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A REVIEW PAPER OF DIVALPROEX SODIUM SUSTAINED RELEASE TABLET IN THE TREATMENT OF EPILEPSY

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INTRODUCTION

Pharmaceutical substances are administered to the body in different routes such as orally, sublingual, intravenously or by trans dermal application. The most common way of introducing a curative medicine like tablets, pills, capsules or liquids is via the oral route.[1] However, it is not always the best choice even though it offers more options for dosage forms, and is more likely to be accepted by patient.[1] For example in case of patients in a vegetative state, dosage forms may nearly be impossible to be swallowed by them creating some inconveniences in treatment and recovery. In addition, conventional solid dosage units may be limited to maximum absorption in the gastrointestinal tract and resistance to dense compact or compression due to their amorphous or low-density characteristics.

With the high expense of discovering new therapeutic compounds, pharmaceutical industry are prioritizing researching innovative delivery mechanisms for current medication to improve their safe and effective capabilities in healing a disease by increasing dose accuracy, patient tolerance, bio availability, and reducing dose frequency and at a more cost-effective dose forms.[2]

Tablets are widely known for their self-administration, compact size, and ease of manufacturing.[3] They are produced through the compression of the active ingredient and the adjuvants combination, with or without a diluent. The strength and the volume of the therapeutic medications are directly correlated with their dimensions and mass.

A bilayered tablet may influence both the effectiveness of the medicinal agents as well as the amount of drug that reaches the receptor sites due to their two layers containing two different medications that distribute like an immediate release and as a delayed release.[4] The stability, molecular weight, solubility, dosage form, protein and partition coefficients are the different characteristics that influence the design of the double layer doses. This system is developed so that the charge per unit of drug particle dissolution in the matrix is significantly greater than the rate of drug diffusion out of the matrix, to establish a controlled drug delivery. Hence, by directing the drug to the specific site of absorption and regulating its rate can maintain an efficacious dose of the drug in solution. Patient suitability is also improved as the frequency of daily dose get reduced compared to conventional tablets.[4]

In this research study, two active ingredients valproic acid and sodium valproate were combined together as two separate layers to form a bilayered tablet known as divalproex sodium. This medication helps to alleviate and treat the symptoms of the epilepsy.[5] Based on a global scale, Epileptic conditions are often observed worldwide and is listed on the third rank of the most prevalent neurological disorder to be experienced by an approximate population percentage of 10 in any individual lifetime.

Divalproex sodium can also be used to treat bipolar disorders and prevent migraines.

The anti-epileptic drug act by reducing the seizure activity in a variety of methods.

These encompass mechanisms such as inhibiting voltage-gated channels (Na+ or Ca2+), enhancing inhibitory GABAergic impulses, and impeding the transmission of excitatory glutamate. It appeared that numerous anti-epileptic drugs target the central nervous system (CNS), and the precise mechanism of action for a number of these drugs still remain unknown.

Some of the common side effects of sodium valproate include gastrointestinal symptoms like stomachache, diarrhoea that occurred at the beginning of the treatment and keep reducing over a maximum days of a week.[6]

Although, sodium valproate dose decreases the seizure, some accidental overdose may happen depending to the patient leading to moderate toxicity, multi-organ failure, cerebral oedema and potentially life threatening.[7]

DOSES	RESPONSE
<200mg/kg	Mild sedation
200-400mg/kg	Moderate toxicity with CNS depression
>400mg/kg	Multi-organ system toxicities
>1000mg/kg	Coma, cerebral oedema, death

One of the way of managing the symptoms in case of ingestion >400mg/kg is the use of the antidote for decontamination after consultation with a toxicologist. A dosage of 100mg/kg IV of Carnitine, followed by 50mg/kg every 8 hours can reduce the acidosis or resolve coma.

On the other hand, the common side effects of divalproex sodium are not heavy compared to those of valproic acid and sodium valproate. The symptoms include drowsiness, blurred vision and dizziness. Hence, it is advised not to drive a vehicle, use machinery, or do other activities that require alertness after taking this medication. In rare cases, the patient with mitochondrial disease and children younger than 2years of age may be at high risk of liver failure. To counteract the toxicity of sodium valproate depending to the patient, dose is calculated based on body weight of the adult or the children in the novel dosage form, divalproex sodium.

For example, the initial dose in adults is 10-15mg/kg of body weight per day. This dose may be gradually augmented by 5-10mg/kg of body weight and usually should not exceed 60mg/kg of body weight per day. If the total dose a day is greater than 250mg, it is divided into smaller doses which are taken 2 or more times a day.

Therefore, the formulated immediate and continuous layers of Divalproex sodium aim to exhibit a high bio availability compared to the extended and delayed release that was previously developed.

DISCUSSION

The illustrative medication chosen was divalproex sodium, a broad-spectrum anti epileptic that could be formulated for both immediate and continuous release. Although divalproex sodium exhibits a moderate solubility in water, it demonstrates remarkable solubility in methanol, phosphate buffer pH6.8, 0.1 N NaOH, 95% ethanol, and chloroform. When compared to alternative solvents, the results indicated that divalproex sodium was completely dissolved in chloroform. While scanning divalproex sodium in the 200-400 nm range with phosphate buffer pH 6.8 and methanol solutions, the highest absorbance was detected at 210 nm.

We tested numerous continuous and fast-releasing layer compositions for this task. Pharmaceutical products were developed using the formulation with the greatest disintegration profile compared to sustained-release and immediate-release layers. The kinetic profile of immediate-release layer formulations (IF1-IF6) showed first-order kinetics with 'r' values from 0.985 to 0.960 and 'n' values above 0.89, supporting Super Case II transport. As illustrated by 'r' (0.9918 to 0.9736) which is much bigger than first-order (0.8986 to 0.7303) and Higuchi's equation (0.9794 to 0.9074), sustained-release layer formulations (SF1-SF8) follow zero-order kinetics. 'n' values from 0.6634 to 0.6064 indicated non-Fickian releases. Table 32 shows that bi-layered tablets stabled at forty degree Celsius/ 75% RH for 3 months did not lose hardness, medication content, or appearance within 2 months. However, a slight change in the hardness and homogeneity of the drug content was seen in the stability data over a three-month period, indicating that storage conditions should be carefully monitored.

Medication distribution did not change much.

--->LITERATURE REVIEW

- A direct compression method was employed to fabricate an oral extended-release matrix tablet of divalproex sodium using Eudragit L100 and HPMC K100M as matrix-forming polymers (**Lakhani KM et al.,**[33]). The manufactured tablets successfully met various physicochemical criteria, including in vitro drug release, content homogeneity, thickness, weight fluctuation, friability, and rigidity. The drug release profile was enhanced through the utilization of 3^2 complete factorial designs, with Eudragit L100 and HPMC K100M serving as the independent variables. After analyzing the ten formulations, it was concluded that batch F8, which comprised 15% HPMC K100M and 10% Eudragit L100, exhibited a dissolving profile nearly identical to that of the commercial product.

- **Vamsy KA et al.,**[34] obtained divalproex sodium tablets through the direct compression method. Five formulations containing different proportions of polymers—including HPC-HF, HPMC K15M, HPMC K4M, and HPMC K100M—were developed in order to produce extended-release tablets of divalproex sodium. FTIR analyses confirmed that the excipients and medication were compatible. The USP type II paddle assay was employed to evaluate the weight variation, rigidity, and in vitro solubility of the compressed tablets. Among the five

formulations evaluated, batch DERT-V, comprising 19.5% HPMC K100M and 4% HPMC K4M, was deemed the most suitable for 18-hour extended-release tablets due to its complete adherence to the specified criteria.

- **Kumar S.D et al.,**[36] formulated a bi-layer floating tablet comprising ziprasidone hydrogen chloride for sustained release and trihexyphenidyl hydrogen chloride for immediate entry. For prolonged drug release, a polymer known as HPMC K4M or HPMC K15M was utilized with a suspended sodium bicarbonate layer. The IR results did not yield any indications of drug-excipient interactions. Weight variation, hardness, thickness, friability, disintegration, and solubility were among the parameters utilized to evaluate the final tablets. The USP XXIII dissolving device was employed to ascertain the release profile of the tablet. One of the twenty formulations that have undergone optimization are F1, F2, F11, and F12. The researchers of the investigation led by **Shivanand K et al.,**[37] produced bi-layer buccal tablets of Tizanidine hydrochloride(TZD HCl) via direct compression. Sodium carboxymethylcellulose, carbopol 934(CP), HPMC K4M, HPMC K15M, and ethyl cellulose serving as the barrier supporting layer were utilized in the production of the tablets. DSC and FTIR analyses conducted by the researchers revealed that the compound remained unaltered when combined with the selected polymers. The oral tablets containing HPMC K4M and CP in a 1:1 ratio (BT1) exhibited the greatest proportion of in vitro drug release within a duration of 6 hours. The mucoadhesive strength ex-vivo was assessed utilizing the balance method. The bio adhesive strength of the HPMC K4M and Na CMC tablets is more than sufficient to maintain their position in the mouth.

- **Remya PN et al.,**[38] employed Povidone k-30 as a binder in their moist granulation process to produce bi-layered tablets containing Methocarbamol and Ibuprofen. A range of 3.23 to 7.34 minutes per second was measured for the in-vitro disintegration time. Due to its accelerated rate of dissolution, formulation-F8 tablets were identified as the optimal composition. By exhibiting a percentage release ranging from 95.1 to 97.2%, formulation F8 proves to be a preferable vehicle for drug release. A viable substitute for the current standard tablets was identified: bi-layer tablets comprising methocarbamol and ibuprofen could be efficiently manufactured.

- In their study, **Patil SS et al.,**[39] utilized a controlled release layer composed of hydroxypropyl methyl cellulose K100M (HPMC K100M) and multiple super disintegrants to fabricate gastro-retentive bi-layer floating tablets of Rosiglitazone maleate via direct compression. Out of the numerous super disintegrants that were evaluated, it was determined that 8% Croscarmellose produced the most rapid medication release, while 50% HPMC by weight of the tablet effectively regulated drug release for twenty-four hours. The optimized tablet (F5), which contained 14%w/w sodium bicarbonate, demonstrated a buoyancy latency time of under 3 minutes. There are a variety of formulations with variable times that span from 10 to 28 hours. Formulation F5's release profiles revealed that an increase in polymer content resulted in a significantly delayed 24-hour release of Rosiglitazone maleate. First-order kinetics governed the reaction of the granules via diffusion. Throughout the stability period, the enhanced formulation demonstrated no alterations in its physicochemical properties or drug release characteristics.

- **Kasid I et al.,**[43] used a twofold compression technique to fabricate bi-layer tablets consisting of an optimal layer for sustained release of gliclazide and a layer for rapid dissolution of Lisinopril. Lisinopril was formulated into a fast-dissolving layer using two super absorbents, sodium starch glycolate and croscarmellose sodium. Physical parameter evaluations and in vitro release experiments were performed on gliclazide as a sustained release layer composed of Hydroxyethylcellulose, hydroxypropyl cellulose, and ethyl cellulose, among others. Lisinopril has been demonstrated to augment the hypoglycemic effects of Gliclazide and maintain stable blood glucose levels for a duration of 24 hours, as evidenced by its in vivo anti-diabetic activity. Combining pharmaceuticals with excipients and polymers is risk-free, according to the findings of the FTIR review.

- **Kulkarni A et la.,**[44] developed bi-layer regioselective floating tablets by employing the direct compression method. These tablets were designed to contain Lovastatin for immediate release and Atenolol for prolonged release. In the immediate release layer of Lovastatin, sodium starch glycolate functioned as the super disintegrants. Conversely, in the sustained release layer of Atenolol, xanthan gum and HPMC K100M were utilized as the release retardants. The bi-layer tablets were manufactured with the gas-producing sodium bicarbonate. Rotentgenography research indicates that each formulation floated for a duration exceeding 12 hours. Over ninety percent of ivastatin was discharged within thirty minutes. Atenolol was released in accordance with a hybridization of the Korsmeyer-Peppas, Hixson-Crowell, and zero order release models. During an eight-hour test in the stomach, the enhanced formulation maintained its buoyancy. In this

investigation, therefore, floating bi-layer tablets were utilized to generate an effective biphasic drug release pattern.

- A bi-layer tablet was developed by **Toma N.M et al.,**[50] that consisted of two distinct layers: one for sustained release of clopidogrel and the other for immediate release of aspirin. The super disposing agent croscarmellose was utilized to create the immediate release layer, whereas carbopol, hydroxypropyl methyl cellulose, ethyl cellulose, or a combination of these substances comprised the sustained release layer. The tablet was manufactured by means of moist granulation. The two substance layers were independently prepared. Eleven distinct formulations of the sustained release layer were developed; among them, the one comprising carbopol and HPMC in a 1:1 ratio exhibited the most favorable buoyancy. A3 has the most reasonable disintegration time of the three formulations of aspirin. Metrics such as thickness, hardness, weight variation, disintegration time, drug content, and in vitro drug release were employed to evaluate the most optimal samples prior to their transformation into bi layer tablets.

- **Lakshmi A.P et al.,**[51] developed bi layer tablets comprising Levofloxacin hemihydrate for extended release and Ambroxol HCL for rapid release. To impede the dissipation of Ambroxol from the Ambroxol layer, HPMC K100M and K4M were employed. The sodium starch glycolate was utilized in the production of the immediate release layer for Levofloxacin. Eleven formulations of Ambroxol HCl and four formulations of Levofloxacin were developed independently. F11 for Ambroxol HCL and F2 for Levofloxacin were selected as the optimal formulations for in vitro drug release, homogeneity of drug content, thickness, hardness, weight variation, friability, and disintegration time, respectively. Throughout a duration of three months, stability experiments were conducted on the bi-layered tablet, encompassing both standard and accelerated conditions.

CONCLUSION

In this study, for Divalproex sodium dosages, moist granulation was used. Super disintegrants such as sodium starch glycolate and croscarmellose speed granule disintegration, create an immediate release layer, whereas polymers like K100M and K4M HPMC give a continual release layer.

Every good layer was selected for the bi-layered tablet and bind together. Bi-layer tablets were tested for physical property fluctuation, consistency, crumbliness, dosage uniformity, drug-polymer compatibility, and medicine administration technique. The findings show that Divalproex sodium bi-layer tablets including disintegrant agents, prolonged-release polymers, and other pharmaceutical additives can display all of the therapeutic properties associated with bi-layer tablets. Medication administration may be reduced, lowering expenses and side effects. Increased patient tolerance and medication effectiveness are possible.

-->Future Perspective

Understanding the patterns and etiology of genetic diseases affecting the brain nerve cells and spinal cord, such as depression, bipolar disorder, migraines, Fragile X syndrome, Familial adenomatous polyposis can increase chances of developing efficacious treatment that provide a strong and long immunity by dis activating or freezing the pathogen causative of abnormal electrical discharge not to react and cause the disease at an affordable price and that can be administered in a single dose by;

- Developing vaccines-immune resistant to the triggering neurons inducing symptoms.

The CNS consists of the brain and spinal cord. It receives and processes information from the PNS and sends out signals to control body functions. It is responsible for higher-level cognitive activities, such as learning, memory, and decision-making.

The PNS connects the CNS to the rest of the body. It consists of sensory neurons, which transmit information from the body to the CNS, and motor neurons, which carry signals from the CNS to the muscles and glands. The PNS controls activities such as movement, sensation, and the regulation of bodily functions. Developing vaccines targeting the electrical signals, known as action potentials, are the primary means of communication within the nervous system. Thus, helping the neurons to generate these electrical impulses normally and transmit them along their branches, called axons.

The axons which connect to other neurons at specialized junctions called synapses. Here, the electrical signal is converted into a chemical signal to bridge the gap between neurons. Preventing this intricate network of electrical signals that allows for the coordination of various bodily functions not to be disturbed.

Overall, the treatment of neurodegenerative disorders is complex and fascinating as it encompass the study of different factors affecting the network of electrical signals that allow for the coordination of muscles, the senses, speech, memories, thoughts, and emotions. for example the impact of the patient suffering from the epilepsy interact with the world and navigate his internal and external environments.

- The impact of inflammatory gut and the inability of regulating the emotion or hyperactivity or coordination of muscle of the patient suffering from epilepsy.

- Research on the relationship between the gut health and the ADHD symptoms

- Strategies on controlling the hyperactivity with the gut management
-Research on the relationship between the gut healthy and the motor skills
-Case studies of individuals with inflammatory gut experiencing coordination difficulties

Keywords: Epilepsy, Bi-layer tablet, Divalproex sodium, CNS.

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