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FORMULATION AND EVALUATION OF A LIQUID ORAL DOSAGE FORM OF SODIUM VALPROIC ACID FOR ENHANCEMENT OF BIOAVAILABILITY

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Abstract

Sodium valproic acid, a common antiepileptic drug, due to its poor aqueous solubility is absorbed very slowly and erratically after oral administration. So in the work under taken, an attempt was made to enhance its solubility, dissolution rate and thus bioavailability by applying solid dispersion technique followed by formulating it as suspension. Solid dispersions of sodium valproic acid were prepared using hydroxyl propyl methylcellulose, polyvinylpyrrolidone and polyethylene glycol-6000 as carriers and formulated as suspensions. The solid dispersions and suspensions were evaluated for drug content and dissolution rate and particle size. Particle size of suspensions formulated from solid dispersions was significantly reduced compared to conventional suspension. A marked increase in dissolution rate and a good suspend ability was exhibited by sodium valproic acid suspension formulated with solid dispersion than that exhibited by conventional suspension. The SVA: HPMC suspension gave the highest in-vitro drug release profile. Nearly fourfold increase in bioavailability was exhibited by SVA:HPMC suspension when compared with that of conventional suspension. Further suspensions were subjected to stability testing for three months and evaluated for particle size, drug release and sedimentation. Suspensions showed no considerable change with all parameters. Hence it was concluded that solid dispersion system of sodium Valproic acid with a hydrophilic carrier HPMC provided a simple method for preparing a suspension of sodium Valproic acid with increased bioavailability.

Keywords: Bioavailbility, Sodium Valproic acid, HPMC, CMC, PVP, PEG6000.

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INTRODUCTION

One of the most persistent problems faced by drugs with poor aqueous solubility is that their oral delivery is frequently associated with implications of low bioavailability and lack of dose proportionality [1]. Efforts are going on to enhance the oral bioavailability of such lipophilic drugs in order to increase their clinical efficacy. Sodium valproic acid, is an antiepileptic drug suffering from the problem of slow and variable absorption because of its poor aqueous solubility. Considering the usefulness of solid dispersions in enhancing the solubility, the present work was undertaken. The objective was to prepare solid dispersions of sodium valproic acid using polymers like hydroxypropyl methylcellulose, polyvinyl pyrrolidone, polyethylene glycol 6000 and use of these solid dispersions in the formulation of a suspension. Solid dispersion technique is thus used extensively for improving solubility of poorly aqueous soluble drugs [2]. Moreover due to reduction in particle size and the effect of carrier on the wettability and solubility of the drug, much of the drug exist in the form of solution and the remaining part of the drug may exist as amorphous precipitates in the carrier. So due to these, enhancement in the solubility and release characteristics of the drug, may be anticipated. Suspensions also possess certain advantages over other dosage form. Because of their liquid character, suspensions represent an ideal dosage form for patients, who have difficulty in swallowing (dysphagia) tablets or capsules [3]. This factor is of particular importance in administration of drug orally to pediatrics or geriatrics because of physiological changes associated with these groups. In addition, disagreeable taste of drug can be masked by formulating a suspension of drug. Drugs in suspension are chemically more stable than in solution. Thus suspensions are a highly effective dosage form in terms of bioavailability ranking second only to solutions when administered orally [4-8]. Sodium valproic acid causes inhibition of opening up of voltage gated Na^+ channels. This action on Na^+ channels (prolongation of inactivated stage) is the fundamental mechanism of action of sodium valproic acid. It also inhibits high frequently repetitive firing in neurons. It also acts presynaptic ally to decrease synaptic transmission. These effects probably accounts for the antiepileptic action of sodium valproic acid [8-14].

MATERIALS AND METHODS

Materials

Sodium valproic acid powder drug was given by the Micro Labs, Bangalore, polyethylene glycol 6000 and hydroxypropyl methylcellulose was given by the Loba Chemie Pvt. Ltd., Mumbai,

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polyvinyl pyrrolidone was given by Ozone International, Mumbai, methanol, dichloromethane, hydrochloric acid, chloroform, propane-2-ol and n-heptane was given by the Merck Limited, Mumbai, carboxymethylcellulose and methyl paraben was given by the Reliance Cellulose Products Ltd.

Methods

UV Spectroscopy:

The first step in preformulation is to establish a simple analytical method so that all future measurements can be quantitative. Most drugs absorb light in the ultraviolet wavelengths (190-390 nm) region, since they are generally aromatic or contain double bonds.

Standard calibration curve for sodium valproic acid in 0.1N HCl Buffer

Sodium valproic acid 100 mg was dissolved in minimum amount of ethanol and volume was made upto 100ml with 0.1N HCl. From this 10ml was withdrawn and transferred into a 100ml volumetric flask and volume was made up to 100ml with 0.1N HCl, in order to get standard stock solution containing 100µg/ml of drug. From the standard, stock solution, series of dilutions were made to get concentration of 2,4,6,8,10,12 and 14µg/ml using 0.1N HCl and the corresponding absorbance values was measured at 285nm in UV/Visible spectrophotometer. A graph of Concentration *vs.* Absorbance was plotted.

Melting Point determination:

Melting point of pure drug and prepared solid dispersions were determined by using capillary type melting point apparatus.

Differential Scanning Calorimetric (DSC) Studies of Solid Dispersions

Pure drug and the prepared solid dispersion were subjected to the DSC studies using Shimadzu DSC-50 Thermal Analyser in temperature range of 0ºC to 300ºC to methodology check compatibility between drug and carrier.

Optimization of method of preparation and drug: carrier ratio

An attempt was made to prepare solid dispersions of Sodium Valproic Acid with hydrophilic carriers like HPMC, PVP, and PEG 6000 by fusion and solvent evaporation method. Fusion method was first tried out. But when the prepared solid dispersions were subjected for drug content estimation, the drug content was found to be very low compared to theoretical values indicating probability of degradation. So solvent evaporation method was tried for the preparation. The drug content estimation of these solid dispersions was found to be almost equivalent to the theoretical values. So solvent evaporation method was chosen as the method of preparation of solid dispersion. SVA: HPMC solid dispersions were prepared in various ratios like 1:0.25,

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1:0.5, 1:1 and 1:2. Among these 1:2 ratio was found to be highly hygroscopic. So other ratios were selected for further studies SVA:PVP solid dispersions were prepared in various ratios like 1:0.25, 1:0.5, 1:1, and 1:2 .Here also 1:2 ratio was found to be highly hygroscopic. So other three ratios were selected for further studies.

In case of SVA: PEG 6000 solid dispersion the drug dissolution was found to increase with concentration of PEG. 1:1, 1:2, 1:5, 1:6, ratios were prepared. But 1:6 ratios were found to be highly hygroscopic. So other three ratios were chosen for further studies.

Formulation of Suspension

Suspension of sodium valproic acid was prepared employing its solid dispersions. Suspensions containing 100 mg of sodium valproic acid in 5ml were prepared as per formulae given below. A conventional suspension prepared from pure sodium valproic acid was also formulated for comparison studies. Two suspending agents, sodium carboxymethylcellulose (1%) and HPMC (1%) were tried as suspending agents for the suspensions

F1=Conventional SVA suspension with sodium CMC as suspending gent

F2= Conventional SVA suspension with HPMC as suspending agent

F3 =SVA: HPMC suspension with sodium CMC as suspending agent

F4 = SVA: HPMC suspension with HPMC as suspending agent

F5 = SVA: PVP suspension with sodium CMC as suspending agent

F6 = SVA: PVP suspension with with HPMC as suspending agent

F7 = SVA: PEG suspension with sodium CMC as suspending agent

F8 = SVA: PEG suspension with with HPMC as suspending agent

Preparation of Sodium Valproic Acid suspension:

Accurately weighed quantity of sodium valproic acid or its solid dispersions was taken in a mortar and was levitated with small portion of suspending agent. When smooth paste was formed the rest of the suspending agent was added in divided portions, while triturating the contents. Sucrose was then added as a solution in water while mixing. Other ingredients were added one after another, mixed and the suspension was transferred to a measuring jar and adjusted to the volume.

Evaluation of suspension:

Drug content determination:

5ml of the suspension (100mg/5ml) was taken into 100ml volumetric flask after shaking the suspension for uniform distribution. A minimum amount of ethanol was added to this and shaken

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well so as to dissolve the drug and volume was made upto 100ml with 0.1N HCl. The suspension was then filtered and UV absorbance of the filtrate was measured. The concentration of drug in solution was calculated from absorbance and standard graph.

Particle size determination:

This was carried out by using an optical microscope along with a calibrated eyepiece micrometer. The products were evenly spread onto a glass slide and then the slide was carefully covered with a coverslip. Then particles present on the slide were counted carefully and average particle size was determined.

Drug release:

For evaluation of drug release, paddle type dissolution apparatus was used. Drug release evaluation was done for conventional sodium valproic acid suspension and for suspensions formulated using solid dispersions.

Conventional suspension and suspension formulated using solid dispersions equivalent to 100mg of pure drug were used for evaluation of drug release. 5ml of suspension (100mg/5ml) was introduced into the jar.

The medium used was 900ml of 0.1N HCl (pH 1.2). The evaluation was done at 100 rpm and a temperature of 37± 0.5°C. 5 ml aliquots of samples were withdrawn at definite time intervals and filtered. From this 1ml was taken and transferred in 10ml volumetric flask and made upto the mark (DF=10) and assayed at 285nm. Three trials were carried out for each samples and average value was taken.

Sedimentation and Redispersibility

To carry out sedimentation studies, all the products were kept undisturbed in 10 ml graduated cylinders. Then the sedimentation time was observed for total settling. Redispersibility can be defined as the ability to resuspend the settled particles with a minimum amount of shaking, after a suspension has been stored for some time. The sediment formed was shaken moderately to check redispersibility.

Stability studies:

Stability studies were carried out as per ICH guidelines at refrigerator temperature (5ºC), room temperature (27ºC), and accelerated temperature(40ºC) for a period upto 90 days, for SVA:HPMC(1:0.5) suspension. After 90 days they were evaluated for particle size, in-vitro drug release and redispersibility.

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Table1: Formulae of Sodium Valproic Acid suspensions prepared

Formulation Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Sod. Valproic Acid(g)	2.0	2.0	-	-	-	-	-	-
SVA-HPMC (g)	-	3.0	3.0	-	-	-	-	-
SVA-PVP (g)	-	-	-	-	3.0	3.0	-	-
SVA-PEG(g)	-	-	-	-	-	-	12.0	12.0
Sod-CMC (1%) (g)	1.0	-	1.0	-	1.0	-	1.0	-
HPMC (1%)(g)	-	1.0	-	1.0	-	1.0	-	1.0
Glycerin (g)	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Sorbitol (g)	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Sucrose (g)	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Methyl Paraben (g)		0.25	0.25	0.25	0.25	0.25	0.25	0.25
Purified water (ml) to	100.0	100.0	100.0	100.	100.	100.0	100.0	100.0

RESULTS

Calibration curve for Sodium Valproic Acid

The value of absorbances for the calibration Curve of sodium valproic acid in 0.1N HCl are given in the following Table.

Table 2: Calibration data of Sodium Valproic Acid in 0.1N HCl

Concentration (µg/ml)	Absorbance*±S.D
2	0.1120±0.001
4	0.2159±0.005
6	0.3130±0.005
8	0.4144±0.005
10	0.5159±0.005
12	0.623±0.006
14	0.726±0.00

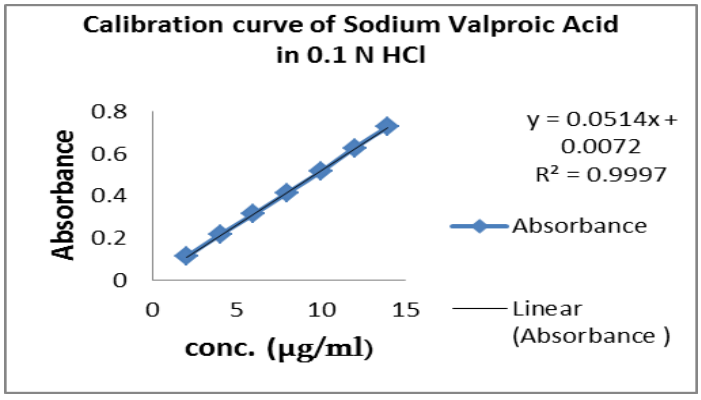

Fig.1: Calibration curve of Sodium ValproicAcid in 0.1N HCl

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Melting point determination:

Melting point of pure sodium valproic acid and solid dispersions were found out. The melting point of solid dispersions was found to lower than that of pure sodium valproic acid. The results obtained are shown in following Table (3).

Table 3: Melting point determination

Drug and solid dispersions	Melting point (°C)
SODIUM VALPROIC ACID(pure drug)	193°C
VA-HPMC solid dispersion 1:0.25 1:0.5 1:1	 190°C 189°C 191°C
SVA-PVP solid dispersion 1:0.25 1:0.5 1:1	 191°C 189°C 191°C
SVA-PEG solid dispersion 1:1 1:2 1:5	 191°C 192°C 190°C

Drug content estimation in solid dispersions:

The solution of solid dispersion of sodium valproic acid was prepared. Its concentration was noted from its measured absorbance at 285nm. The results obtained are shown in following Table.

Table 4: Drug content estimation of Sodium ValproicAcid in solid dispersions

Absorbance* ± SD	Concentration (µg/ml)	% drug content
Sodium Valproic Acid-HPMC		
0.5009 ± 0.008	9.6	96
0.5089 ± 0.011	9.76	97.6
0.4782 ± 0.018	9.17	91.7
SVA-PVP solid dispersion		
0.5108 ± 0.013	9.8	98.00%
0.5120 ± 0.008	9.82	98.20%
0.4721 ± 0.011	9.05	90.50%
SVA-PEG solid dispersion		
0.5001 ± 0.010	9.59	95.90%
0.5038 ± 0.008	9.66	96.60%
0.5111 ± 0.003	9.8	98.00%

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Discussion

The percentage drug content in all the solid dispersions was found to be excellent being more than 90%. This proves that solvent evaporation method adopted for the preparation of solid dispersion is suitable and there is no loss of drug in the process.

Formulation of suspension using solid dispersions

The *in-vitro* drug dissolution studies revealed that SVA:HPMC (1:0.5), SVA:PVP (1:0.5), SVA:PEG (1:5) ratios gave the highest dissolution rates and thus the same were selected for further studies by formulating into suspension.

Two suspending agents, sodium carboxy-methylcellulose (1%) and hydroxylpropyl methylcellulose (1%) were used for comparison.

(a) Drug content estimation:

Drug content estimation was done as per procedures given:

Table 5: Drug content estimation of Sodium Valproic Acid suspensions formulated with sodium CMC (1%) as supending agent

S. No.	Suspension	Absorbance*± S.D	Concentration (c)µg/ml	Drug content
1	SVA:HPMC (1:0.5)	0.5081 ± 0.003	9.74	9.74
2	SVA:PVP (1:0.5)	0.5022 ± 0.018	9.63	96.3
3	SVA:PEG (1:5)	0.5048± 0.011	9.76	97.6

Table 6: Drug content estimation of Sodium Valproic Acid suspensions formulated with HPMC (1%) as suspending agent

S. No.	Suspension	Absorbance* ± S.D	Concentration (c)µg/ml	Drug content
1	SVA:HPMC (1:0.5)	0.5018 ± 0.003	9.62	96.2
2	SVA:PVP (1:0.5)	0.5006 ± 0.008	9.60	96.0
3	SVA:PEG (1:5)	0.4998± 0.011	9.58	95.8

(b) Drug release

Drug release from the suspensions were found out as per the procedure . The results are given in tables (7, 8) below

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Table 7: Drug release for Sodium Valproic acid pure drug and from F1-F4 formulation

Drug Released						
S.No.	**Time (min.)**	**SVA(pure drug)**	**F1**	**F2**	**F3**	**F4**
1.	5	8.68	13.63	13.09	64.6	65.28
2.	10	18.10	20.31	20.14	78.4	78.6
3.	15	19.01	21.18	18.80	79.0	79.8
4.	20	20.12	22.65	22.63	80.2	82.
5.	30	32.17	31.11	30.60	83.1	82.4
6.	40	37.77	39.86	39.46	83.9	82.7
7.	50	41.20	42.25	41.03	94.0	83.9
8.	60	43.34	43.19	41.90	97.4	90.1
9.	70	43.47	45.97	45.61	97.9	95.1
10.	80	44.51	46.44	46.22	98.32	96.5
11.	90	44.86	46.86	46.46	99.70	98.6

Table 8: Drug release for Sodium Valproic acid pure drug and from F5-F8 formulation

% Drug Released						
S.No.	**Time (min.)**	**SVA(pure drug)**	**F5**	**F6**	**F7**	**F8**
1.	5	8.68	56.94	56.35	55.3	62.27
2.	10	18.10	57.31	57.65	67.33	65.7
3.	15	19.01	61.83	60.25	70.8	71.2
4.	20	20.12	66.78	65.80	75.9	73.0
5.	30	32.17	75.17	73.43	80.0	77.5
6.	40	37.77	77.24	79.11	82.0	80.7
7.	50	41.20	84.60	83.33	83.2	81.8
8.	60	43.34	86.47	83.72	84.3	82.9
9.	70	43.47	88.0	87.68	85.5	84.6
10.	80	44.51	90.82	91.11	85.8	86.2
11.	90	44.86	93.20	92.37	86.8	88.5

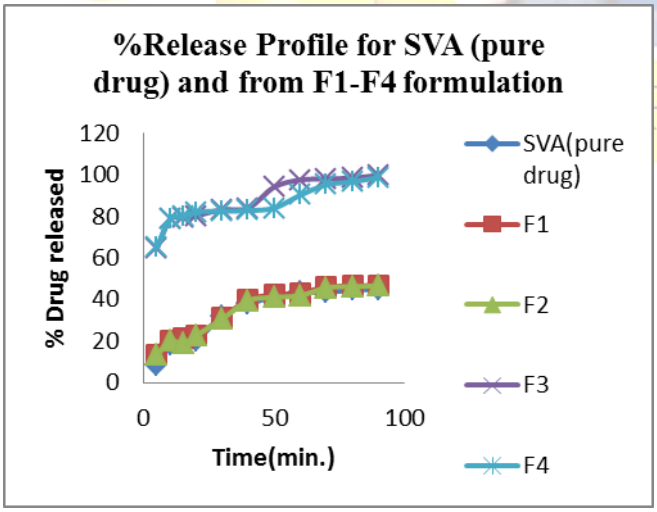

Fig. 2 : %Release Profile of SVA (pure drug) drug) and from F1-F4 formulation

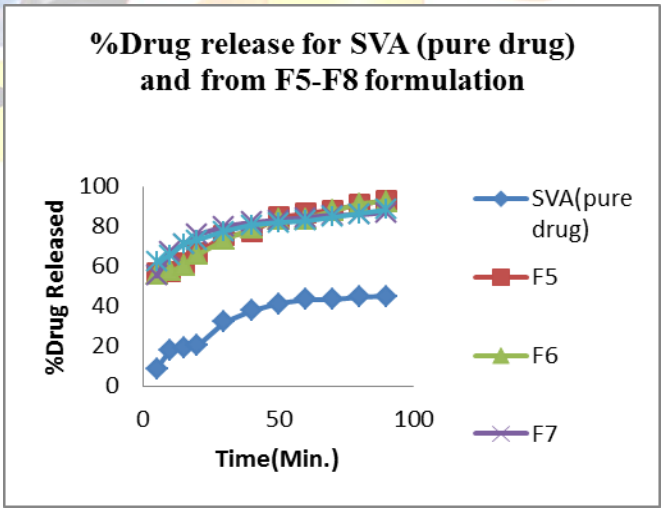

Fig. 3 : %Drug release for SVA (pure and from F5-F8 formulation

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Discussion

Based on the drug release comparison studies, it was revealed that, no significant difference in drug release was observed between suspensions formulated using sodium CMC (1%) and HPMC (1%) as suspending agent. But the suspensions formulated with sodium CMC (1%) as suspending agent showed a slight enhancement in drug release. So sodium CMC (1%) was selected as the suspending agent for the suspensions. Comparison studies also revealed that, of all the suspensions formulated, SVA:HPMC (1:0.5) suspension with sodium CMC (F3) as suspending agent showed the highest drug release.(99.7% in 90 min) So the same was selected for further *in vivo* bioavailability studies.

(c) Sedimentation and Redispersibility

Sodium valproic acid conventional suspension showed complete sedimentation within 24h. All the suspensions formulated using solid dispersions showed complete sedimentation after 48h only. Sedimentation after 48h only. Sedimentation volume measurement could not be carried out because there was no clear boundary formed by the sediment. Hence only Redispersibility was assessed. All the products have shown easy Redispersibility on moderate shaking.

(d) Stability studies

Stability studies was conducted for SVA:HPMC suspension according to procedure described in methodology. There was no significant change in *in-vitro* drug release and redispersibility even after storage at 5ºC, 27ºC, and 40ºC as per ICH Guidelines. The details of various evaluation studies done are given below.

(e) Drug Release

Drug release from suspensions stored at 5°C, 27°C, and 40°C, were done as per the procedure mentioned. The results are shown in tables below:

Table 9: % Drug release after storage at 5 ºC, 27 ºC and 40 ºC.

S.No.	Time (min.)	F3 formulation	5ºC	27ºC	40ºC
1.	5	64.6	63.8	63.9	63.5
2.	10	78.4	77.3	77.2	77.5
3.	15	79.0	79.3	79.1	79.3
4.	20	80.2	81.3	81.45	81.1
5.	30	83.1	82.5	82.4	82.2
6.	40	83.9	83.1	83.4	83.1
7.	50	94.0	84.6	84.6	84.8
8.	60	97.4	89.5	90.0	89.7
9.	70	97.9	93.45	93.4	93.0
10.	80	98.32	98.18	98.0	98.0
11.	90	99.70	98.53	98.1	98.2

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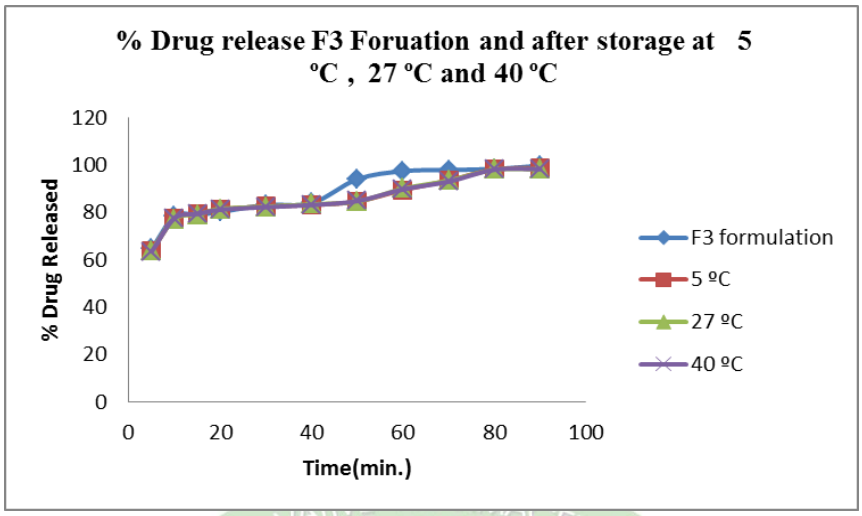

Fig.4: Stability studies after storage at 5ºC, 27ºC and 40ºC

(f) Sedimentation and Redispersibility

Sodium valproic acid conventional suspension showed complete sedimentation within 24h. All the suspensions formulated using solid dispersions showed complete sedimentation after 48h only. Sedimentation volume measurement could not be carried out because there was no clear boundary formed by the sediment. Hence only redispersibility was assessed. All the products have shown easy redispersibility on moderate shaking after storage at 5°C and 40ºC.

SUMMARY AND CONCLUSION

Sodium valproic acid was the drug of choice which is a poorly water soluble drug. As a result it is having a poor dissolution profile and hence poor bioavailability. By increasing its water solubility by solid dispersion approach, the rate of its absorption and hence the bioavailability was expected to be enhanced remarkably. Solid dispersions of sodium valproic acid were prepared with various hydrophilic carriers like polyethylene glycol 6000, hydroxypropyl methylcellulose and polyvinylpyrrolidone in different ratios using solvent evaporation method. This prepared solid dispersion was characterized for drug content, dissolution profile, IR spectral studies and DSC studies. Drug content was found to be in accordance with theoretical values which indicate the uniform drug distribution and the reproducibility of the method. In-vitro dissolution studies in 0.IN HCl for sodium valproic acid and its solid dispersion systems showed the enhancement in the dissolution characteristics. The best ratios of drug: carrier was chosen as per in-vitro dissolution profile, SVA:HPMC(1:0.5), SVA:PVP(1:0.5), SVA: PEG (1:5) exhibited highest dissolution rate compared to other ratios. These solid dispersions were formulated as suspensions using sodium carboxymethylcellulose and HPMC as suspending agent. Based on

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comparison of *in-vitro* dissolution studies, sodium carboxymethylcellulose was selected as the suspending agent. The dissolution rate was found to be in the following order-

SVA: HPMC (1:0.5) > SVA: PVP (1:0.5) > SVA: PEG (1:5).

So, SVA: HPMC (1:0.5) solid dispersion was selected as best suspension and *in-vivo* bioavailability studies in rabbits were done for the same. *In-vivo* bioavailability studies in rabbits revealed that bioavailability of sodium valproic acid have been improved significantly when formulated as solid dispersion system. The relative bioavailability of SVA HPMC suspension to the conventional sodium valproic acid suspension was found to increase nearly by four folds. t_{max} of SVA HPMC suspension to the conventional sodium valproic acid suspension was found to decrease by two times. The enhancement in bioavailability sodium valproic acid in the presence of HPMC as carrier can be related to the increase in solubility and dissolution rate of the drug. Due to reduced particle size and the amorphous nature of the drug. Stability studies were carried out at three different temperatures(5°C, 27°C, 40°C) and suspension were evaluated for particle size, sedimentation, redispersibility drug release All suspensions showed no considerable changes with respect to all parameters. Hence it was concluded that a solid dispersion system of sodium valproic acid with a hydrophilic carrier HPMC provided a simple method for preparing a suspension of sodium valproic acid with increased bioavailability. The study illustrated the potential use of a solid dispersion system for the delivery of hydrophobic drug, sodium valproic acid by formulating as a suspension.

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