INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

PREPARATION AND EVALUATION OF ENTERIC COATED TABLET OF SODIUM VALPROATE

Pranav Palshikar*, Anshu Sharma, Chetan Singh Chauhan and Ravindra Kamble

Bhupal Nobels' College of Pharmacy, Udaipur, Rajasthan, India.

ABSTRACT

The objective of this study was to develop an enteric coated tablet of sodium valproate using cellulose acetate phthalate as enteric coating material. Core tablet were prepared by non aqueous granulation method and seal coated with PVP K-30 which act as moisture barrier. This seal coated tablet was further coated with cellulose acetate phthalate to dissolve in the intestinal fluid. The in vitro release result showed that enteric coated were capable of restricting release in the acidic media.The optimized batch is capable of releasing the drug in as same manner of a marketed formulation of sodium valproate.

Keywords: Sodium valproate, enteric coating, *in-vitro* dissolution.

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 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.

A tablet is a pharmaceutical dosage form comprising a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. The excipients can include glidants (flow aids), diluents, binders or granulating agents and lubricants to ensure efficient tableting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavours to

enhance taste; and pigments to make the tablets visually attractive. A polymer coating is often applied to enhance the tablet's appearance or to make the tablet smoother and easier to swallow and to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life). “Caplets” are those tablets which are in the shape of capsules.

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. After making a good tablet, one must often coat it.

Coating may be applied to multiple range of oral solid dosage form, including tablets, capsules, multiparticulates and drug crystals. When coating composition is applied to a batch of tablets in a coating pan, the tablet surfaces become covered with a tacky polymeric film. Before the tablet surface dries, the applied coating changes from a sticky liquid to tacky semisolid and eventually to a non-sticky dry surface pans. The entire coating process is conducted in a series of mechanically operated acorn-shaped coating pans of galvanized iron stainless steel or copper. The smaller pans are used for experimental, developmental, and pilot plant operations, the larger pans for industrial production.[4-6]

An enteric coating is a barrier that controls the location of oral medication in the digestive system where it is absorbed. The word “enteric” indicates small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine. The enteric coated polymers remain unionise at low pH, and therefore remain insoluble. But as the pH increases in the GIT, the acidic functional groups are capable of ionisation, and the polymer swells or becomes soluble in the intestinal fluid. Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac, plastics and plant fibers. There are four reasons for putting such a coating on a tablet or capsule ingredient:

- Protection of active pharmaceutical ingredients, from the acidic environment of the stomach (e.g. enzymes and certain antibiotics).
- To prevent gastric distress or nausea from a drug due to irritation (e.g. sodium salicylate).
- For the delivery of drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.
- To provide a delayed-release component for repeat action.
- Required for minimizing first pass metabolism of drugs. [7, 8]

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.

MATERIAL AND METHODS

Material

Sodium Valproate (Anjan Drug Pvt. Ltd. Chennai), syloid and sodium starch glycolate(Grace GMBH& Co. Germany), microcrystalline cellulose (FMC Biopolymer USA),PVP K-30 (ISP technology) Isopropyl alcohol (Finar chemicals India). Cellulose acetate phthalate was a gift sample provided by G.M. Chemicals Mumbai. All other chemicals used were of analytical grade and were used as received.

Methods

MANUFACTURING PROCEDURE OF ENTERIC COATED TABLETS

Weighing & Sifting: Accurately weigh requires quantity of didanosine and sifted through #40 mesh.

Mixing: Microcrystalline cellulose, povidone were passed through #40 mesh and Isopropyl alcohol was added to the above material and blended for 5 min and prepare damp mass and finally pass through #24 mesh and allow the granules for drying at 40^0C. Sodium starch glycolate was then added in the granules.

Lubrication: Magnesium stearate and talc were passed through 60#and added to the above blended material.

Compression: compress the blend into tablets with punch size of 20 x 7mm rod shaped.
Formula of various formulation is given in table no.1

Seal Coating: Tablets are taken in a coating pan and coating was done.
Preparation of coating solution: Take required quantity of isopropyl alcohol stir with propeller stirrer to form vortex. Add quantity of PVP, talc and PEG-600 in vortex stir for 25 mins. Maintain the solution without air bubbles then use the solution for coating. Quantity of tablets to be coated is 100 Tab. Formula of seal coating is given in table no.2.

Enteric Coating: Tablets are taken in a coating pan and coating was done.
Preparation of coating solution: Take the required quantity of ethanol and acetone in 1:3 ratio and stir with propeller stirrer to form vortex. Add Cellulose acetate phthalate, titanium dioxide, dibutyl phthalate in vortex stir for 25 mins. Maintain the solution without air bubbles then use the solution for coating. Quantity of tablets to be coated is 100 Tab. Formula of enteric coating is given in table no.3.

EVALUATIONS OF ENTERIC COATED TABLETS

Hardness: The tablet crushing strength was tested by commonly used Pfizer tablet hardness tester. A tablet is placed between the anvils and the crushing strength, which causes the tablet to break, was recorded.

Friability: Tablet strength was tested by Roche friabilator. Preweighed (Model: ED-2, Electrolab) tablets were given 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets.

Uniformity of weight: Randomly selected twenty tablets from all the three formulations were weighed individually and together on electronic balance (Metteler Toledo electronic balance: Model P G 03-S) .The average weight was noted.

Drug content studies: The drug content in tablets were determined by randomly choosing ten tablets from all three enteric coated formulations and powdered using mortar & pestle. A quantity equivalent to 500 mg of sodium valproate. it was weighed and dissolved in methanol (diluted if necessary),then absorbance was taken on 215 nm on (Shimadzu Corp., Japan) at wavelength 215 nm.

Disintegration time: Disintegration time was determined using the disintegration apparatus USP (Electrolab, Bangalore, India) in 0 .1 N HCl for 2 h and then in phosphate buffer pH 6.8 for 1 hour maintaining the temperature at 37±2°C .[8, 9]

In vitro Dissolution test

Drug release profile was evaluated in vitro, using a dissolution test apparatus. The USP XIII Type II (paddle type) method (TDT-08L,

Electrolab, Mumbai, India.) was selected to perform the dissolution profile of azithromycin enteric coated tablets .The dissolution of enteric coated tablet is performed into 0.1 N HCl for 2 hours and then the phosphate buffer pH 6.8 for 1 hour. The temperature was maintained at 37±0.5°C and a constant paddle rotation speed of 100 rpm.

Samples (5 ml) were withdrawn at regular intervals and filtered. The samples were analyzed by hplc (Shimadzu Corp., Japan).[10]

RESULT AND DISCUSSION

As mentioned above the sodium valproate drug 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 sodium valproate 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, diarrhoea, abdominal pain, headeach, vomiting, unexplained rashes, pilling of skin , abnormal swelling like side effects .

The purpose of formulation of the enteric coated tablets of sodium valproate is to delay the release of drug and to allow release in lower part of gastrointestinal tract . The reason behind this delaying of release is , to prevent the the conversion of sodium valproate into free valproic acid in upper gastro intestinal tract.So by releasing the drug in lower gastrointestinal tract(ileum and large intestine) we can safely administer sodium valproate without side effects and without altering its absorption.

Two different core tablets were prepared each with varying concentrations of binding agent (PVP K-30). Then the other excepients like MCC(diluent) ,magnesium stearate(lubricant) and talc (glident) were used. The Prepared tablets were subjected to tests like hardness, friability, weight variation were employed for these core tablets.

The seal coat may act as moisture barrier and also increase the mechanical strength of tablets during enteric coating process.

The enteric coating was applied with the consideration of transit time of food or dosage form from stomach to jejunum of small intestine (2hrs) and from percent release verses time plot was plotted.

The following effect were observed on the release profile of the enteric coated sodium valproate tablet:

1. Effect of binder concentration
2. Effect of high kneading time
3. Effect of granules sizing through 20# mesh
4. Effect of low % LOD

Various tests like hardness, friability, uniformity of weight, content uniformity was given the table no.4

Disintegration test result was shown in the table no. 5 it shows that tablet of every batch showed no sign of softening or cracking in 0.1 N HCl and disintegrate within 10 minutes in phosphate buffer pH 6.8.

For F-1 batch, in place of 0.5% PVP-K 30 was used as a binder and also added as a dry like other excipients with no change in the other excipients to match the dissolution profile with DEPAKENE's dissolution profile. Seal coating was done upto 3% weight gain then enteric coating was applied upto 8% w/w gain.

Adding the binder dry avoids the need to determine the optimal binder concentration and a separate manufacture for the binder solution. Dissolution analysis revealed that there was no release in 0.1N HCl for two hours but dissolution in 6.8 pH phosphate buffer was faster than DEPAKENE's dissolution profile.

In the next F-2 batch, in place of 1.0% PVP-K 30 was used and remaining formulation and process parameters were kept similar as batch F005 to match the dissolution profile of test with DEPAKENE's dissolution profile.

Dissolution analysis showed that dissolution profile was nearly superimposed in both media 1.2 pH 0.1N HCl and 6.8 pH phosphate buffer with DEPAKENE.

The next batch (F-3) was taken to see the effect of high kneading time for optimization of granules. The kneading time was increased by two minutes as compared to batch F-2 and other process parameters, formulation kept similar as F-2, no changes were observed on physical parameters of tablets. Dissolution analysis was carried out to asses the effect on dissolution profile. Dissolution profile showed slight retardation in middle time points because granules become larger and more uniform. So, dissolution profile showed minor impact of high kneading time.

Batch F-4 was also taken to check the effect of granules sizing for optimization of granules. Dried granules were passed through 20# sieve and formulation, other process parameters were kept same as F-2. Disintegration time of core tablets was reduced four minutes as compared to batch F-2 but there was no impact on other physical parameters of tablets. Dissolution analysis showed faster dissolution than DEPAKENE because a smaller screen size produced a smaller particle size and greater number of fines as compared to 16# screen size. It was indicative of corrective action needs to be taken during scale up study because large load and/or machine speed may affect granules size.

Batch F-5 was taken to check the effect of low % LOD of granules for optimization of granulation process. Granules were dried upto 0.5% LOD and formulation as well as other process parameters were kept similar as that of batch F-2. No impact was observed on compression process and in process parameters. Dissolution profile was superimposed with DEPAKENE dissolution profile. Hence, 0.5% LOD was selected as optimized batch.

Table 1: Formula for core tablet

Ingredients	F-1	F-2
Sodium valproate	576	576
Syloid FP 244	80	80
Microcrystalline cellulose	46	42
Pvp K-30	3.95	7.91
IPA	q.s	q.s
Syloid FP 244	10	10
Microcrystalline cellulose	17.35	17.55
Purified talc	30	30
Magnesium sterate	9.2	9.2
Sodium starch glycolate	18.3	18.3

Table 2: Formula for seal coat

Ingredient	Quantity (%)
PVP K- 30	9
talc	2
PEG-600	1
Isopropyl alcohol	q.s.

Table 3: Formula for enteric coat

Ingredient	Quantity (%)
Cellulose acetate phthalate	10
Titanium dioxide	1.5
Quinoline yellow lake	0.2
Sunset yellow lake	0.5
Ethanol :acetone (1:3)	q.s.

Table 4: various test parameters

Parameters	F-1	F-2	F-3	F-4	F-5
Hardness(Kg/cm$^{2)}$	4.2	3.9	4.1	4.3	4.0
Friability (%)	0.12	0.15	0.13	0.13	0.14
Weight variation (%)	±2.5	±2.8	±2.1	2.3	2.4
% drug content	98.42	96.58	99.48	97.24	98.00

Table 5: Disintegration test of enteric coated tablet in medium 0.1 N HCl and phosphate buffer (pH 6.8)

Formulation No.	Observation in 0.1 N HCl	Observation in phosphate buffer (pH 6.8)
F-1	No sign of cracking or softening after 2 hours	6±1.2 min
F-2	No sign of cracking or softening after 2 hours	7±1.0 min
F-3	No sign of cracking or softening after 2 hours	6±1.5 min
F-4	No sign of cracking or softening after 2 hours	7±1.5 min
F-5	No sign of cracking or softening after 2 hours	8±1.0 min

Table 6: Dissolution profile of marketed product, F-1 and F-2 formulation

Media	Time (min)	% drug release		
		Marketed	F-1	F-2
0.1 N HCl	0	0.0	0.0	0.0
	120	0.0	0.0	0.0
Phosphate buffer pH6.8	125	0.1	0.0	2.4
	130	3.4	7.6	4.1
	135	9.8	11.2	7.2
	150	28.8	40.6	24.2
	165	42.3	60.0	39.8
	180	53.3	75.5	51.8
	240	85.7	99.8	82.9

Table 7: Dissolution profile of marketed product, F-3, 4 and F-5 formulation

Media	Time (min)	% drug release			
		Marketed	F-3	F-4	F-5
0.1 N HCl	0	0.0	0.0	0.0	0.0
	120	0.0	0.0	0.0	0.0
Phosphate buffer pH6.8	125	0.1	1.5	0.0	0.0
	130	3.4	2.6	5.4	1.5
	135	9.8	4.8	11.0	5.0
	150	28.8	20.4	32.3	27.8
	165	42.3	35.9	50.3	40.0
	180	53.3	52.4	70.0	53.2
	240	85.7	86.0	94.9	84.5

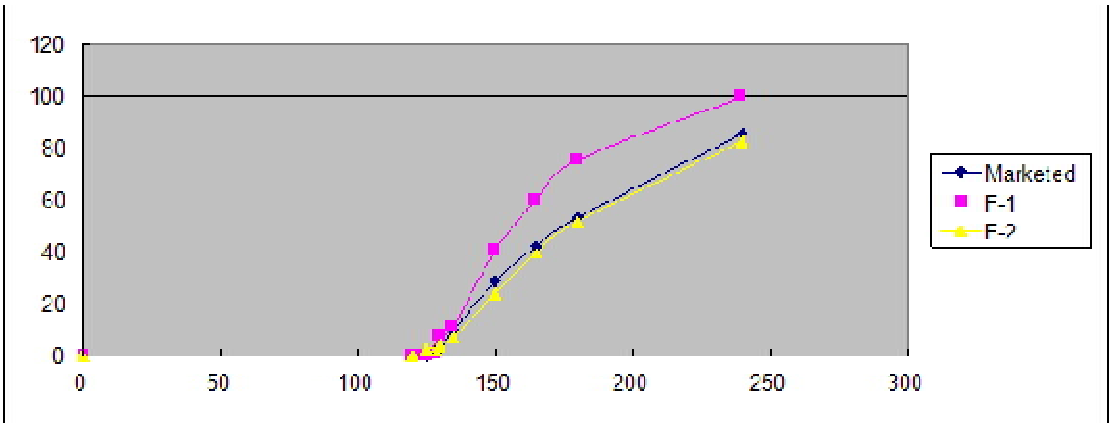

Fig. 1: Dissolution profile of marketed product, F-1 and F-2 formulation

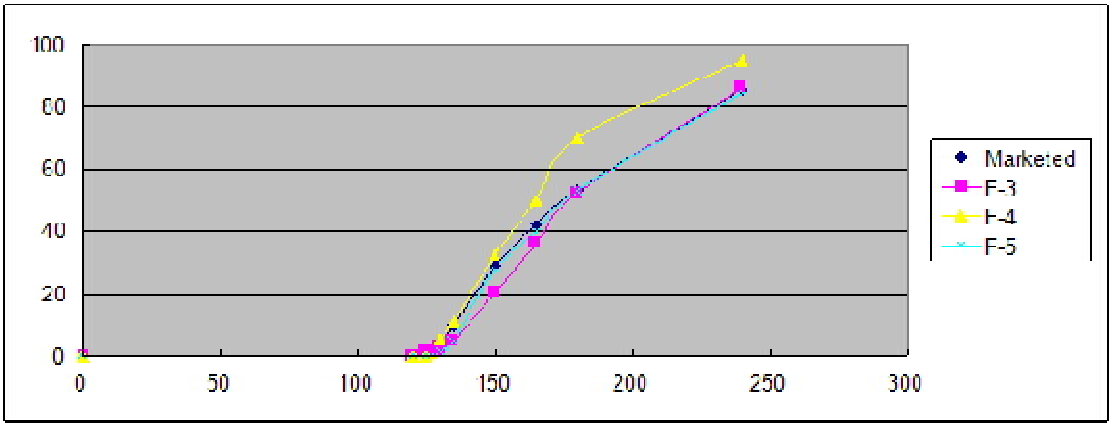

Fig. 2: Dissolution profile of marketed product, F-3, F-4 and F-5 formulation

CONCLUSION

From the above study it is concluded that, enteric coated sodium valproate tablets were prepared by nonaqueous granulation compression techniques, showed promising results when compared with marketed drug.

REFERENCES

1. Ibrahim AA, Omar M, Belal F. Valproic Acid and sodium valproate comprehensive profile, Profiles Of Drug substances, Excipents And Related Methodology. 2005; 32: 209-232.
2. Gupta RK, Singh UK, Kumar S, Moothan B. Estimation of Sodium Valproate in Tablet Dosage Form by RP-HPLC without Prior derivatization: Application to Dissolution Studies. Int J Pharm Sci Drug Res 2009; 1(2): 103 -106.
3. Theodore WH, Fisher RS. Brain stimulation for epilepsy. Lancet Neurol 2004; 3 (2): 111–118.
4. Lachman L, Lieberman HA, Joseph LK. The Theory and Practice of Industrial Pharmacy. Varghese Publishing House; Mumbai; Third Edition: 297-321.
5. Lachman L, Liberman H, Kanig J. The Theory and Practice of Industrial Pharmacy; Third Edition: 293-345, 346-373.
6. Aulton M. Pharmaceutics: The Science

of Dosage Form Design. International Student Edition: 304-321, 347-668.

7. Kumar Vinay. KV, Sivakumar T and Tamizh mani. T, Colon targeting drug delivery system: A review on recent approaches, International Journal of Pharmaceutical and Biomedical Science, 2, 2011, 11-19.
8. S.Bozdag ,S.Calis and M. Summu. Formulation and stability evaluation of enteric coated omeprazole formulations S.T.P.PHARMA SCIENCES.1999;9:321-327.
9. Lee TW., Robinson JR., In Remington:The science and practice of pharmacy;Gennaro, Ed.; Lippincott Williams and Wilkins: Baltimore; 2000; (2); 903- 929.
10. Sinha VR, Kumria R. Coating polymers for colon secifi c drug delivery:A comparative in vitro evaluation. Acta pharm. 2003; 53: 41-47.