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FORMULATION AND EVALUATION OF ENTERIC COATED TABLETS OF SODIUM VALPROATE

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ABSTRACT

In the present research paper, anticonvulsant Sodium valproate tablets were prepared using two different disintegrating agents in different ratio. Acrycoat-L-100 polymer was used as an enteric coating material. The tablets were formulated using direct compression method. Further post formulation parameters like hardness, friability, weight variations and content uniformity were studied. The results suggested, that the prepared enteric coated tablets specifics all the criteria of the standard formulation as per specified in monographs.

Keywords: Sodium valproate, anticonvulsant, polymer, enteric coated

INTRODUCTION

Sodium valproate, chemically sodium-2-propyl pentanoate, is first line drug used for its unique anticonvulsant properties[1]. It is quite dissimilar to other established anticonvulsants such as barbiturates, hydantoins, succinamides, oxazolidin- ediones and acetylureas in that it has no nitrogen or aromatic moiety. Sodium valproate works by stabilizing electrical activity in the brain[2]. When abnormally rapid and repetitive electrical signals are released in the brain, the brain becomes over-stimulated and normal function is disturbed. This results in fits or seizures. Sodium valproate prevents epileptic fits by preventing the excessive electrical activity in the brain. This is achieved by increasing the activity of a neurotransmitter called GABA in the brain[3]. Sodium valproate is thought to increase the production and prevent the breakdown of GABA in the brain. This increases the calming activity of GABA in the brain, which stabilizes

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the electrical nerve activity and helps prevent fits. Sodium valproate may also stabilize the electrical nerve activity by preventing sodium from entering the nerve cells when they begin to fire rapid and repetitive electrical signals. A build up of sodium in the nerve cells is necessary for an electrical signal to build up and be passed on, so sodium valproate may also prevent fits in this way. In addition to its licensed use for treating epilepsy, sodium valproate is used off-license by specialists as a mood stabilizer for treating people with the psychiatric illness, bipolar affective disorder.

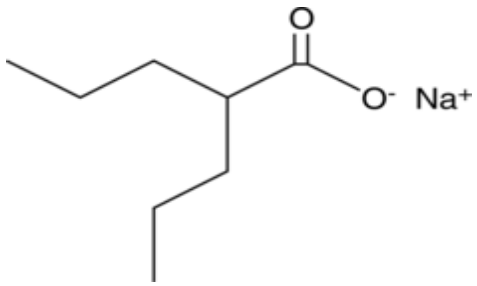

Figure 1: Chemical Structure of Sodium valproate

As far as the literature goes the number of evidence can be spotted for the formulation, development and evaluation of the enteric coated drug formulations [4-8]. Kamble *et al.*[9] formulated and developed the enteric coated dosage form using Ketorolac Tromethamine. They try to overcome the side effect of the drug by using the coat of polymers like Guar gum, Xanthan Gum, Ethyl cellulose and Sodium alginate. Kannan *et al.*[10] prepared Aspirin delayed release tablet and evaluated the parameters like half life, disintegration etc. using micro crystalline cellulose, maize starch, cross carmilose sodium. Jayanthi *et al.*[11] studied the use of extended-release products having potential advantages in patient convenience, compliance and therapeutic outcomes. Henry Zhao *et al.*[12] developed a robust two-step dissolution test for enteric-coated immediate- and extended-release solid oral dosage formulations with fast HPLC analysis. Kumar *et al.*[13] formulated enteric coated Esomeprazole magnesium trihydrate tablets using direct compression and enteric coated with Acryl EZE. The parameters like compressibility, hardness and flow behavior were also studied. The compression parameters after enteric coating were found to be uniform and consistent. The hardness (Kg/cm2) was found in the range of 4.133±0.321 to 4.833±0.153. The enteric coated tablets were not disintegrated in simulated gastric fluid. Undralla *et al.*[14] formulated and carried out *in vitro* evaluation of enteric coated tablets of Didanosine, using different polymers as release retarding agent. Preformulation study was also done initially and results directed for the further course of formulation.

MATERIAL AND METHODS

Materials

Sodium Valproate was a gift sample provided by Shausan Chemicals and Drugs Limited Chennai. Croscarmellose sodium and Sodium Starch glycolate (Signet labortaries, Mumbai) were used as received. All other chemicals used were of analytical grade and were used as received.

Methods

Preparation of Enteric coated tablets of Sodium Valproate was done by direct compression method using different drug: disintegrant ratio. Croscarmellose sodium and Sodium Starch glycolate were used as disintegrant material. Formulations F_1 and F_2 were prepared by using 1: 0.05 and 1: 0.10 Croscarmellose sodium whereas, the L_1 and L_2 formulations were prepared using 1: 0.075 and 1: 0.12 drug: disintegrant ratio. Acrycoat-L-100 polymer (Qualigenes Fine Chemicals, Mumbai) was used to coat the prepared tablet in order to make the tablet enteric coated. Table 1 represents the formulation of enteric coated tablets.

Table 1: Formulation of enteric coated tablets

S. No.	Active drug with excipients	Quantity of materials for one tablet & Ratio of drug with disintegrator			
		F1 (1:0.05)	**F2 (1:0.10)**	**L1 (1:0.075)**	**L2 (1:0.12)**
1.	Sodium valproate	500 mg	500 mg	500 mg	500 mg
2.	Croscarmellose sodium	25 mg	50 mg	----------	----------
3.	Sodium starch glycolate	----------	----------	37.5 mg	60 mg
4.	Micro crystalline cellulose	195 mg	170 mg	182.5 mg	160 mg
5.	Dibasic calcium phosphate	73.32 mg	73.32 mg	73.32 mg	73.32 mg
6.	P.V.P.K-30	20 mg	20 mg	20 mg	20 mg
7.	Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S
8.	Magnesium stearate	33.6 mg	33.6 mg	33.6 mg	33.6 mg
9.	Sodium starch glycolate	23.2 mg	23.2 mg	23.2 mg	23.2 mg
10.	Silicon dioxide (colloidal)	13.6 mg	13.6 mg	13.6 mg	13.6 mg
11.	Talc	33.6 mg	33.6 mg	33.6 mg	33.6 mg

Evaluation of Enteric Coated Tablets

The prepared enteric coated tablets were evaluated for the following parameters:

Hardness: Hardness of the enteric coated tablets was measured using Monsanto tablet hardness tester.

Weight Uniformity: Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percent deviation was calculated using the following formula:

$$\text{Percentage deviation} = \frac{\text{Individual wt - Average wt}}{\text{Average wt}} \times 100$$

Friability test: Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friabilator. It was rotated at a rate of 25rpm. After 100 rotations (4 min.) the tablets were taken out from the friabilator and intact tablets were again weighed collectively. The percent friability was determined using the following formula:

$$\text{Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where, W_1= Weight of the tablets before test

W_2= Weight of the tablets after test

Content uniformity:

The content uniformity of the prepared sample was determined using chromatographic technique.

Specific condition for assay: The chromatographic column used was C_{18} (octadisail). The flow rate of the mobile phase was maintained at 1 ml/min and the column temperature 45°C. Detection was carried out at 220 nm and the injection volume was 50 µm. Run time was 10 min.

Mobile phase preparation and Standard preparation: The buffer is a 0.025 KH_2PO_4. Buffer and acetonitrile was mixed in the ratio of (55:45) pH was adjusted to 3 and the mobile phase was filtered through 0.45 µm membrane filter and sonicated prior to use. The mobile phase was used as diluent. About 100 mg of sodium valproate working standard was weighed accurately in 100 ml volumetric flask and mobile phase was added, sonicated to dissolve and diluted to the mark to obtain a concentration of 1 mg/ml.

Assay of Sodium valproate in tablet dosage form: Twenty tablets were weighed and convert it into powder form, then take equivalent of 100mg tablet powder with 100ml of mobile phase. The solutions were injected at above chromatographic conditions and peak areas were measured to determine the Sodium valproate content.

***In-vitro* Drug release studies**

Dissolution studies were performed using USP standard dissolution apparatus at 37 ± 0.5ºC.Using one tablet at a time in a vessel. The basket was immersed in 900ml of dissolution

medium and rotated at 50 rpm. The dissolution Media used was initially 0.1N Hcl up to 2hrs, then continuation with fasted buffer having pH6.8. During the test 10ml of the sample was withdrawn at specific time intervals of one hour and same volume of fresh dissolution medium was added to maintained sink conditions. Different aliquots were suitably diluted.

RESULTS AND DISSCUSION

Evaluation of Sodium valproate

All the formulated batches of Sodium valproate tablets were evaluated according to the specification and following results were obtained. The formulation variables and various physico-chemical properties of prepared enteric coated tablets are shown in Tables 2& 3.

Hardness: Hardness of the enteric coated tablets was measured using Monsanto tablet hardness tester.t was shown in Table 2.

Table 2: Hardness of enteric coated Sodium valproate tablet

S. No.	Formulation	Hardness (kg/cm^2)			
		F1	F2	L1	L2
1.	E.C sodium valproate	4.85	4.75	4.17	4.57
2.	E.C sodium valproate	4.57	4.92	4.28	4.92
3.	E.C sodium valproate	5.00	4.17	4.00	4.44
4.	E.C sodium valproate	4.28	5.00	4.75	5.00
5.	E.C sodium valproate	4.17	4.28	4.57	4.28
6.	E.C sodium valproate	4.00	4.28	5.00	4.57
7.	E.C sodium valproate	4.85	4.00	4.44	4.17
8.	E.C sodium valproate	5.00	4.17	4.92	4.28
9.	E.C sodium valproate	4.00	4.28	4.28	4.92
10.	E.C sodium valproate	4.28	4.75	4.85	4.17

Friability test: The percent friability was determined using the formula. Result was shown in Table 3.

Table 3: Friability of enteric coated Sodium valproate tablet

S. No.	Formulation	Friability (%)			
		F1	F2	L1	L2
1.	E.C sodium valproate	0.02	0.02	0.01	0.02
2.	E.C sodium valproate	0.01	0.01	0.01	0.01
3.	E.C sodium valproate	0.01	0.02	0.02	0.01
4.	E.C sodium valproate	0.02	0.01	0.02	0.02
5.	E.C sodium valproate	0.02	0.02	0.01	0.02
6.	E.C sodium valproate	0.01	0.01	0.02	0.01
7.	E.C sodium valproate	0.01	0.01	0.02	0.02
8.	E.C sodium valproate	0.02	0.01	0.01	0.01
9.	E.C sodium valproate	0.01	0.02	0.01	0.02
10.	E.C sodium valproate	0.02	0.02	0.01	0.02

Weight variation: Result of weight variation shown in Table 4.

Table 4: Weight variation of enteric coated Sodium valproate tablet

S.N	Formulation	Weight variation (mg± %)			
		F1	F2	L1	L2
1.	E.C sodium valproate	985.76	987.12	988.06	988.06
2.	E.C sodium valproate	986.65	993.54	983.34	987.12
3.	E.C sodium valproate	987.12	985.76	991.01	985.76
4.	E.C sodium valproate	993.54	988.06	990.23	983.34
5.	E.C sodium valproate	990.23	990.54	985.76	993.54
6.	E.C sodium valproate	988.06	987.76	987.76	991.01
7.	E.C sodium valproate	987.76	986.65	987.12	990.23
8.	E.C sodium valproate	983.34	990.23	993.54	990.54
9.	E.C sodium valproate	991.01	991.01	986.65	987.76
10.	E.C sodium valproate	990.54	983.34	990.54	986.65

Content uniformity by HPLC Method:

The graphs obtained from HPLC shows (Figure 2) a very little difference in AU value which clearly indicates the content uniformity in sodium valproate enteric coated sample prepared in comparison to standard sodium valproate tablets.

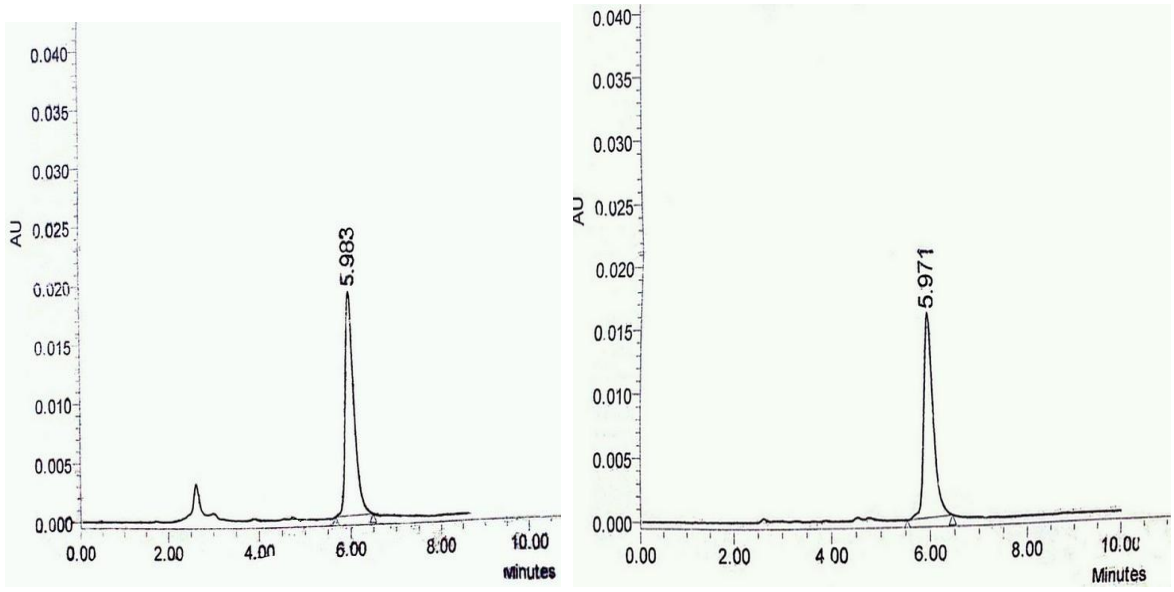

Figure 2: Graphical representation of (a) Sodium Valproate Standard (b) Sodium Valproate

In vitro drug release

In vitro drug release of formulation F1 to F4 initial 2 hours drug was no release of drug. Acrycoat-L-100 polymer prevents the release of drug for the first 2hrs.Result was shown in Table 5 and Figure 3.

Table 5: Cumulative % drug Release profile

Time (hr)	Cumulative % drug Release			
	F1	F2	L1	L2
1	0	0	0	0
2	0	0	0	0
3	18.29	18.00	13.00	11.06
4	20.18	24.12	17.10	23.13
5	27.10	35.24	22.34	36.88
6	40.19	41.14	27.99	40.30
7	47.11	53.22	35.44	50.66
8	59.53	64.90	41.67	54.36
9	71.80	73.44	47.00	59.99
10	82.29	77.80	54.22	67.11
11	86.30	81.42	61.16	72.73
12	89.04	86.33	62.38	75.44

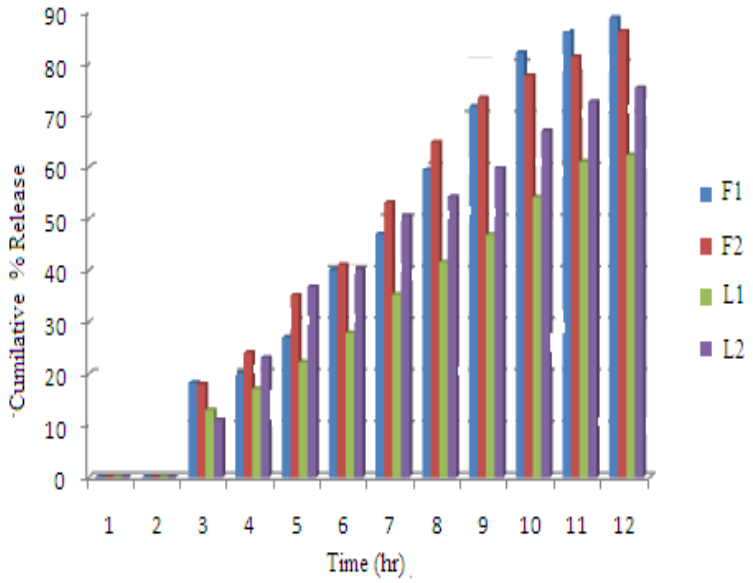

Figure 3: Graphical representation of Cumulative % drug Release Sodium Valproate

CONCLUSION

From the ongoing studies, it was concluded that, sodium valproate enteric coated tablets prepared by direct compression techniques, showed promising results. Acrycoat-L-100 polymer prevents the release of drug for the first 2hrs. The enteric coated tablets are cost effective and exhibit predictable release behavior. Moreover, the hardness, friability and weight variation parameters studies further strengthen the effectiveness of prepared enteric coated formulation.

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