

Original Research Article

Formulation development of a stable solid oral dosage form of Valproic acid using colloidal silica

Naveen A. Khetarpal^{*1}, Aay R. Sav¹, Leena Rao², Purnima D. Amin¹

***Corresponding author:**

Naveen A. Khetarpal

¹Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Mumbai. 400 019, Maharashtra, India

²Department of Chemistry, SIES College of Arts, Science and Commerce, Mumbai-400022, Maharashtra, India

Abstract

Valproic acid (VA) is a liquid drug used as an anticonvulsant. Although Valproic acid or its salts have known utility as anticonvulsants, a number of problems are associated in formulating them in a solid form. The aim of present study was to develop a stable solid dosage form for plain VA by a simple adsorption process. Various solid and inert carriers like Soluplus[®], Kollidon[®] VA 64, Magnesium oxide (MgO), AEROSIL[®]300 Pharma and AEROPERL[®] 300 Pharma were selected for the study. As desirable results were not obtained with Soluplus[®], Kollidon[®] VA 64, Magnesium oxide (MgO). Further work was continued with silica AEROSIL[®] 300 Pharma and AEROPERL[®]300 Pharma. Maximum drug loading of 60% and 66.7% was achieved with VA: AEROPERL[®] 300 Pharma with a ratio of 1.5:1 and 2:1 for VA: AEROSIL[®] 300 Pharma. By characterization studies like flow property, FTIR, DSC, the optimized batch was found to show good flow property and absence of chemical interaction between drug and excipients. It was found by SEM study AEROPERL[®] 300 Pharma has better adsorption potential because of its granular nature and pearl like cavity. Drug content analysis of VA:Silica system by GC method showed high drug content uniformity with 104% VA. Dissolution study of developed capsule dosage revealed 100% drug release at the end of 90 min of dissolution. Optimized batches were kept for stability study at 25°C, 60% RH and 40°C, 75% RH for 3 months as per ICH guidelines. Stability study result was found to be uniform for the drug content and dissolution behaviour showed insignificant changes.

Keywords: : Valproic acid (VA), AEROSIL[®] 300 Pharma, AEROPERL[®] 300 Pharma, solid dosage form, GC

Introduction

Valproic acid was first produced in 1882 as an organic solvent. The eight-carbon branched chain fatty acid derived its name from the chemical name of 2-propylvaleric acid. Valproic acid is also known as 2-propylpentanoic acid and n-dipropylacetic acid[1]. Marketed formulations of Valproic acid are available in the form of either syrups or soft gelatin capsules. Till date there are no solid formulations containing plain Valproic acid available and marketed solid dosage forms of VA are either in the form of one of its pharmaceutically equivalent salts (sodium valproate or divalproex sodium) or as a combination of Valproic acid with its salts. Moreover sodium valproate is hygroscopic which limits its use and divalproex sodium is a new entity produced via a reaction between Valproic acid and Sodium valproate [2-6]. Non hygroscopic sodium valproate compositions were also prepared using different solid carrier like carbomer and cyclodextrin [7,8]. Although the formulations described in many patents were promising, their production require that such dosage forms

should be manufactured in dry atmosphere cabinet, at less than 30% RH which is a serious disadvantage.

Valproic acid is an anticonvulsant and mood-stabilizing drug used primarily in the treatment of epilepsy and bipolar disorder. It is also used to treat migraine headaches and schizophrenia. VA increases the concentration of inhibitory neurotransmitter GABA (γ -Amino Butyric Acid) in brain by acting on GABA transaminase which catabolize GABA or blocking the reuptake of GABA into glia and nerve endings. Valproic acid may also work by inhibiting voltage-gated Sodium channel there by suppressing the repetitive neuronal firing. It is also a histone deacetylase inhibitor and can be effective in HIV and cancer disorders [9].

The purpose of this work was to overcome the above discussed problems associated with VA solid dosage formulations and to provide a simple and industrially feasible method for the development of solid dosage form of VA alone without any strict environmental condition.

A simple method was tried which involved adsorption of VA on solid, inert carrier like

Soluplus[®], Kollidon[®] VA 64, Magnesium oxide, AEROSIL[®]300 Pharma and AEROPERL[®] 300 Pharma. Soluplus[®] is a graft copolymer composed of polyethyleneglycol/polyvinylcaprolactam/polyvinylacetate [10]. Kollidon[®]VA 64 is vinylpyrrolidone-vinylacetate copolymer used in the pharmaceutical industry as dry binder in tablets, as granulating agent, as retarding and as film forming agent [11]. AEROSIL[®] 300 Pharma is a high purity amorphous anhydrous colloidal silicon dioxide used as viscosity increasing agent to thicken and thixotropize liquids, improves storage and temperature stability of semi-solid and liquid dosage forms [12]. AEROPERL[®] 300 Pharma is a granulated form of colloidal silicon dioxide unlike highly disperse AEROSIL[®] products, AEROPERL[®] 300 Pharma consists of bead like mesoporous granules with a particle size of 30 to 40 μm [13].

Materials and Methods

Materials

Valproic acid was received as a gift sample from InChem Laboratories Pvt. Ltd. (Hyderabad, India). Soluplus[®] and Kollidon[®] VA 64 were obtained as gift samples from BASF (Mumbai, India). Magnesium oxide was purchased from S. D. Fine Chemicals Limited (Mumbai, India). AEROPERL[®] 300 Pharma and AEROSIL[®] 300 Pharma were kindly supplied by Evonik Industries (Mumbai, India). All other materials and solvents were of analytical reagent grade.

Preparation Valproic acid colloidal silica solid system

Initially work was started with Soluplus[®], Kollidon[®] VA 64 and magnesium oxide. Solid dispersion was prepared in the drug: solid carrier ratio of 1:1 and 3:1. These solid carriers were used to prepare a free flowable solid dispersion system which subsequently can be formulated into tablet or capsule dosage form. But these solid systems showed poor drug loading and change in color appearance with formation of sticky mass upon drying which made processing difficult whereas with magnesium oxide exothermic reaction was observed. Hence further work was started with silica materials AEROSIL[®] 300 Pharma and AEROPERL[®] 300 Pharma. Solid dispersion was prepared in drug: silica ratio of 1:1, 1.5:1, 3:1 with the aim to achieve higher drug loading. Weighed amount of drug was added on to a specified amount of solid silica carrier, mixed properly with gentle hand mixing and dried at room temperature. These solid systems were found to be free flowing, white powder and stored in a well closed container till further study.

Drug content analysis

Drug content analysis of VA in prepared solid systems was done by gas chromatographic method official in USP 30 for Valproic acid Capsule. Standard and test samples were prepared as mentioned in official pharmacopoeia. The gas chromatograph was equipped with flame-ionization detector and a 2 mm \times 1.8 m glass

column packed with 10% phase G34 on 80 to 100 mesh support S1A. The column temperature was maintained at about 150 $^{\circ}\text{C}$ and the injection port and the detector block temperatures were maintained at about 250 $^{\circ}\text{C}$. Dry helium was used as the carrier gas at a flow rate of about 40 ml/min. About 1 μl of the Standard preparation and assay preparation was injected into the chromatograph, chromatogram was recorded and the peak responses for Valproic acid (standard) and Biphenyl (internal standard) was measured. The amount of VA present in sample was determined by following formula:

$$100 C (R_U / R_S),$$

where C is the concentration (mg/ml) of USP Valproic acid RS in the standard preparation; and R_U and R_S were the peak responses obtained from the assay preparation and the Standard preparation, respectively.

Evaluation of physical parameters

Colloidal silica solid system of VA prepared with AEROPERL[®] 300 Pharma and AEROSIL[®] 300 Pharma was evaluated for physical characteristics.

Density measurement

Loose bulk density and tapped bulk density was measured by standard measuring cylinder method. Loss bulk density (LBD) is the mass of solid system by packing volume. For tapped bulk density (TBD), solid powder sample of 100 ml was poured in a measuring cylinder and the weight of poured volume was recorded after taping a measuring cylinder 500 times on a tapped density USP 1 apparatus (VEEGO) from a height of 1.5 cm [14].

Flowability parameters

Angle of repose

Fixed funnel method was adopted for measuring the angle of repose [15]. In this method, powder was passed through a funnel (8 cm diameter at top and 1.7cm diameter at efflux tube) that is fixed at predetermined height (2cm) and allowed to pass with or without shaking to get precise vibration. For the calculation of angle of repose value equation $\tan \theta = 2h/D$ was used, where D (diameter) and h (height) of the formed heap was measured to calculate the angle of repose (θ).

Hausner's ratio (Hr)

Hausner's ratio is also an indication of powder flow property. Equation used for calculating Hausner's ratio: $Hr = TBD/LBD$, so it is the ratio of tapped bulk density and loss bulk density. A Hausner value less than 1.25 is indication of good flow [16].

Compressibility (%)



Compressibility of a powder mixture plays an important role if the formulation is to be compressed like a tablet. Following equation was used to calculate the Compressibility (%) [17]:
Compressibility (%) = $CI = (TBD - LBD) \times 100 / TBD$.

Development of dosage form

Tablet and capsule formulation was developed for the optimized VA colloidal silica solid system. The compositions for tablet formulation are given in table (1). For tablet preparation, colloidal solid system of VA with AEROPERL® 300 Pharma and AEROSIL® 300 Pharma VA equivalent to 150 mg VA was weighed and mixed with required amount of lactose monohydrate. A 5% starch paste was used to granulate the above mentioned mixture. The wet mass so formed was passed through 12 mesh sieve and kept for drying at 60 °C temperature for 2-3h. Dried granules were further passed through 40 mesh sieve. Dried granule were mixed with the remaining ingredients in specified amount and compressed into tablets on a single stroke tablet machine using standard 11mm round concave punch. For capsules preparation, VA loaded on AEROPERL® 300 Pharma and AEROSIL® 300 equivalents to 150mg VA was weighed and directly filled into hard gelatin capsule and evaluated for dissolution rate.

Table1. Compositions for tablet formulation

Ingredients	Quantity (mg)
Valproic acid:Silicas	150 (equivalents)
Lactose monohydrate	100
Starch	4.16
Ac-di-sol	10
Alfacel	72.5
Magnesium stearate	5
Total	400

In vitro dissolution study

Dissolution study of developed formulation containing VA was carried out using eight station USP apparatus II (paddle) (Electrolab, TDT-08L, India) in 900 simulated intestinal fluid TS media containing 0.5% SLS (pH 7.5) at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. At regular time intervals of 30, 60, 90 and 120 min, 10 ml of aliquots were withdrawn and same amount replaced with fresh medium to maintain sink condition. The withdrawn samples were suitably diluted and analysed by GC method following the procedure given in USP.

Stability study

100 capsules were manually filled with 250 mg of Valproic acid: AEROPERL® 300 Pharma and 225 mg of Valproic acid:AEROSIL® 300 Pharma solid system equivalents to 150 mg VA. These capsules formulation were packed in high density polyethylene (HDPE) bottles and were kept at 25°C, 60% RH and 40°C, 75% RH for 3 months stability studies as per ICH guidelines and the drug content and dissolution profile was determined at an interval of one month.

Characterizations of VA colloidal silica solid system

Fourier Transform Infrared Spectroscopy (FTIR)

An FTIR spectrum was recorded for AEROSIL® 300 Pharma, AEROSIL® 300 Pharma, VA, VA: AEROPERL® 300 Pharma and VA : AEROSIL® 300 Pharma solid system. Samples and KBr were compressed in a hydrostatic pressure to give a disk of uniform size. An FTIR spectrum of the obtained disk was performed on a PERKIN ELMER FTIR spectrophotometer (Spectrum RX1, USA). The scanning range was 500 to 4000 cm^{-1} and the resolution was 4 cm^{-1} .

Differential scanning calorimetry (DSC)

DSC thermogram was recorded for AEROSIL® 300 Pharma, AEROSIL® 300 Pharma, VA: AEROPERL® 300 Pharma, VA: AEROSIL® 300 Pharma. DSC analysis was performed using PERKIN ELMER DSC Pyris-6 (USA) on 2 to 8 mg sample. Samples were heated in an open aluminum pan at a rate of 10°C / min within a 40 to 300°C temperature range under a nitrogen flow of 20 ml/min. An empty sealed pan was used as a reference.

Scanning electron micrograph (SEM)

The SEM analysis of plain AEROPERL® 300 Pharma, AEROSIL® 300 Pharma, Valproic acid: AEROPERL® 300 Pharma and Valproic acid : AEROSIL®300 Pharma was performed to investigate the surface morphology and homogeneity of the particles. Samples were recorded by using a Scanning electron microscope (JEOL JSM-680 LA 5KV-Japan). Samples were fixed on an aluminum stub with conductive double sided adhesive tape and coated with gold in an argon atmosphere (50 Pa) at 50mA for 50 s. The samples were scanned at a voltage of 5kV.

Results and Discussion

Preparation Valproic acid-colloidal silica solid systems and drug content analysis

VA colloidal silica solid system was prepared in the ratio from 1:1 to 3:1 of (drug: silica) and an enhancement in drug loading was tried. GC analysis of VA colloidal silica system showed that the maximum drug loading achievable was 60% and 66.7% with 1.5:1 ratio of VA: AEROPERL® 300 Pharma and 2:1 ratio of VA: AEROSIL® 300 Pharma colloidal solid system respectively. Drug content by GC method was found to be 104.35% and 104% for VA: AEROPERL® 300 Pharma and VA: AEROSIL® 300 Pharma colloidal solid system respectively Figure (1). This optimized ratio was further evaluated for flow, density and compressibility.

Flow property

It is necessary that formulation compositions to be compressed purpose should possess good flow ability which makes uniform

transfer of drug excipient mixture from hopper to die cavity. Flow property was evaluated and calculated using different equation defining the flow property. Results founds are as shown in table (2). It was found that VA colloidal silica solid system prepared with both grades of silica has excellent flow property (angle of repose value less than 30). Hausner's ratio also indicated that colloidal solid system has good flow property ($H_r < 1.25$). Flow property for the VA colloidal silica solid system used for the tablet preparation was also evaluated and it was observed that due to effect of glidant and other excipients, flow property further is improved.

Density

Table (2) bulk and tapped density are found to be higher for VA: AEROPERL® 300 Pharma colloidal solid system as compared to AEROSIL® 300 Pharma colloidal solid systems due to the comparatively higher granular property of AEROPERL® 300 Pharma as compared AEROSIL® 300 Pharma.

Compressibility

Table (2) compressibility (%) value for VA: AEROSIL® 300 Pharma and VA: AEROPERL® 300 Pharma colloidal solid system was found to be poor (>21). However with excipients mixture an improvement in compressibility was observed.

Dosage form development

Attempts of tablet to the compression mixture was found to be unsuccessful since compression force generated during tableting was found to cause defragmentation of structure of AEROPERL® 300 Pharma and AEROSIL® 300 Pharma, leading to oozing out of VA, further generating problems like sticking, picking and discoloration of tablets.

Therefore capsules were considered to be suitable dosage form since VA loaded AEROPERL® 300 Pharma and AEROSIL® 300 Pharma exhibited good flow and could be easily filled in a capsule. Moreover capsule filling did not have any structural effect like tablet and didn't require any additional excipients.

In vitro drug dissolution

Figure (2) Dissolution study was carried out as per USP 30 specified for capsule dosage form. It was found that colloidal silica solid system showed 100% drug release at the end of 90 min of dissolution. As per USP specification not less than 85% of the labelled amount of VA must dissolve in 60 min. With colloidal solid system drug release was found to be around 78% after 60 min. To achieve complete drug release, the dissolution period was extended for another hour. VA: AEROSIL® 300 Pharma colloidal solid systems showed slow release as compared to VA: AEROPERL® 300 Pharma but both the system were found to release 100% drug after 90 min.

Table2. Physical parameters characterization

Parameters	Without excipients		With excipients	
	VA:AEROPERL® 300 Pharma	VA: AEROSIL® 300 Pharma	VA:AEROPERL® 300 Pharma	VA: AEROSIL® 300 Pharma
Angle of repose (θ)	6.55	18.8	10.11	21.32
Bulk density(g/ml)	0.53	0.40	0.47	0.37
Tapped density(g/ml)	0.67	0.52	0.58	0.45
Compressibility (%)	20.89	23.07	15.51	17.77
Hausner's ratio	1.25	1.43	1.12	1.15





Figure 1. Gas chromatogram of (A) Standard Valproic acid, (B) Valproic acid:AEROSIL® 300 Pharma (C) Valproic acid:AEROPERL® 300 Pharma colloidal silica solid system

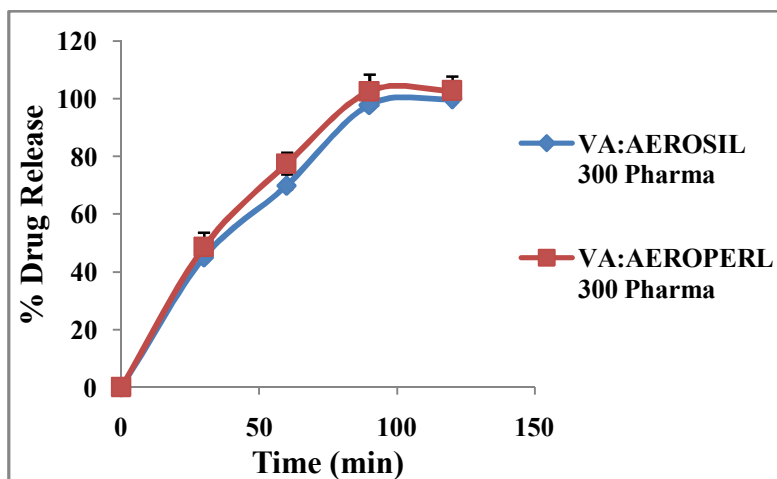


Figure 2. *In vitro* drug release of Valproic acid from colloidal silica solid system



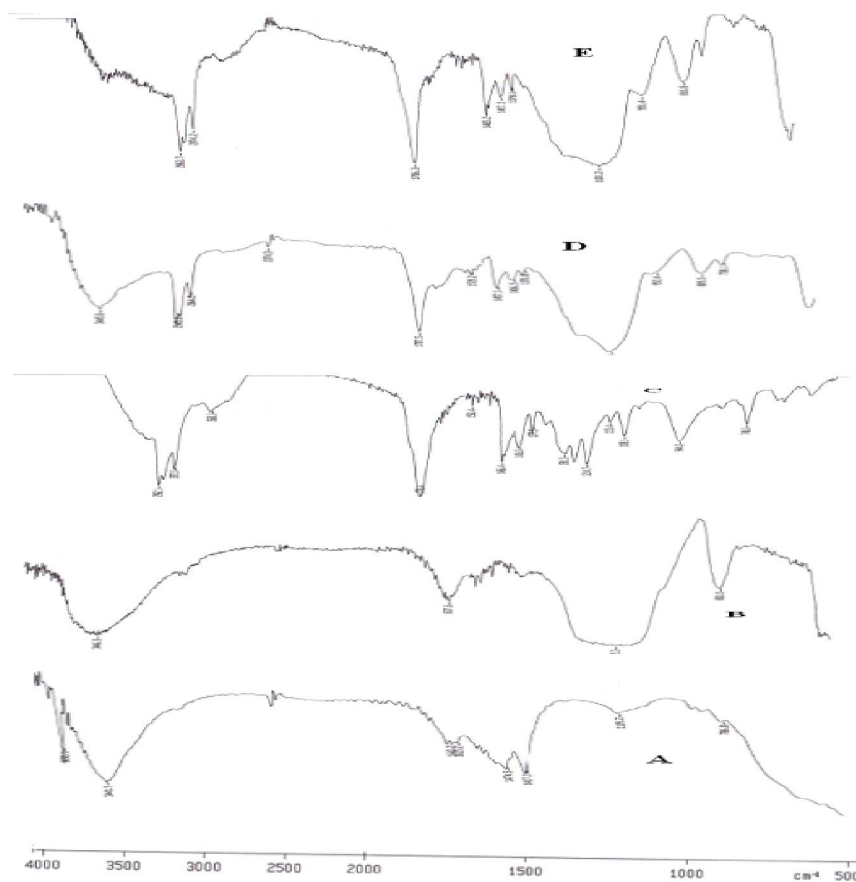


Figure 3. FTIR spectra of (A) AEROSIL® 300 Pharma, (B) AEROPERL® 300 Pharma, (C) VA: AEROSIL® 300 Pharma and (D) VA: AEROPERL® 300 Pharma colloidal silica solid system

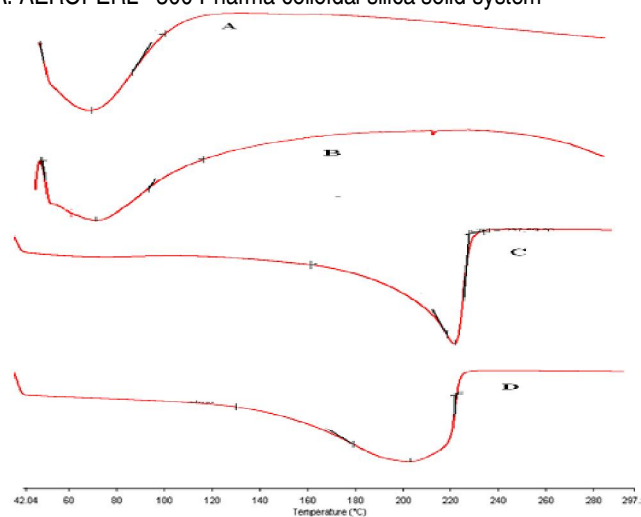


Figure 4. DSC thermogram of (A) AEROSIL® 300 Pharma, (B) AEROPERL® 300 Pharma, (C) VA: AEROSIL® 300 Pharma and (D) VA: AEROPERL® 300 Pharma colloidal silica solid system



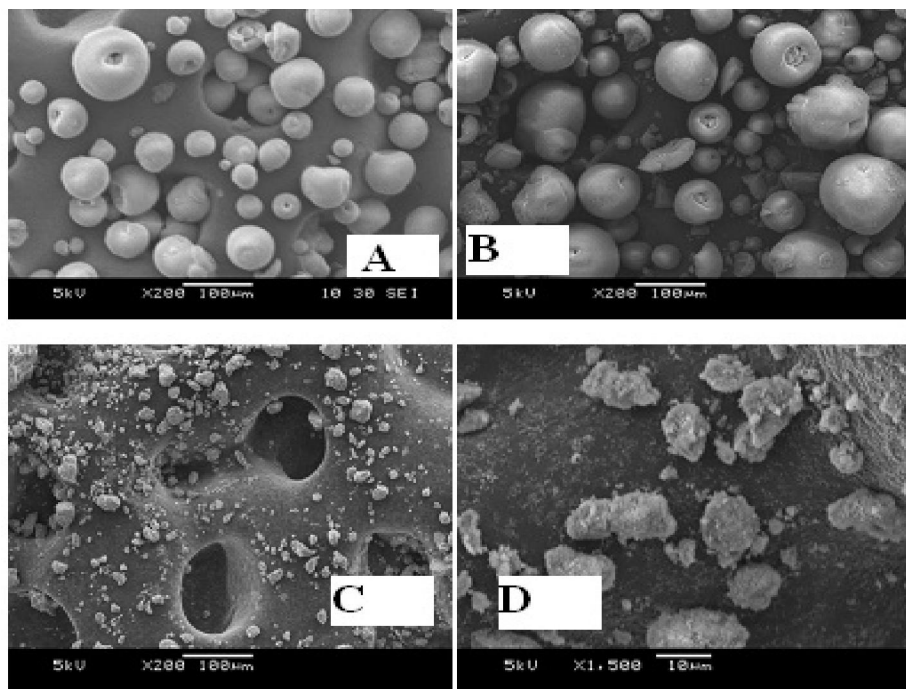


Figure 5. SEM of (A) AEROPERL® 300 Pharma, (B) VA: AEROPERL® 300 Pharma (C) AEROSIL® 300 (D)VA: AEROSIL® 300 Pharma colloidal silica solid system

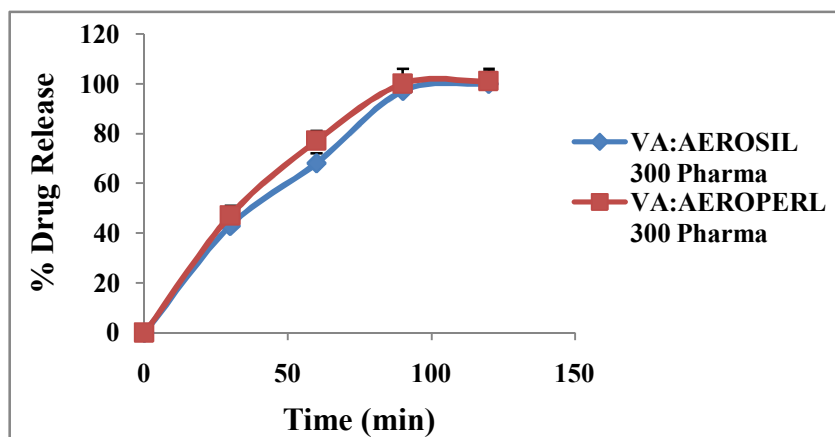


Figure 6. In vitro drug release of stability samples kept at 25 °C and 60% RH after three months



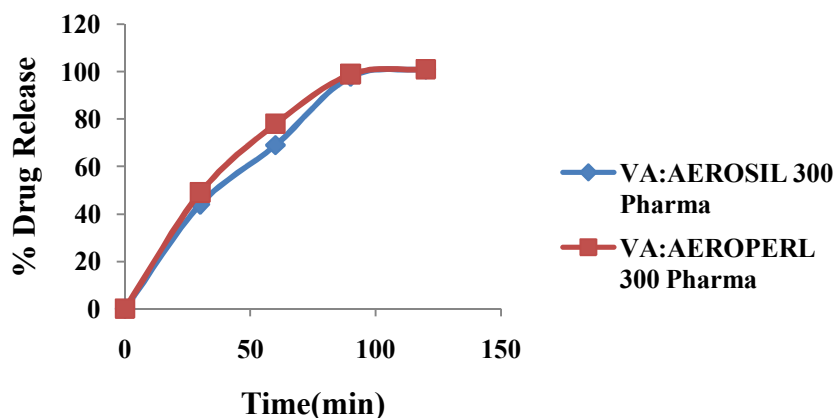


Figure 7. In vitro drug release study of stability samples kept at 40 °C and 75% RH after three months

Fourier Transform Infrared Spectroscopy (FT-IR)

A characteristic stretching vibration of O-H at 3435 cm^{-1} , aliphatic C-H at 2965 cm^{-1} , C=O stretching vibration at 1705 cm^{-1} was observed for Valproic acid in Figure (3). These characteristic functional groups were retained in VA: AEROSIL® 300 Pharma and VA: AEROPERL® 300 Pharma colloidal solid system. So, it was inferred that there were no chemical interaction between drug and silica.

Differential Scanning Calorimetry (DSC)

Initial endotherm in case of AEROSIL® 300 Pharma and AEROPERL® 300 Pharma was observed due to presence of moisture and showed amorphous nature of silicas. DSC thermograms obtained in the case of VA: AEROSIL® 300 Pharma and VA: AEROPERL® 300 Pharma was similar to the endotherm obtained for pure Valproic acid suggesting absence of any interaction between Valproic acid and silica materials Figure (4).

SEM

SEM of plain AEROPERL® 300 Pharma showed granular and pearl like cavity. Whereas VA: AEROPERL® 300 Pharma showed that liquid VA was adsorbed on the surface as well as inside the cavity and was found to form free flowing solid system. SEM of VA: AEROSIL® 300 Pharma indicated that adsorption of drug took place from the surface only and flat, irregular structure was observed Figure (5).

Stability study

Figure (6, 7) Optimized batches kept for stability study showed high drug content uniformity around 105% VA. Dissolution profile of stability subjected formulation was found to be similar to profile obtained as initially obtained on first day.

Conclusions

A capsule solid dosage form for liquid Valproic acid was developed in combination with silica materials. Developed solid formulation of Valproic acid neither requires any special conditions like temperature, humidity control nor any chemical reaction and is simple to prepare, process and handle. AEROPERL® 300 Pharma was found to be a better solid carrier over conventional AEROSIL® 300 Pharma as it has pearl like cavity, granular, good flow property and high density which makes technological processing easy.

Author's contributions

Mr. Naveen Khetarpal is the main author who has done the literature survey and designed the whole work, mostly work has been done by him. Mr. Ajay Sav has carried out analytical method development like GC method for drug content and in vitro drug release study and also did the manuscript drafting. Mrs Leena Rao who is lecture in Chemistry subject helped us in different analytical data interpretation and discussion. Mrs Purnima D. Amin who is professor in pharmaceuticals has helped us by supervising our work at each and every process step and made all process smooth by providing her intellectual knowledge and permission to use departmental facility for experiment and also in final drafting of manuscript.

Conflict of Interests: The author declare no conflict of interests



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sample of AEROPERL® 300 Pharma and AEROSIL® 300 Pharma.

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