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Formulation and Characterization of Sodium Valproate 200mg Enteric Coated Tablets

Elham Mohammed Elameen Widaa [1], Eltayeb Suliman Elamin[1], Abutalib Alamin Abdallah[2], Alaa E. Elawni[2]*

[1] *Department of Pharmaceutics, Faculty of Pharmacy, Omdurman Islamic University, Khartoum, Sudan.*
[2] *Department of Research and Development, Azal Pharmaceutical Industries Co. Ltd., Khartoum, Sudan.*

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ABSTRACT

PURPOSE: Enteric-coated oral tablets have a coating that protects the tablet from stomach acid and protects the lining of the gastrointestinal tract from irritation by the drug. The aim of this study was to formulate and optimizesodium valproate enteric coated tabletsto reduce the gastrointestinal tract side effects.**METHODS:** Core tablets were prepared by wet granulation. The formulation optimization was done by applying Taguchi orthogonal design L9. Nine formulations were prepared by variation in three levels of four factors, namely, diluents type (microcrystalline cellulose, dibasic calciumphosphate, maize starch), punch shape (diamond, round, almond), coatingtype (Instacoat, Wincoat, Colorcon) and coat percentage (20%, 24%, 28%).**RESULTS:**The results showed that almost all factors had a significant effect on the weight variation except punch shape. Also, type of diluent and punch shape had significant effects on the hardness and the punch shape may affect the thickness. Coat type had a significant effect on the disintegration time while it`s percentage had a significant effect on the assay. All factors had no significant effect on in vitro drug release but it might slightly be affected by the type of diluents and coat.**CONCLUSIONS:**It can be concluded that the best formula could be formulated byInstacoatas a type of coat, 24% percentage of coat, dibasic calciumphosphate as a diluent and round tablet shape. The present study showed the possibility of formulating sodium valproate in good enteric coated tablets to reduce its side effects and to increase patients' compliance.

Keywords: Sodium valproate, enteric coat, experimental design, percent of coat, dye shape

I. INTRODUCTION

1.1. Tablet Coatings

Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits that broadly ranges from facilitating product identification to modifying drug release from the dosage form(1).Tablet coatings perform one or more of the following functions;they may mask the taste of unpalatable drugs, protect the drug from deterioration due to light, oxygen or moisture, separate incompatible ingredients, they control the release of medicament in the gastrointestinal tract and they provide an elegant or distinctive finish to the tablet (2). Coating a solid dosage form in a polymeric film may generate a product that exhibits a controlled release of active components, protection from external conditions and provides physical and chemical protection to the specified component (3). The materials used for coating may largely comprise sucrose as sugar coating, water-soluble film-forming polymers as film coatingor substances which are soluble in the intestinal secretions but not in those of the stomach as enteric coating (2).Functional coating of tablets include coating to modified drug release from the delivery systems such as delayed release (Enteric coated drug delivery system), sustained release (extended release), Controlled release (Site specific and Receptor targeting) (4).

1.2. Enteric Coating

Enteric-coated oral tablets have a coating that protects the tablet from stomach acid and protects the lining of the gastrointestinal tract from irritation by the drug. Enteric-coating is also a technique used in making sustained-release tablets (5). Delayed release dosage forms are the best formulations which are used for drugs that are destroyed in the gastric fluids, or cause gastric irritation, or are absorbed preferentially in the intestine. Such preparations contain an alkaline core material comprising the active substance, a separating layer and enteric coating layer. Enteric coatings are usually formulated with synthetic

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polymers that contain ionizable functional groups that render the polymer water soluble at a higher pH value (6).

Enteric coating, gastro-resistant coatings, of a tablet or capsule is a technique commonly employed to protect a solid oral dosage form from the acidic environment of the human stomach. However, the coating will break down rapidly in a neutral environment or slightly acidic, pH 5.5 or greater. Enteric-coated tablets and capsules are considered delayed-release formulations because drug release is retarded until the drug product is exposed to the neutral environment of the upper intestinal tract (7).

Enteric coating primarily used for protection of acid-labile drugs from gastric fluid (e.g. enzymes and certain antibiotics), prevention of gastric distress or nausea due to irritation from a drug (e.g. sodium salicylate), deliver drugs intended for local action in the intestines (e.g. intestinal antiseptics could be delivered to their site of action in a concentrated form and bypass systemic absorption in the stomach), deliver drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form, provide a delayed-release component for repeat action tablets (8).

1.3. Materials Used for Enteric Coating

Enteric materials currently in use are normally synthetic or semi-synthetic pH sensitive polymers containing ionizable carboxylic acid groups. These remain un-ionized in the low pH environment of the stomach but become ionized at the higher pH of the small intestine, allowing the coating to dissolve and the drug to be released. However, the in vivo performance of enteric coated products results from the complex interplay between the formulation and gastrointestinal physiology variables such as transit time, gastrointestinal pH, feeding status and gender. The rapid dissolution of enteric-coated products in the commonly used in vitro medium, compendial pH 6.8 phosphate buffer, has led to a common misconception that these products, in vivo, disintegrate rapidly in the small intestine, after gastric emptying. However, in vivo studies using gamma scintigraphy have shown that there can be a delay of up to 2 h for the disintegration of such products in the human small intestine following gastric emptying, with different enteric polymer coatings exhibiting a range of disintegration times (9). The choice of the polymer and the thickness of the coated layer are critical to control the pH solubility profile of the enteric coated dosage form (8).

The ideal properties of polymers used for enteric coating of tablets include resistance to gastric fluids, susceptible/permeable to intestinal fluid, compatible with most coating solution components and the drug substrate, Formation of continuous film, Nontoxic, cheap and ease of application and have ability to be readily printed(10).

1.4. Enteric Coating Methods

Enteric coated tablets can be prepared by spray coating technique in which core tablets are prepared as follow; granules were prepared using wet granulation method, lubricated and compressed in to tablets using shallow concave plain/plain punch. Enteric coating solution is prepared by weighing the required amount of a polymer such as pectin, dissolving in water while a hydrophobic polymer such as ethyl cellulose is dissolving in isopropyl alcohol. The two solutions are then mixed well to form a homogeneous solution and finally a suitable plasticizer is added. Enteric coating of the core tablets is achieved by standard coating pan technique. Tablets are coated in a pan coater at specific rpm, temperature and flow rate. Coating solution is applied by spraying method using spray gun at appropriate pressure and the coated tablets are primarily dried using heat blower and secondarily dried in tray drier (11).

From extensive practice of coating there are some important considerations should be aware for proper coating; (a) there should always be a negative air pressure maintained in the pan i.e. more air out than in, (b) after start-up before making changes in fluid and/or air flows, always allow a minimum of 15 minutes for exhaust temperature to equilibrate, (c) to achieve highest enteric quality and adhesion between the core and enteric interface, the spray rate of coating solution should be reduced by 15%, for the first 1% weight gain, if any tackiness or sticking is noticed, (d) once coating solution delivery has begun, keep a constant flow rat and finally (e)keep gun needles in an open position during the coating process(10).

1.5. Sodium Valproate (SV)

Sodium Valproate (SV), chemically sodium-2-propyl pentanoate, is the first line drug used for its unique anticonvulsant properties in the treatment of primary generalized seizures, partial seizures and myoclonic seizures (12). 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. SV works by stabilizing electrical activity in the brain (13).

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SV is having many side effects which are related with the upper gastrointestinal tract, means stomach and duodenum mainly. These side effects are mainly due to the conversion of SV into free valproic acid. This free valproic acid causes the side effect in the stomach and duodenum. Due to this free acid the patient suffers from gastric irritation, peptic ulcer, nausea, loose stool, diarrhea, abdominal pain, headache, vomiting, unexplained rashes, pilling of skin, abnormal Swelling like side effects. The purpose of formulation of the enteric coated tablets of SV is to delay the release of drug and to allow release in lower part of gastrointestinal tract. So, by releasing the drug in lower gastrointestinal tract (ileum and large intestine) we can safely administer SV without side effects and without altering its absorption (1).

Currently, no studies were found reporting formulation of SV enteric coated tablets by Experimental Design comparing and evaluating different coating materials, coating concentrations, diluents and punch shapes. Therefore, the present study was aimed to formulate and optimize sodium valproate enteric coated tablets using Taguchi L9 Design, then studying and evaluating the effects of the formulation and process variablesby using quality control tests as responses.

II. MATERIAL AND METHODS

2.1. Materials

Sodium Valproate (SV) was purchased from Sun Pharma(India), Sodium starch glycolate was purchased from JRS Pharma (Germany), Colloidal Silicon Dioxide was purchased from Evonik (India), Microcrystalline cellulose was purchased from FMC Biopolymer (Ireland), Dibasic Calcium Phosphate anhydrous was purchased from DI-CAL Pharma Private Limited (India), Maize starch was purchased from Roquette (Egypt), Povidone-K30 was purchased from BASF SE (Germany), Magnesium Stearate was purchased from Merck KGaA (Germany), Purified Talc was purchased from IMERYS (Italy),Colorcon Acryl-Eze orange was purchased from Colorcon (UK), Instacoat EN Super-II was purchased from Ideal Cures PVT. LTD (India), Wincoat WT-NAQ-01127 Yellow was purchased from Wincoat Colours and Coatings PVT.LTD (India), Potassium di-hydrogen phosphate (Monobasic) was purchased from Duksan (Korea), Acetonitrile (HPLC grade) was purchased from Chem. Lab(Belgium), Potassium hydroxide, Sodium hydroxide,Hydrochloric acid and Phosphoric acid were purchased from Scharlau (Spain).

2.2. Experimental design used for formulation optimization

Table 1: Factors-levels in orthogonal-design experiments of L9

Factors	Type of diluents	Punch shape	Type of coat	% of coating material
Level 1	MCC	Diamond11.3×8.1mm	Instacoat	28%
Level2	DB	Round biconcave 9.7mm	Wincoat	20%
Level3	MS	Almond 12.2mm	Colorcon	24%

MCC: microcrystalline cellulose, DB: dibasic calciumphosphate, MS: maize starch

Table 2: Formulations runs according to Taguchi design

Run	F1	F2	F3	F4
1	DB	Almond	Colorcon	28%
2	MCC	Round biconcave	Colorcon	24%
3	DB	Diamond	Wincoat	24%
4	MCC	Almond	Wincoat	20%
5	MS	Diamond	Colorcon	20%
6	MS	Almond	Instacoat	24%
7	MCC	Diamond	Instacoat	28%
8	DB	Round biconcave	Instacoat	20%
9	MS	Round biconcave	Wincoat	28%

Table 1 shows the four processing and formulation variables selected in the optimization study. A standard orthogonal array L9 was used to examine this four-factor system. L and subscript 9 denote the Latin square and the number of the experimental runs, respectively. The run involved the corresponding combination of levels to which the factors in the experiment were set. The four

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factors had three levels and all experiments were performed in triplicate. The quality control tests of conventional tablets were considered to be the responses (Table 2).

2.3. Pre-formulation Studies

Pre-formulation experiments were done to select the suitable experimental design with suitable variables and levels. Therefore, five experiments were carried out.

The formula of pre-formulation contains sodium valproate SV, microcrystalline cellulose MCC, maize starch MS, dibasic calcium phosphate DB, povidone, sodium starch glycolate, talc, aerosil and magnesium stearate. Direct compression, dry and wet granulations (ethanol, Distilled water) were done.

Flow properties of granules prepared from different formulations were characterized byAngle of repose; the angle of repose of granules was determined by the funnel method. The diameter of the powder cone was measured and angle of repose was calculated using the following equation: ($\tan\theta = h/r$);where, h and r are the height and radius of the powder cone, respectively.Also, the bulk density, tapped density, compressibility index and Hausner's ratiowere measured.

1.6. Preparation of SV Enteric Coated Tablets

The required amount of SV was put in an oven for 5min at 55-60ºC and then accurately weighed and sifted through sieve size 2.0 mm and added to the specified amounts of required diluents, povidone and sodium starch glycolate. Obtained powder was wet granulated with ethanol for 5 min, finally passed through sieve size 2.0 mm and the granules were allowed to dry at 55-60ºC in an oven till 1.0 - 2.0 % LOD. Specified amount of magnesium stearate, aerosil and talc were added to the resulted granules and passed through sieve size 1.0 mm. The blend was compressed into tablets with different shapes.

1.7. Enteric Coating of Prepared SV Tablets

One litre of purified water was put in beaker, 100gm of each coating polymers was added and the dispersion was stirred for 45min, sieved by sieve size 125 µm and maintained without air bubbles, then the dispersion was used for coating in multi-functional experimental pharmaceutical machine, core tablets were put in a conventional coating pan with one spray gun and coated with varied amount of enteric coating polymer and evaluated for tablet coating property. The coating process took half an hour and the coated tablets obtained were characterized (14).

1.8. In Vitro Characterization of Prepared SV Enteric Coated Tablets

1.8.1. Appearance, Weight Variation and Thickness

The general appearance and elegance of tablet was identified visually, which included tablet size, shape, color, presence or absence of an odour and surface texture etc.

Twenty tablets were selected at random and average weight was determined using an electronic balance. Dimensions of the tablets and thickness were measured.

1.8.2. Hardness and Friability Test

Twenty tablets were selected randomly from individual formulations and their hardness was measured by using the hardness tester. Twenty tablets were weighed and placed in the friability tester which operated at 25 rpm for 4 minutes. The tablets were then dedusted and weighed. The percentage loss in tablet weight was determined by the following formula:

$$\text{Friability} = \frac{Iw - Fw}{Iw} \times 100\ \%$$

Where,Iw = Total Initial weight of tablets;Fw = Total final weight of tablets.

1.8.3. Disintegration Test

The disintegration time was measured by using USP disintegration tester. Six tablets were placed in tubes and the basket was kept positioned in a disintegration medium of 0.1N HCl for 2 hrs followed by phosphate buffer (pH 6.8) maintained at 37± 20ºC and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29-32 cycles per minute, through a distance of 55 ±2 mm.

1.8.4. Assay of SV in the Prepared Enteric Coated Tablets

Chromatographic system:

The analysis was carried out using high performance liquid chromatography (HPLC) system. The analytical column was Kromasil ® C18 (4 × 150 mm), 5.0 mm particle size. Mobile phase acetonitrile: phosphate buffer solution (45:55) was used, Detection was carried out at 220 nm, the flow rate was 1.0 ml/minute and the column temperature 45°C. 50µL of the sample was injected into the HPLC. Run time was 10 min and the data processing was done using the LC-Solutions on Pentium computer (13).

Preparation of solutions and samples:

Mobile phase was prepared by adding phosphate buffer 0.025M KH_2PO_4 to acetonitrile in ratio of (55:45), then was adjusted to pH 3. The mobile phase was filtered through 0.45 µm membrane filter and sonicated prior to use. The

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mobile phase was used as diluents when required.About 100 mg of SV working standard was weighed accurately in 100 ml volumetric flask and diluent was added gradually with sonication for 1 min to obtain a concentration of 1 mg/ml.

Twenty tablets were weighed and crushed into powder, then an equivalent of 100 mg SV from the powder was dissolved into 70ml of diluents, sonication for 1 min then completed the volume to obtain a concentration of 1 mg/ml and finally injected into HPLC system.

1.8.5. In-Vitro Drug Release Studies

The Calibration curve for working standard of SV was drawn by preparing different concentrations (0.4, 0.6, 0.8, 1.0, 1.2, 1.4 and 1.6) from the stock solution having a concentration of 5mg/ml.

The release of SV from the prepared enteric coated tablets was studied in two dissolution medium, 0.1N HCl and phosphate buffer at pH 6.8. For preparation of SV standard solution, about 10 mg of SV working standard was weighed accurately in 100 ml volumetric flask, added 70 ml of buffer dissolution medium then sonicated for 1 min and the volume was completed. 2ml of the obtained SV solution was taken in another 100 ml volumetric flask and diluted by buffer dissolution medium to obtain a concentration of 0.002 mg/ml.

Release studies were performed using USP standard dissolution apparatus 1 at 37 ± 0.5ºC. Six tablets were taken by the basket, immersed in 900ml of dissolution medium and rotated at 50 rpm. The dissolution medium used was initially 0.1N HCl up to 2hrs, then replaced by phosphate buffer pH6.8 for 1 hour.

1.9. Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

III. RESULTS AND DISCUSSIONS

3.1. Pre-formulation Studies

3.1.1.Preparation by Direct Compression

The formulations showed a poor compression with bad flow and sticking problems when using DB, MCC or MS as diluents. But when use MCC in addition of aerosil the resulted formula was compressed with bad flow properties.

3.1.2.Preparationby Granulation

The formula containing DB as diluent could not be compressed by dry granulation. When the granulation was done by distilled water (DW) and MCC as diluent, the formula was not compressed even in addition of aerosil. But, when the ethanol was used instead of DW with different diluents (DB and MCC), the formula containing DB as diluent was compressed with good hardness while that containing MCC gave tablets without any hardness with binding force near to be zero,whichwas solved by addition of aerosil.

Table 3: Composition of enteric coated formulations of Sodium Valproate prepared by wet granulation

Ingredients	WT/tab (in mg)
Sodium Valproate	200
Diluents*	66
Povidone	4
Sodium Starch glycolate	12
Talc	3
Magnesium stearate	3
Aerosil	12
Total	300

*Diluents: DB, MCC or MS

Presence of aerosil in the formulation resulted in tablets with long disintegration time which was decreased by doubling the disintegrant percentage.Pre-formulation studies showed that:

1. The wet granulation by ethanol was the proper method for the formulation.
2. Using different types of diluents had shown a great effect on compression process which may affect the coating process too.
3. With trial and error the percentages of excipients were determined as shown below.

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3.2. Formulation Optimization

3.2.1. Powder Characteristics

Table 4: Powder characteristics of SV powder

Tapped Density (gm/cm^3)	Bulk Density (gm/cm^3)	Angle of Repose (○)	Carr's Index (%) (compressibility)	Hausner's Ratio
0.417	0.357	33.7	14.39	1.17

Table 5: Granular characteristics for three different formulations of SV

Formula Code	Tapped Density gm/cm^3)	Bulk Density (gm/cm^3)	Angle of Repose (○)	Carr's Index (%)	Hausner's Ratio
F1	0.502	0.426	32.0	14.33	1.17
F2	0.395	0.334	32.7	14.37	1.17
F3	0.489	0.419	33.3	14.31	1.16

F1=DB F2=MCC F3=MS

Angle of repose, compressibility and the Hausner's Ratio indicated that the flow properties were good. But during the preparation process, the powder of SV showed a problem of high absorption of humidity and therefore it was decided to be made as granules. MS was observed to have the highest value of angle of repose and the lowest values of compressibility and Hausner's Ratio when compared with MCC and DB.

Table 6: Some quality control tests of SV enteric coated tablets by wet granulation

FC	Type of diluents	Punch Shape	Coat type	Coat%	Wt.V (RSD)	H (Kp)	Th (mm)	DT (min)	Content %	% DR
F1	MS	D	C	20%	2.1	10.9	5.0	33:3	98.9	29. 5
F2	DB	A	C	28%	1.9	12.4	5.0	24:3	102.5	59.9
F3	MCC	R	C	24%	1.9	16.5	4. 6	20:5	105.2	99.1
F4	MS	A	I	24%	2.0	14.2	5.2	25:6	102.1	98.6
F5	DB	R	I	20%	1.3	14.5	4.6	31:7	99.4	59.2
F6	MCC	D	I	28%	1.5	14.0	5.2	30:6	101.5	99.8
F7	MS	R	W	28%	2.1	13.4	5.1	35:2	101.1	102.0
F8	DB	D	W	24%	1.8	11.3	5.0	43:3	101.0	100.3
F9	MCC	A	W	20%	1.6	16.4	5.5	50:6	99.0	92.8

FC: Formulation Code,Wt.V: Weight variation, H: Hardness, Th:Thickness, DT: Disintegration time, MS: Maize Starch, DB: Dibasic calcium phosphate anhydrous,MCC=Micro crystalline cellulose, D: Diamond, A: Almond, R: Round biconcave,C: Colorcon, I: Instacoat, W: Wincoat, DR: Drug release in Phosphate buffer ph 6.8 (60 min).

3.2.2 Post-formulation tests of the Prepared SV Enteric Coated Tablets

3.2.2.1. Effects of type of diluents on weight variation

As shown in table 6 and 7, all tablets showed RSD in the range of 1.3 to 2.1, and the type of diluents had a significant effect on the value of RSD with p-value (0.0041) the lowest level of RSD associated with DB, while the highest level of RSD associated with MS. Whereas, the MCC was in between. These results might be explained by difference in some properties such as compressibility; binding index and flow which would result in a variation in tablets weight.

3.2.2.2 Effects of type and percentage of coat on weight variation

Table7 showed that the shape of the punch had no significant effect on weight variation (P-value > 0.05) while, the type of coat and the percentage of coat had a significant effect on weight variation (P-value: 0.0065-0.0209). The high level of weight variation associated with Wincoat type and 28% as highest percentage of coating while the lowest one was with Instacoat

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type and 20% as lowest percentage of coating, whereas Colorcon type was in between. So Instacoat type of coat and 20% percentage of coating is the best one to decrease weight variation problems.

Table 7: Analysis results of weight variation test of SV enteric coated tablets

Removed	F Value	P- Value Prob > F	R-Squared	MSE	
Punch shape	-	1.0000	0.9977	6.333E-004	
Source	Sum of Squares	df	Mean Square	F Value	P- Value Prob > F
Model(significant)	0.56	6	0.093	146.98	0.0068
Type of diluents	0.30	2	0.15	240.21	0.0041
Type of coat	0.20	2	0.098	153.95	0.0065
Coat %	0.059	2	0.030	46.79	0.0209
Residual	1.267E-003	2	6.333E-004	-	-
Cor Total	0.56	8	-	-	-

3.2.2.3. Hardness of prepared S.V tablets

Table 8 indicated that the type of coat and thepercentage of coat had no significant effect on hardness (P-value > 0.05), while the type of diluents and the shape of the punch had a significant effect on hardness (P-value: 0.0163-0.0230).

The highest hardness of tablet was seen withMCC round biconcave shape which might be related to its higher binding index and efficiency than MS and DB which showed the lowest values of tablet hardness. These results were in line with weight variation results.

Table 8: Analysis results of hardness test of SV enteric coated tablets

Removed	F Value	P-Value Prob > F	R-Squared	MSE	
Coat %	-	1.0000	0.9697	0.48	
Type of coat	1.46	0.4064	0.9255	0.59	
Source	Sum of Squares	df	Mean Square	F Value	P- Value Prob > F
Model(significant)	29.39	4	7.35	12.42	0.0158
Type of diluents	16.15	2	8.08	13.65	0.0163
Punch shape	13.24	2	6.62	11.19	0.0230
Residual	2.37	4	0.59	-	-
Cor Total	31.76	8	-	-	-

3.2.2.4 Effects of tablet shape and type of coat on thickness

As shown in table 9, the type of diluents, the type of coat and the percentage of coat had not significant effect onthickness (P-value > 0.05) while the shape of the punch might have an effect on thickness because (P-value: 0.0824 near to 0.05). The highest value of tablet thickness showed with Wincoat and almond shape while the lowest value was with Colorcon and round biconcave shape.

Table 9: Analysis results of thickness test of SV enteric coated tablets

Removed	F Value	P- Value Prob > F	R-Squared	MSE
Coat %	-	1.0000	0.9500	0.017
Type of coat	2.53	0.2836	0.8238	0.030
Type of diluents	2.94	0.1639	0.5649	0.049

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Source	Sum of Squares	df	Mean Square	F Value	P- Value Prob > F
Model(not significant)	0.38	2	0.19	3.89	0.0824
Punch shape	0.38	2	0.19	3.89	0.0824
Residual	0.29	6	0.049	-	-
Cor Total	0.68	8	-	-	-

3.2.2.5 Disintegration time for the prepared S.V tablets

The type of diluents, the shape of the punch and the percentage of coat had not significant effect on disintegrationtime (P-value > 0.05) while the type of coat has a significant effect on disintegration time (P-value:0.0320). Disintegrationtime was of highest value with Wincoat as compared with Instacoat and Colorcon. This might indicate that the type of enteric coat had a marked effect on tablet disintegrationtime.Jon and his coworkers found that the type of coat had a significant effect on their prepared enteric coated tablets (15).

Table 10: Analysis results of disintegration test of SV enteric coated tablets

Removed	F Value	P- Value Prob > F	R-Squared	MSE
Coat %	-	1.0000	0.9855	5.17
Punch shape	6.55	0.1324	0.8908	19.51
Type of diluents	3.81	0.1183	0.6826	37.80

Source	Sum of Squares	df	Mean Square	F Value	P- Value Prob > F
Model(significant)	487.92	2	243.96	6.45	0.0320
Type of coat	487.92	2	243.96	6.45	0.0320
Residual	226.83	6	37.80	-	-

3.3. Validation of HPLC Method for Assay and Dissolution Tests of the Prepared S.V Tablets

The validation was done to the method by linearity, purity and sensitivity.

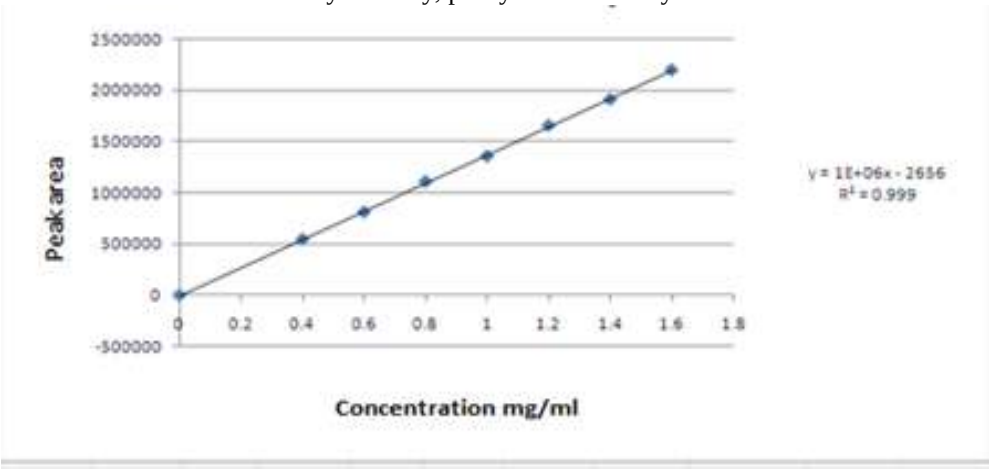

Figure 1: Calibration curve of standard solutions of Sodium valproate

3.3.1. Linearity: The absorption of different concentrations was measured and found to be in linearityofR^2 =0.999. This indicates strong correlation between the concentrations of standard and obtained peaks.

Table 11: Chromatogram parameters of the SV standard

Injections No.	Retention time	Peak Area	Average Peak Area	Theoretical plate	Tailing factor

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1	5.618	1389800		7214.092	1.267
2	5.616	1388616		7245.325	1.264
3	5.614	1390059	1389548.2	7253.28	1.266
4	5.614	1389879		7229.754	1.266
5	5.613	1389387		7222.984	1.266

3.3.2. Sensitivity and Repeatability:

The obtained chromatogram insured the high sensitivity and good repeatability, the same concentration was injected 5 times and was given similar retention time, peak area and average peak area.

3.3.3. Purity of Peak:

As shown in fig.2 and fig.3, the chromatogram of standard SV showed good purity of the peak in the specified retention time. Sharp and straight base line symmetrical peak was obtained, eluted at 5.616 min in STD and 5.615 min in sample. The chromatogram of SV from the prepared tablet showed that the peak obtained was excellent with no tailing and clear which indicated that the excipients used in tablet formulations did not interfere with the assay of SV and so the method was valid to measure SV in the prepared tablet.

Figure 2: Chromatogram of SV standard for assay

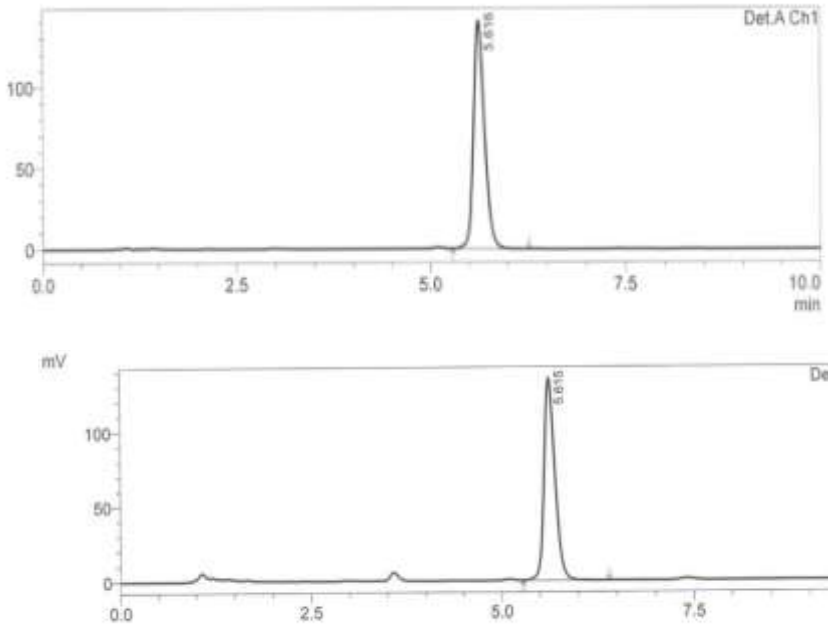

Figure 3: Chromatogram of SV sample for assay

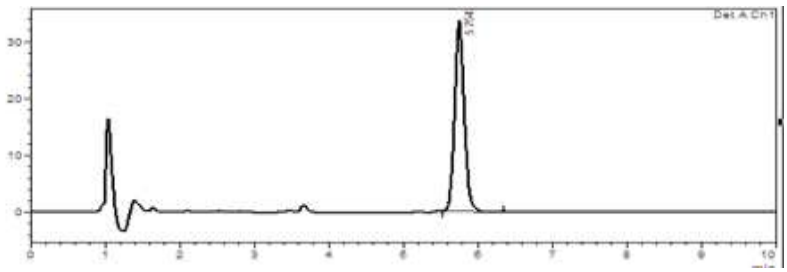

Figure 4: Chromatogram of SV standard for dissolution

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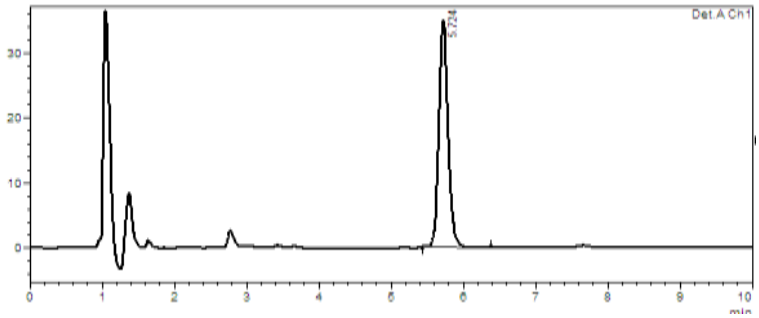

Figure 5: Chromatogram of SV sample for dissolution

3.4. Assay and Dissolution Tests of the Prepared S.V Tablets:

As shown in table 6,the assay of SV was found to be within the acceptable range.According to the designthe type of diluents, the shape of the punch and the type of coat had no significant effect on assay (P-value > 0.05) while the percentage of coat had a significant effect on assay (P-value:0.0364).

The formulations coated by 20% coat showed a drug content of about (98.9%, 99.4%, and 99.0%), 24% coat of about (105.2%, 102.1%, and 101.0%) and 28% coat of about (102.5%, 101.5%, and 101.1%).

Table 12: Analysis results of assay test of SV enteric coated tablets

Removed	F Value	P- Value Prob > F	R-Squared	MSE
Type of coat	-	1.0000	0.9304	1.13
Punch shape	1.39	0.4178	0.8334	1.35
Type ofdiluents	1.98	0.2525	0.6685	1.79

Source	Sum of Squares	df	Mean Square	F Value	P- Value Prob > F
Model(significant)	21.66	2	10.83	6.05	0.0364
Coat %	21.66	2	10.83	6.05	0.0364
Residual	10.74	6	1.79	-	-
Cor Total	32.39	8	-	-	-

The drug release characteristics were studied in 0.1 HCl (120 min) and Phosphate buffer pH 6.8 after 2 hours as approved for ideal entericcoating. Percentage Drugrelease in 0.1 HCl (120 min) was found to be zero for all prepared formulations. From the design the used factors and the levels had no significant effect on the dissolution test. But we could observe that the type of coat and diluents might affect the percent of drug release. The best results of drug release were obtained with the use of Instacoat coat with MS and MCC (F4 and F6), while Wincoat coat with MS and DB (F7 and F8) and Colorcon coat with MCC (F3). The percent drug release was decreased when Colorcon coat was used with MS and DB (F1 and F2), Instacoat coat with DB (F5) and Wincoat coat with MCC(F9). So, the proper selection of suitable type of coat and diluents must be considered.Saravanan and his coworkers found that the type of diluents, coat had a significant effect on their prepared enteric coated tablets (16).

Table 13: Analysis results of dissolution test of SV enteric coated tablets

Removed	F Value	P- Value Prob > F	R-Squared	MSE
Punch shape	-	1.0000	0.9700	82.64
Type of diluents	6.13	0.1403	0.7861	294. 59
Coat %	3.32	0.1415	0.4313	522.10
Type of coat	2.28	0.1839	-0.0000	688.59

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Source	Sum of Squares	df	Mean Square	F Value	P- Value Prob > F
Model	0.000	0	-	-	-
Residual	5508.74	8	688.59	-	-
Cor Total	5508.74	8	-	-	-

IV. CONCLUSION

From the above study it is concluded that enteric coated SV tablets were prepared by wet granulation, compression techniques, showed promising results. It was concluded that the type of diluents, the type of coat and the percentage of coat had a significant effect on weight variation while the type of diluents and the shape of the punchhad a significant effect on hardness. Also, the shape of the punchmay affect the thickness.

The results showed that the type of coat had a significant effect on disintegration time and the percentage of coat had a significant effect on assay. While the uses of the factors and the levels had no significant effect on the dissolution test but it can be suggested that the type of diluents and coat might have an effect on it.

From the above results it can be concluded that the best formula of sodium valproate enteric coated tablets was by usingInstacoat type of coat, 24% coat percentage, DB as diluent and round shape punch.

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Conflict of Interest:

All authors declare that they have no conflict of interest.

Authors Contribution:

Elham Mohammed Elameen Widaa performed all experiments. Eltayeb Suliman Elamin supervised all the work and prepared the manuscript draft. Abutalib Alamin Abdallah helped in performing the experiments. Alaa E. Elawni helped in performing the experiments and revised and edited the manuscript.

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