Business, Management and Economics Engineering
ISSN: 2669-2481 / eISSN: 2669-249X
2024 Volume 22 Issue 01

DESIGN AND EVALUATE MOUTH DISSOLVING TABLETS OF DIVALPROEX SODIUM USING SUPERDISINTEGRANT

Nitin N. Mali, Abhijeet B. Survase, Priyanka K. Shinde, Pranita S. Kavitake, Saundarya S. Kurde

1*Associate Professor, Vidya Niketan College of Pharmacy, Lakhewadi
2Associate Professor, Vidya Niketan College of Pharmacy, Lakhewadi
3Assistant Professor, Vidya Niketan College of Pharmacy, Lakhewadi
4Assistant Professor, Vidya Niketan College of Pharmacy, Lakhewadi
5Assistant Professor, Vidya Niketan College of Pharmacy, Lakhewadi

ABSTRACT

The aim of the present work was to formulate and evaluate mouth dissolving tablets of Divalproex sodium using superdisintegrants, exhibiting adequate mechanical strength and disintegration time. Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. In the present investigation, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug, Divalproex sodium by inclusion complex method using β -cyclodextrin. Hence formulate Divalproex sodium mouth dissolving tablets by using β-cyclodextrin and superdisintegrants to enhance the solubility of the drug.

KEY WORDS: β -cyclodextrin, microcrystalline cellulose, croscarmellose sodium, Divalproex sodium.

Introduction

Psychosis refers to an abnormal condition of the mind, and is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality". People experiencing psychosis may exhibit some personality changes and thought disorder. Depending on its severity, this may be accompanied by unusual or bizarre behavior, as well as difficulty with social interaction and impairment in carrying out daily life activities.

Mouth dissolving or oro-dispersible or fast dissolving tablets are defined as a solid dosage form comprising a medicinal constituent, which instantaneously disperses within seconds into the saliva when kept on the tongue. Mouth dissolving tablet (MDT) definition as per the WHO “MDT are uncoated tablets or film-coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion.”1-4 Oral delivery of the drug is most preferred route of administration which have wide acceptance up to 50- 60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance.5-6 Among the dosage forms administered orally, the tablet is the most desired dosage forms for its ease of preparation, ease in administration, correct dosing and stability related with oral liquids and more tamper proof than capsules3 . Immediate release may be provided by way of an

appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption.7-8 Disintegrating agents are substances routinely included in the tablet formulations to aid in the breakup of the compacted mass when it is put into a fluid environment. They promote moisture penetration and dispersion of the tablet matrix. In recent years, several newer agents have been developed known as “Superdisintegrants”. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs.

The natural superdisintegrants involve various natural substances like gums, mucilage, and other substances of natural origin which are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Some natural substances like gum karaya, modified starch and agar have been used in the formulation of MDT’s. Mucilage of natural origin is preferred over semi synthetic and synthetic substances because they are comparatively cheaper, abundantly available, nonirritating and nontoxic in nature.

Materials and Methods

Physical appearance of drug was examined for various organoleptic characters such as color, odor, taste etc. Melting point of the Divalproex sodium was determined by open capillary tube method using Thieles tube apparatus. Temperature was noted at which solid drug changed into liquid. SolubilityThe solubility of Divalproex sodium was determined in water and buffer. An excess quantity of the drug was mixed with 10ml of each solvent in volumetric flask with stopper and shaken on constant water bath shaker for 24 hours at 250C. The solutions were examined physically for the absence or presence of drug particle.

Spectroscopic Analysis:

I) Preparation of calibration curve: Preparation of 0.2 M potassium phosphate (monobasic) - Dissolve 27.220 gm of monobasic potassium phosphate (KH_2PO_4) in water, and dilute with water to 1000 ml.

II) Preparation of 0.2 M sodium hydroxide- Add 8gm of NaOH in 1000 ml volumetric flask containing distilled water to prepare 0.2M sodium hydroxide.

III) Preparation of phosphate buffer pH 6.8- Place 50 ml of 0.2 M monobasic potassium phosphate in a 200 ml volumetric flask, add 22.4 ml of sodium hydroxide solution, then add water to make volume up to 200 ml.

Infrared spectroscopy: The pellet of approximately 10 mm diameter of drug was prepared grinding 3-5 mg of sample with 100-150 mg of potassium bromide using hydrostatic press. The sample pellet was mounted in IR compartment and scanned at wavelength and spectra are observed. IV) Differential scanning calorimetry

DSC: DSC studies were carried out using thermal analyzer (DSC METTLER DSC30s). The samples were thermetically sealed in an aluminum pans and heated at constant rate of

100C/min over a temperature range of 0-3000C. Inert atmosphere was maintained by purging nitrogen gas at a flow of 50 mL/min.

Result

Determination of Saturation solubility of Divalproex sodium

Table no. 1: Saturation solubility of Divalproex sodium

Solvent	Solubility*(mg/ml)
Distilled Water	0.121±0.006
pH 6.8 phosphate buffer	0.487±0.009

*Mean ± SD, n= 3

Spectroscopic analysis:

Standard calibration plot:

The standard calibration curve of Divalproex sodium was obtained by plotting Absorbance Vs Concentration in µg/ml Table no.: 2 shows the absorbance values of Divalproex sodium.

Table no.2: Standard calibration curve of Divalproex sodium at 204 nm in pH 6.8 phosphate buffer

Sr. No.	Concentration µg/ml	Absorbance (A°)
1	00	00
2	2	0.138
3	4	0.257
4	6	0.35
5	8	0.49
6	10	0.59

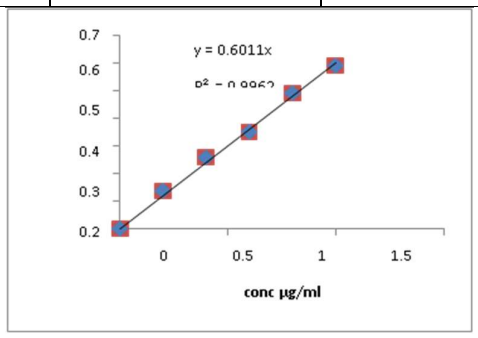

Fig no.1: Standard calibration plot of Divalproex sodium

1) Determination of λ max:

Ultraviolet absorption in the range 200 to 400 of a 10 µg/ml solution of phosphate buffer (pH 6.8) was measured. The absorption maxima of Divalproex sodium (10µg/ml) in this solution was found to be 204 nm which is concordant with the Indian pharmacopoeia shown in figure no.:1

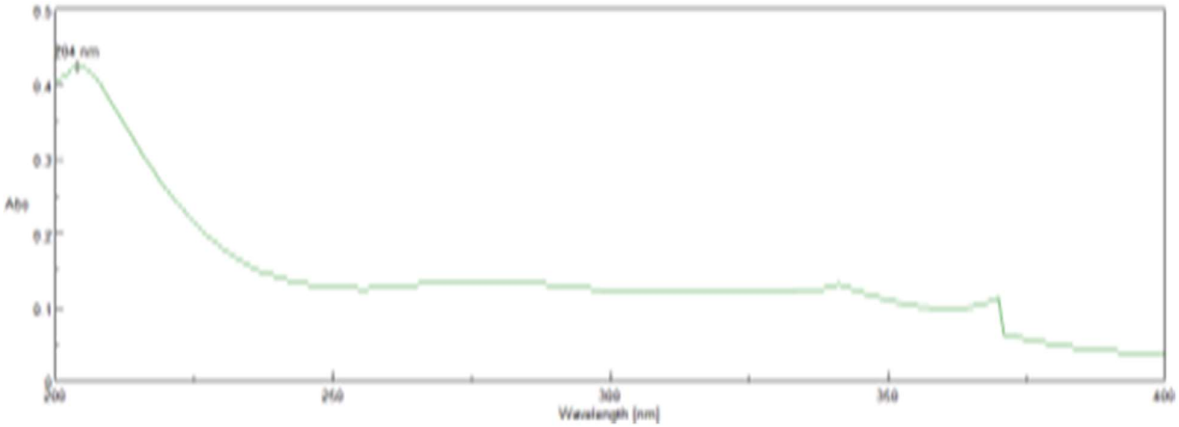

Fig no.2: UV spectrum of Divalproex sodium in pH 6.8 phosphate Buffer

Infrared spectroscopy:

Divalproex Sodium:

The pellet of approximately 10 mm diameter of the drug was prepared grinding 3-5 mg or sample with 100-150 mg of potassium bromide using hydrostatic press. The sample pellet was mounted in IR compartment and scanned at wavelength 4000cm-1 - 500cm-1

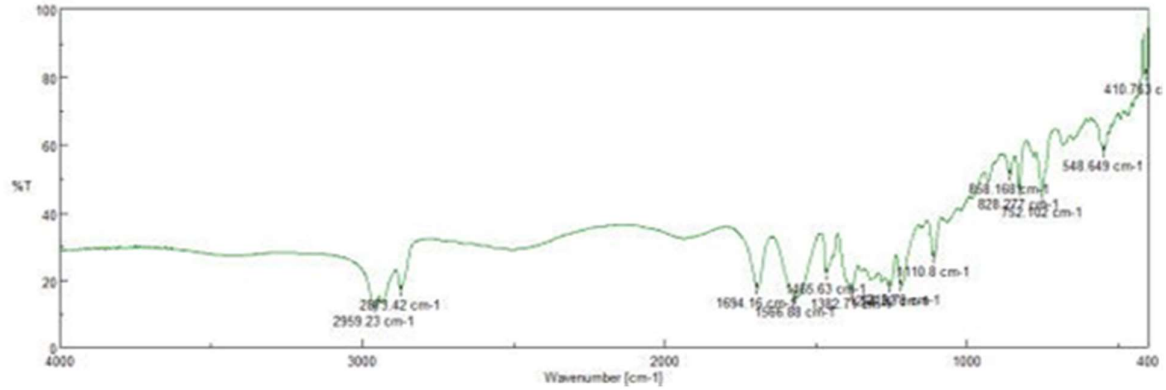

Fig no. 3:F.T.I.R spectra of pure drug Divalproex sodium

Table no. 3: Interpretation of Divalproex Sodium

Peak no.	Peak Position	Functional Group
1	2873.42 cm^{-1}	C-H Stretch.
2	2959.23 cm^{-1}	C-H Stretch.
3	1694.16 cm^{-1}	C=O Stretch.
4	1566.88 cm^{-1}	C-H Stretch.
5	1465.634 cm^{-1}	C-H Stretch.
6	858.16 cm^{-1}	C-C Stretch
7	828.27cm^{-1}	C-C Stretch

Interpretation of I. R. spectra of Divalproex sodium +Crosscarmellose sodium

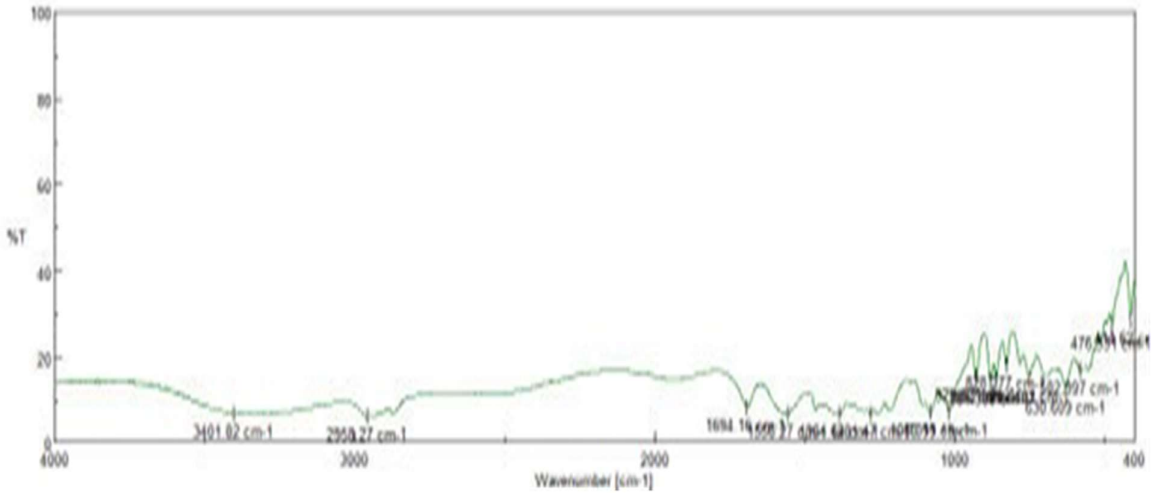

Fig no.4:F.T.I.R spectra of Divalproex sodium + Crosscarmellose sodium Table no.4: Interpretation of Divalproex sodium +Crosscarmellose sodium

Peak no.	Peak Position	Functional Group
1	3401.82cm^{-1}	N-H Stretch
2	2958.27cm^{-1}	C-H Stretch
3	1694.16cm^{-1}	C=O Stretch
4	1556.88cm^{-1}	N=O Stretch
5	1465.63cm^{-1}	C-H Stretch
6	1487.13 cm^{-1}	C-H Stretch

Differential scanning calorimetry (DSC):

The DSC thermograms of pure drug Divalproex sodium show an endothermic peak at 210-2230C. This corresponds to its melting point 2220C of the substantial amorphous & crystalline form respectively. So drug sample considered as authentic.

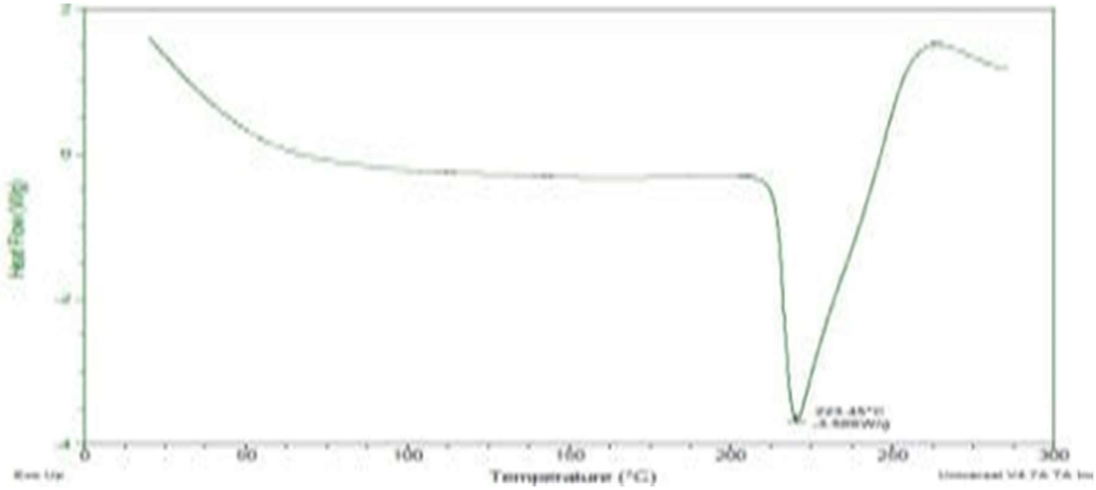

Fig no.5: Differential scanning calorimetry of Divalproex sodium

Preparation of Divalproex sodium inclusion complex:

Table no.5: Formulations of inclusion complex batches.

Ratio (Drug:Carrier)	Batches	
	Solvent evaporationmethod	Kneading method
1:1	A1	B1
1:2	A2	B2
1:3	A3	B3
1:4	A4	B4

Characterization of inclusion complex by D.C%:

Table no.6: Characterization of inclusion complex by D.C%

D:P	code	S_{EV}	D.C%	Percentage Yield (%)	code	S_{KN}	D.C%	Percentage Yield (%)
1:1	A1	4.2	95.7	85.33	B1	2.0	89.6	76.77
1:2	A2	5.6	97.4	89.77	B2	2.8	92.4	87.91
1:3	A3	5.6	96.9	81.55	B3	2.8	91.0	78.22
1:4	A4	5.6	97.2	85.65	B4	2.8	93.2	88.89

D: P=drug polymer ratio SKN=solubility for kneading method SEV=solubility for solvent evaporation D.C=drug content

In-vitro dissolution studies of Divalproex sodium inclusion complex

Table no. 7: Results of Dissolution Profiles of inclusion complex Batches A1, A2, A3, A4

min	%drug release of pure drug	%drug release of A1	%drug release of A2	%drug release of A3	%drug release of A4
00	0	0	0	0	0
10	31.55±1.10	35.84±0.31	51.93±1.48	44.34±0.21	60.11±1.01
20	34.61±0.31	39.82±0.45	59.81±2.33	47.66±1.14	69.75±2.66
30	40.87±1.03	45.29±2.22	68.11±1.45	53.84±1.48	70.16±2.19
40	45.44±1.12	48.46±1.08	75.51±0.44	61.05±0.55	83.32±1.18
50	50.98±2.12	55.67±2.14	85.77±1.01	65.55±0.96	87.59±0.18
60	57.43±1.98	60.59±0.33	93.99±2.88	70.44±1.15	88.8±0.13

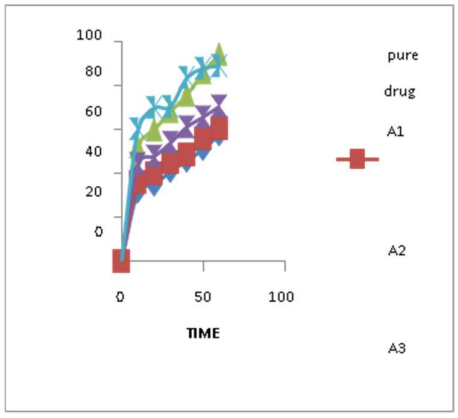

Fig no. 6- Dissolution Profiles of inclusion complex Batches A1, A2, A3, A4

Conclusion

Preformulation studies of Divalproex sodium -β-Cyclodextrin complex were performed; the FTIR analysis revealed that there is no any chemical interaction of Divalproex sodium and β-Cyclodextrin Preformulation studies of Divalproex sodium solid dispersion were performed; FTIRØ compatibility analysis revealed that the superdisintegrants and excipients used were compatible with Divalproex sodium. From the results of saturation solubility, drug content and in-vitro dissolution study ofØ solid dispersions of Divalproex sodium indicated that the solubility was increased with increasing the concentration of β-CD. Interpolymeric Divalproex sodium and β-Cyclodextrin complex as a showed significant configuration in the different ratios in combination rather than their individual contribution. The final formulation developed (combination of Divalproex sodium and β -CyclodextrinØ complex) also had showed improved disintegration time as well as the tablets exhibited higher crushing strength. MDTs of Divalproex sodium can be prepared by direct compression method usingØ superdisintegrants namely croscarmellose sodium and microcrystalline cellulose. The formulated tablets showed satisfactory disintegration time, wetting time, in vitroØ drug release and other physical parameters like hardness, friability, content uniformity etc. A combination of croscarmellose sodium and microcrystalline cellulose was found toØ have superdisintegrant activity. Overall Batch F3 was found to be optimized batch which showed rapid wettingØ undergoes quick disintegration in the oral cavity even though the tablet was prepared at a crushing strength more than 3.5 kg/cm2 and showed maximum drug release up to 97.8%.

Reference

1. Suryadevara V, Lankapalli SR, Danda LH, Pendyala V, Katta V. Studies on jackfruit seed starch as a novel natural superdisintegrant for the design and evaluation of irbesartan fast dissolving tablets. Integr Med Res 2017;6:280-91.
2. 2Chauhan V, Kumar K, Teotia D. Fast dissolving tablets: A promising approach for drug delivery. Univ J Pharm Res 2017;58-64.
3. Hirani JJ, Rathod DA, Vadalia KR. Orally disintegrating tablets: A review. Trop J Pharm Res 2009;8:161-72.
4. Kalia A, Khurana S, Bedi N. Formulation and evaluation of mouth dissolving tablets of oxcarbazepine. Int J Pharm Pharm Sci 2009;1:12-3.
5. Poovizhi Ponnammal, Parijat Kanaujia, Yin Yani ID, Wai Kiong NG, Reginald Tan BH, Orally Disintegrating Tablets Containing Melt Extruded Amorphous Solid Dispersion of Tacrolimus for Dissolution Enhancement, Pharmaceutics, 10(35), 2018, 2-15. 2
6. Shaikh Siraj, Molvi KL, Khan GJ, Shaoor Ahmad, ShaikhMohsin, Shaikh Salman, Review on floating with Bio adhesion, A Unique Expansion in Gastroretetive Drug Delivery System, American Journal of Pharmatech Research, 5(6), 2015, 21-32.
7. Nayyar Nawaz, Anam Nasir, Ayesha hameed, Zoya shah, Javeria saleem, Sana naeem, Superdisintegrants, Proceedings of Second International Multi-Disciplinary Conference 19-20 December 2016, Gujrat, Pakistan.
8. Nyol S and Gupta M, Immediate Drug Release Dosage Form, A review Journal of Drug Delivery and Therapeutics, 3(2), 2013, 155-161.