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A Review on Formulation and Evaluation of Sustained Release Tablet of Devilproex Sodium

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ABSTRACT

An appropriately designed drug delivery system can be a major step towards solving these two problems. This technique for the drug administration is termed as 'sustained release' or 'controlled release. Drugs with dosage not exceeding 125mg – 325mg are more suited as extended release products in order to limit the size of the delivery system. In the case of soluble matrix the matrix swells or dissolves. These matrices then undergo surface erosion with little or no bulk erosion. Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. One of its most important characteristics is the high gelation velocity and viscosity, which has a significant effect on the release kinetics of the incorporated drug. It was proven that HPMC at high concentration promoted the drug release approaching to a zero-order release kinetic because of its gelation properties

Keywords: HPMC, Divalproex sodium, sustained release and zero-order release kinetic

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1. Introduction:

New and more sophisticated sustained release drug delivery systems are constantly being developed and tested. Successful fabrication of sustained release products is usually difficult and involves consideration of the physicochemical properties of the drug, pharmacokinetic behaviour of the drug, and route of administration, diseased state to be treated and most importantly placement of the drug in a dosage form that will provide the desired temporal and spatial delivery pattern for the drug.[1-3] There are literally dozens of names associated with sustained release products such as continuous release, controlled release, delayed release, delayed action, depot, extended action, gradual release, long acting, long lasting, long-term release, prolonged release, repository retard, slow acting, slow release, time coat, sustained release, sustained action, timed disintegration, timed release etc. Spatial placement relates to the targeting of the drug to a specific organ or tissue while temporal delivery refers to controlling the rate of the drug delivery to the target tissue. An appropriately designed drug delivery system can be a major step towards solving these two problems. This technique for the drug administration is termed as 'sustained release' or 'controlled release. Drugs with dosage not exceeding 125mg – 325mg are more suited as extended release products in order to limit the size of the delivery system. In the case of soluble matrix the matrix swells or dissolves. These matrices then undergo surface erosion with little or no bulk erosion.[4-6] The surface area of the matrix decreases with time, with a concomitant decrease in drug release. The diffusion depends on the solubility of the drug in the polymer. The drug release mechanism across the membrane involves diffusion of water through the membrane to the inside of the core, dissolution of the drug and then diffusion of the drug into the surrounding fluid. In reservoir dissolution control system the drug particles are coated or encapsulated by one of the several micro encapsulation techniques with slowly dissolving materials like cellulose derivatives, poly ethylene glycols, waxes etc., the resulting reservoirs may be filled as such in hard gelatin capsules or compressed into tablet.

Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to

increased brain concentrations of Gamma Amino Butyric Acid (GABA). The absolute bioavailability of Divalproate ER tablets administered a single dose after a meal was approximately 90% relative to intravenous infusion. Formulation of Divalproex sodium ER tablets expected to reduce Divalproex sodium ER is used by patient for treatment of chronic epilepsy. So reduces the frequent administration of dose (twice in a day), avoids first pass metabolism, improved patient compliance, maintain therapeutic action by administration of a single dose in a day. [7]

2. Reasons for developing an sustained release formulation

Reasons for developing an sustained release formulation are not limited to improving tolerability and, as a result, effectiveness, or to allowing use of longer dosing intervals. An additional reason is simply the pharmaceutical industry's desire to extend exclusivity rights for their products. In fact, it is no surprise that many extended-release formulations are introduced at the time exclusivity rights for the immediate-release product approach the expiration date. Regulatory approval for extended-release formulations does not require any comparison of efficacy and safety with the immediate-release product; to the contrary, pharmacokinetic data and, at least in the United States, demonstration of superiority over placebo in a single trial is generally sufficient for marketing approval. This regulatory scenario implies that high-quality data on the comparative efficacy and tolerability of the extended- and immediate-release forms of most AEDs are usually unavailable.[8]

3. Bioavailabillity of Divalproex Extendend-Release Tablets

It has been reported that the absolute oral bioavailability of divalproex-ER is 89%, while the oral absorption is practically 100% for divalproex-DR.5 Steady state 24-hour average plasma valproate concentration after once-daily administration of divalproex-ER was between 81 and 89% (fasting and non fasting conditions respectively) of that obtained after twice-daily dosing of divalproex-DR.6 A meta-analysis of divalproex-ER once-daily/divalproex-DR twice-daily relative bioavailability across five multiple-dose studies, under different meal conditions, revealed a mean value for AUCss (area under the steady state total plasma drug concentration curve) ER/DR ratio of 0.89.[9-11]

4. Polymer used for formulation of suatined release of divalproex:

HPMC is the major hydrophilic carrier material used for the preparation of oral controlled drug delivery systems. One of its most important characteristics is the high gelation velocity and viscosity, which has a significant effect on the release kinetics of the incorporated drug. It was proven that HPMC at high concentration promoted the drug release approaching to a zero-order release kinetic because of its gelation properties.[12] Lactose is widely used as a binder, filler-binder, and flow aid in direct compression tableting. The particle size of lactose influences parameters like flow; in general, a decrease in particle size will decrease the flow which is due to the drug/fine particle fraction (14). SiO_2 is a fine and amorphous powder consisting of particle about 7–40 nm in size that has been used in the tablet manufacturing as a glidant.[13]

5. Requirements for formulation of sustained release of divalproex:

Suatined release of divalproex formulation is a unit process that may serve one or more of the following function: to mask odour or taste; to ease the swallowing of the dosage form; to improve mechanical integrity; to enhance product identification and elegance; to improve product stability; and to modulate the release properties. The benefits of film coating more than justify the exposure of the product to the rigour of the coating process, during which the tablets (and the applied coating) are constantly subjected to mechanical stress along with conditions of elevated temperature and humidity. Therefore, core must be designed using more stringent criteria compared with uncoated dosage form to guarantee a product robust enough to withstand the additional stress imparted by the film coating process. The design of such a substrate has to be considered in term of [14,15]

1. The ability of the core to withstand the mechanical stress of the process.
2. Maximized adhesion of coating to the tablet surface.
3. A film coat with uniform thickness.

6. Preformulation studies of Divalproex Sodium pure drug

6.1 Preparation of standard calibration curve of Divalproex Sodium

10 mg of drug was dissolved in 0.1 N HCl and final volume was make up to 100 ml in 100 ml volumetric flask. The staock solution concentration was 100 mcg/ml obtained. It was diluted with 0.1 N HCl to obtain solution of Concentration range10 to 60 µg/ml. Absorbance of µg/ml solution was measured at 250 nm by using of Shimadzu UV-1601 UV/Vis double beam spectrophotometer and 0.1 N HCl as reference standard.[16]

6.2Melting point determination

The Melting point of Divalproex Sodium was determined using open capillary method. The capillary filled with drug powder was placed in Thiel's tube containing liquid paraffin. The tube was heated and the melting point of the drug powder was noted. The average of three values was considered as the melting point of drug.

6.3Drug excipient compatibility study

The interaction of the drug and the co-formers were carried out by FTIR method to know the physiochemical interaction occur in the drug and excipient. The drug and co-formers were taken in 1:5 ratios and placed in a vial and rubber stopper was placed on the vial and sealed properly for 6 month at $40^0C \pm 2^0C/75\%RH \pm 5\%RH$.

6.4Differential scanning calorimetry

The DSC of Tabletwasrecorded by differential scanning calorimeter equipped with a computerized data station. TheDSC measurements were performed on a DSC 60, Shimadzu, Japan instrument. Accuratelyweighed sample were placed in a sealed aluminum pans before heating under nitrogen flow(20ml/min) at a scanning rate of 100c/min. An empty aluminum pan was used as a reference.Melting point was determined for identification of API and co-crystal former.

6.5Solubility Studies

The equilibrium solubility at a room temperature is determined by the shake flask method. According to this method the compound is added in to a certain medium and shaken at a predetermined time, usually 24h or longer. The

saturation is confirmed by observation of the presence of undissolved material. Saturation can also be reached if the solvent and excess solute is heated and then allowed to cool to the given temperature.

7. Evaluation of Divalproex Sodium powder blend[17-18]

7.1 Angle of Repose

The angle of repose of powder was determined by the funnelmethod. The accurately 10 gm weighed powder were taken ina funnel. The height of the funnel was adjust and the powderwas allowed to flow through funnel freely onto the surface.The diameter of the powder cone was measured and angle ofrepose was calculated using the following equation:

Tan θ=h/r , Where θ = angle of repose, h = height of thecone, r = radius of the cone base.

7.2Bulk Density

A quantity of 10 g of powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 50 ml measuring cylinder. The bulk volume and mass of the powder was determined. The bulk density was calculated using following formula:

Bulk density= Weight of granules/ Volume of granules

7.3Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume occupied in the cylinder and the mass of the blend was measured. The tapped density was calculated using the following formula:

Tapped density= Weight of granules/ Volume of granules after 100 tapping

7.4 Carrs Index

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which amaterial can be induced to flow is given by Carr¡¦s index which is calculated as follows:

Carr's index (%) = Tapped Density – Bulk Density/Tapped DensityX 100

Where,

BD = Bulk density

TD = Tapped density

6.5 Hausners ratio

Hausners ratio value is less than 1.25 indicates good flow andgreater than 1.5 indicates poor flow property which wascalculated by using following formula:

Hausnre's ratio = Tapped density/ Bulkdensity

8. Conclusion:

Divalproex sodium ER tablets expected to reduce Divalproex sodium ER is used by patient for treatment of chronic epilepsy. So reduces the frequent administration of dose (twice in a day), avoids first pass metabolism, improved patient compliance, maintain therapeutic action by administration of a single dose in a day. Suatined release of divalproex formulation is a unit process that may serve one or more of the following function: to mask odour or taste; to ease the swallowing of the dosage form; to improve mechanical integrity; to enhance product identification and elegance; to improve product stability; and to modulate the release properties

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