaprolacaprolactone, tween 80 and water could be prepared satisfactorily by solvent evaporation method.
3. The results of particle size drug suspension studies in Malvern particle size analyser are presented in Fig.1 It was expected that the optimum formulation of this study which matches the particle size requirement of below 200 nm. Hence particle size of the drug suspension from all the prepared formulations were compared from which F6 is selected as best formulation for further granulation process.
4. Scanning electron microscope was used to evaluate the morphology of freshly prepared raw drug, which was deposited on glass slides followed by evaporating the solvent. Fabricated nanosuspension was evaluated using TEM. Sample was dropped on a copper 200 mesh formvar/carbon coated grid and allowed to dry the results found satisfactory for drug nano suspension. Morphology of nano suspension found uniform outer layer and results are below 300nm.
5. All formulation are evaluated for Particle size are found from range 100 nm to 2000nm the PDI value determined by the marvern zetasizer were in range from 0.2 to 0.8. the PDI value of F6 0.2 confirm the uniformity of particle size.
6. F6 nano suspension of Ganaxolone selected for wet granulation to formulate Ganaxolone SR tablet .
7. The drug loading of the Nano suspension studied using centrifuge method results of F6 formulation found 97.93% which is highest among all formulation.

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