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DESIGN DEVELOPMENTAND EVALUATION OF MOUTH DISSOLVING TABLETS CONTAINING ANTIPSCHYCOTIC DRUG

M. M. Nitalikar*, Rupali R.Mohite

Department of Pharmaceutics, Rajarmbapu College of Pharmacy, Kasegaon, M.S. India.

Keywords:

β-cyclodextrin, microcrystalline cellulose, croscarmellose sodium, Divalproex sodium

For Correspondence:

Dr. M. M. Nitalikar

Department of Pharmaceutics, Rajarmbapu College of Pharmacy, Kasegaon, M.S. India

E-mail:

mmnitalikar@gmail.com

ABSTRACT

Mouth dissolving drug delivery systems have gained popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. Faster the drug into solution, quicker is the absorption and onset of clinical effect. Divalproex sodium is antipschycotic drug having poor aqueous solubility so its solubility has to be enhanced. Better method of increasing bioavailability was by preparing its inclusion complex with β-cyclodextrin. Divalproex sodium – β-Cyclodextrin (β-CD) solid complexes were obtained by solvent evaporation method. The complexes were confirmed solubility, FT-IR and DSC studies. Dissolution profile of Divalproex sodium was improved by complexation with β-CD.The prepared complexes were formulated in the form mouth dissolving tablets using microcrystalline cellulose, croscarmellose sodium as superdisintigrants by direct compression techniqueand evaluated for thickness, content uniformity;hardness, friability, wetting time; disintegration and *in-vitro* dissolution time and the formulations exhibited no alteration in the physical appearance or content of the tablet. *In- vitro* dissolution studies had shown that the batch F3 proved to be better in drug release.

INTRODUCTION

Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self-medication, non invasive method and ease of administration leading to high level of patient compliance.[1]The most popular dosage forms are being conventional tablets and hard gelatin capsules. One important drawback of such dosage forms is "Dysphagia" or difficulty in swallowing for many patients; almost 50% of the population is affected by such problem. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy.[2]Recently, mouth dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance.[3] Mouth dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. Faster the drug into solution, quicker is the absorption and onset of clinical effect. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric patients. To overcome such problems, mouth dissolving tablets or orally disintegrating tablets has emerged as an alternative dosage form.[4]

Many antipschycotic drugs are available in market are poorly water soluble eg. Divalproex sodium, Risperidone etc drug whose aqueous solubility is less will definitely create bioavailability problem and thereby effecting therapeutic efficiency, once if we are able to increase the aqueous solubility of a drug, then disintegration and dissolution properties can be easily altered, as a result, an increase in bioavailability can be easily achieved so solubility of drug is enhanced by Solubility enhancement techniques for gaining better bioavailability Divalproex sodium, is a poorly water soluble drug and widely used as antipschycotic and antimannic . It posses very poor bioavailability and shows significant first pass metabolism, thus there is need to improve bioavailability of Divalproex sodium, by increasing its aqueous solubility and overcoming the first pass metabolism, if it is to be delivered by oral route.

MATERIALS AND METHODS

The materials used include Divalproex sodium (gift sample from Roaqchemicals, Vadodara, Gujrat), β-cyclodextrin, Crosscarmellose sodium, Microcrystalline cellulose, Lactose, Magnesium Stearate, Talc and all others chemicals of analytical reagent grade were procured from (Research-Lab Fine Chem Industries, Mumbai).

Preparation of Divalproex sodium -β –Cyclodextrin inclusion complex:[6, 7]

Inclusion complex of Divalproex sodium in β-CD were prepared by kneading,and solvent evaporation methods as follows:

Solvent evaporation method:

Drug and carrier were mixed in the ratios (1:1, 1:2, 1:3and 1:4) in a glass mortar methanol was added portion-wise with constant continuous stirring until the mixture completely dissolved. Methanol was evaporated under reduced pressure and the resultant inclusion complexes werecollected.[6]

Kneading method:

In a glass mortar, 50% Methanol solution was added portion wise to the calculated carrier amount according to the selected drug/ carrier ratio with trituration until slurry like consistency was obtained. The drug was incorporated into the slurry and trituration was further continued for 1 h, air dried at 25^{o}C for 48 h and the resulting dried product was pulverized and passed through 80#.[7]

Solubility studies:

The 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 25^{0}C. The solutions were examined physically for the absence or presence of drug particle. Formulations of inclusion complex batches are shown in table no 1.

Table no.1: Formulations of inclusion complex batches.

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

EVALUATION OF INCLUSION COMPLEX:

Based on the results of solubility studies, the inclusion complex showing superior Solubility(1:2) was selected and subjected to further evaluation by DSC and FTIR, and for drug Content and *in vitro* release.

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 10^{0}C/min over a temperature range of 0-300^{0}C. Inert atmosphere was maintained by purging nitrogen gas at a flow of 50 mL/min. Results are shown in figure no. 2.

Infrared spectroscopy (FTIR):

Drug and various polymers were thoroughlymixed with 300 mg of potassium bromide,compressed to a 2 mm semitransparent disk andplaced in the light path for 2 min. The FTIRspectra were recorded over the wave length range from 400 - 4000 cm^{-1} using FTIRspectrometer (Jasco 4100, Japan.). Results are shown in figure no. 1

Drug content determination of prepared inclusion complex:

Inclusion complexes equivalent to 10 mg of Divalproex sodium were weighed accurately and dissolved in suitable quantity of solvent mixture methanol. The drug content was determined at 204 nm by UV spectrophotometer.Drug content determination of prepared inclusion complexshown in table no.3

***In-vitro* dissolution studies of Divalproex sodium inclusion complex:**

Preliminary dissolution tests under gastric conditions, intended for selecting the inclusion complex system with superior dissolution properties to be incorporated into the formulation of mouth dissolving tablet, were performed using the United States Pharmacopoeia (USP) dissolution apparatus II at 50 rpm. A sample equivalent to 100mg of Divalproex sodium was placed in the dissolution vessel containing 900mL of phosphate buffer pH 6.8 maintained at 37 +0.5^{0}C. At appropriate intervals, samples from the dissolution medium were withdrawn and filtered, and concentrations of Divalproex sodium were determined spectrophotometrically at204 nm. The dissolution studies were conducted in triplicate and the mean values were plotted *versus* time.*In-vitro* dissolution studies of Divalproex sodium inclusion complex shown in fig no 3.

PREPARATION OF MOUTH DISSOLVING TABLETS BY DIRECT COMPRESSION METHOD:

Divalproex sodium: carrier shows in Table no.1 represents Compositions of mouth dissolving tablets based on its superior dissolution properties in water 1:2 ratio of inclusion complex were selected. Microcrystalline cellulose was mixed thoroughly with Divalproex sodium inclusion complex. Crosscarmalose sodium added as superdisintigrant and mixed with above mixture in a glass mortar using pestle for 30 min. Magnesium stearate was then added as lubricant to above mixture and mixed for 30 min. talc is added as diluents. The resultant powder blend was then compressed under constant pressure using KBr press machine into 500mg tablet, each containing a total of 100 mg Divalproex sodium.Formulation table of mouth dissolving tablets is shown in table no 2.

Table no.2: Formulation table of mouth dissolving tablets

Ingredients (mg)	F1	F2	F3	F4	F5
Drug-β CD complex	300	300	300	300	300
Microcrystaline cellulose	150	-	100	50	75
Crosscarmellose sodium	-	150	50	100	75
Lactose	40	40	40	40	40
Talc	5	5	5	5	5
Mg Stearate	5	5	5	5	5

EVALUATION OF MOUTH DISSOLVING TABLETS: [8-11]

***Weight variation*:**

The weight variation test was carried out in order to ensure the uniformity of weight in a batch. 20 tablets were selected randomly from each formulation and weighed individually. The US Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Thickness: Tablet thickness can be measured using a simple procedure. 5 tablets were taken and their thickness was measured using Varnier calipers.

Content uniformity: Four tablets were weighed and powdered. Then weighed powder contain equivalent to 100 mg of drug was taken and transferred into a 100 ml volumetric flask containing 25ml PH 6.8 phosphate buffer. The drug was allowed to dissolve in the solvent and sufficient quantity of pH 6.8 phosphate buffer was added up to the mark. After few minute the solution was filtered, and take 5 ml from above solution were diluted up to10 ml with pH 6.8 phosphate buffer. Preparedsolution was analyzed at wavelength 204 nm using UV spectrophotometer. The amount of Divalproex sodium was estimated by using standard calibration curve of drug.

Hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester.

Friability: The friability of the tablet was measured using Roche friabilator. For tablet with an average weight 500mg or less take a sample of whole tablets corresponding to about 500mg and for tablets with an average weight of more than 500mg take sample of 10 whole tablets. Dedust and weigh accurately the required number of tablets. Place the tablets in the drum and rotate them 100 times. The tablets were dedust and weighed again. The percentage friability was measured using formula:

$$\% F = \{(W0 - W1) / W0\} \times 100$$

Where, % F = friability in percentage

W0 = initial weight of tablets

W1 = final weight of tablets

In vitro dispersion time:

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specification. Tablets were placed in each of the 6 tubes of the basket the disc was added to each tube and apparatus was run by using pH 6.8(simulated saliva fluid) maintained at 37±2°C as the immersion liquid. The assembly was raised and lowered between 30 cycles per minute. The time in seconds taken for complete disintegration of tablet with no palpable mass remaining in the apparatus was measured and recorded.

Wetting time (WT):

Five circular pieces of tissue paper (10 cm diameter) were placed in a Petri dish and10 ml water was added. A tablet was carefully placed on the surface of the tissue paper. The time required for the water to appear on the upper surface of the tablet was noted.

***In vitro* drug release studies:**

The following procedure was employed throughout the study to determine the *in vitro* dissolution rate for all the formulation. The amount of Divalproex sodium released from MDTs was evaluated by using USP dissolution apparatus II – paddle using 900 ml of pH 6.8 phosphate buffers as dissolution medium at 37±0.5°C and stirring speed of 50 rpm. 10 ml volume withdrawn at different time intervals were immediately filtered through 0.45 µ membrane filter and analyzed by using UV spectrophotometer at 204 nm. The concentration of the drug was determined from standard calibration curve.

STABILITY STUDIES: [15]

The formulations F3 were selected for stability studies on the basis of their lower disintegration time wetting time and high % drug release. The stability studies were carried out as per ICH guidelines at 40±2°C/75%±5% RH for 3 months the tablets were analyzed for hardness, friability, *in vitro* disintegration time, wetting time, drug content uniformity and % drug release. The formulation F3 showed not much variation in any parameter. The results obtained are tabulated in Table no.8. Form the results it was concluded that, formulation F3 are stable and retained their original properties.

RESULTS AND DISCUSSION

The present study involves the study of release of drug from tablets prepared using inclusion complexes of β-cyclodextrin to increasethe solubility of Divalproex sodium. The solubility of the drug was found tobe increased considerably by complexation. The results were asshown in table no.4.The drug and complexes were characterized forsolubility, DSC, FT-IR studies. The IR spectra's were shown in fig.1. Thermograms of pure drug, β-CD and β-CD complex wereshown fig 2. The results of Dissolution Profiles of inclusion complex Batches A1, A2, A3, A4 is shown in fig 3.*In vitro* dissolution profile of the formulations F1 to F5 were indicated in table no.7 and graphically shown as fig 3.Stability data for optimized formulation F3 stored at 40°C/75% RH is shown in table no.8.

Table no.3: Evaluation of inclusion complex

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

S_{KN}=solubility for kneading method

S_{EV}=solubility for solvent evaporation

D.C=drug content

Table no.4: Enhancement in Solubility of Divalproex Sodium in Folds

Solvent	Divalproex Sodium (mg/ml)	Divalproex Sodium:β-CD by S_{EV} (mg/ml)	Enhancement in folds	Divalproex Sodium:β-CD by S_{KN} (mg/ml)	Enhancement in folds
Water	0.121	0.56	4.62	0.28	2.31

Table no.5: Evaluation of pre-compression parameters

Batch No.	Bulk density* (gm/ml)	Tapped density* (gm/ml)	Hausner's ratio*	Compressibility Index* (%)	Angle repose* (θ)
F1	0.33±0.05	0.39±0.06	1.15±0.01	13.68±0.1	25.11±0.11
F2	0.35±0.08	0.40±0.09	1.11±0.03	14.13±0.2	24.35±0.10
F3	0.34±0.08	0.39±0.09	1.16±0.02	14.23±0.4	23.41±0.16
F4	0.33±0.08	0.38±0.08	1.15±0.01	12.92±0.3	24.89±0.09
F5	0.33±0.07	0.38±0.07	1.14±0.02	13.09±0.6	25.32±0.10

Table no.6: Evaluation of Mouth dissolving tablets

Batch no	Thickness (mm)	Friability %	Hardness Kg/cm^2	Weight variation** (mg)	Wetting time*(sec)	Disintegration time* (sec)	%drug content
F1	2.33 (±0.03)	0.24	3.26 (±0.2)	497.95±1.34	36.00±1.78	52	97.1 ± 1.0 (±0.27)
F2	2.49 (±0.03)	0.15	3.70 (±0.28)	497.90±1.21	38.16±1.94	47	97.0 ±0.1 (±0.21)
F3	3.68 (±0.002)	0.11	3.98 (±0.2)	498.40±1.45	26.83±1.16	40	98.6 ± 0.5 (±0.219)
F4	3.71 (0.02)	0.14	3.95 (0.1)	496.95±1.34	29.40±1.96	43	96.8 ± 0.2 (±0.271)
F5	3.76 (±0.09)	0.20	3.81 (±0.005)	498.00±1.31	28.33±1.21	45	95.29 ± 0.3 (±0.235)

Table no.7: *In vitro* dissolution profile of the formulations F1 to F5

Time in min		*In vitro* Drug release %			
	F1	F2	F3	F4	F5
2	41.4 ±0.76	47.2 ±0.53	50.2±0.65	49.2±0.65	49.7±0.60
4	52.9± 0.86	55.1±1.02	61.2±0.60	60.2±0.60	58.1±0.96
6	73.1±0.28	67±0.77	76.9 ±1.12	68.9 ±1.12	65.2±0.62
8	85.1 ±0.49	76.5 ±0.45	86.4 ±0.64	74.4 ±0.64	79.2±0.82
10	93.6±0.63	95.2±0.69	97.8±0.66	96.5±0.66	94.2±3.27

Table no.8: Stability data for optimized formulation F3 stored at 40°C/75% RH

Formulation	Parameters evaluated	After 3 months
F3	Hardness (kg/cm^2)	3.98
	Disintegration time (sec)	41
	Wetting time (sec)	26.84
	Friability (%)	0.11
	% drug release	97.8

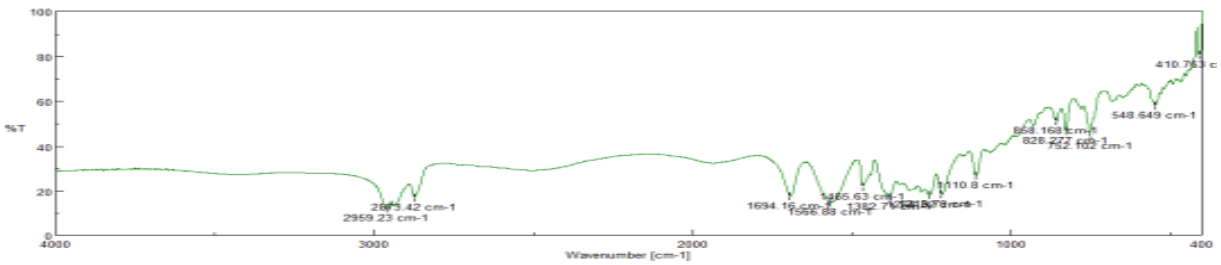

Fig. 1: (i) FTIR spectrum of Divalproex sodium

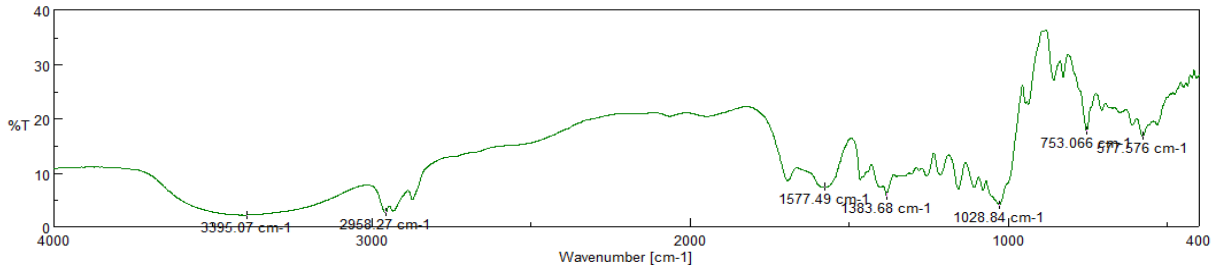

Fig. 1: (ii) FTIR spectrum of Divalproex sodium +β-CD

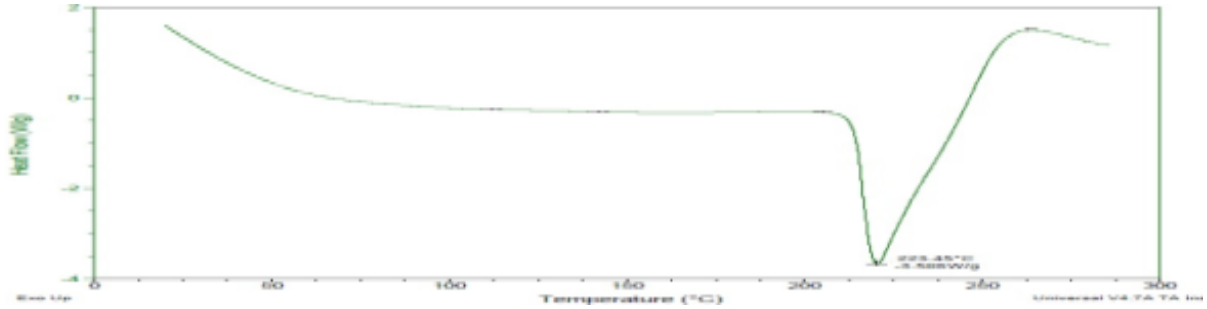

Fig. 2: (i) DSC thermogram of Divalproex sodium

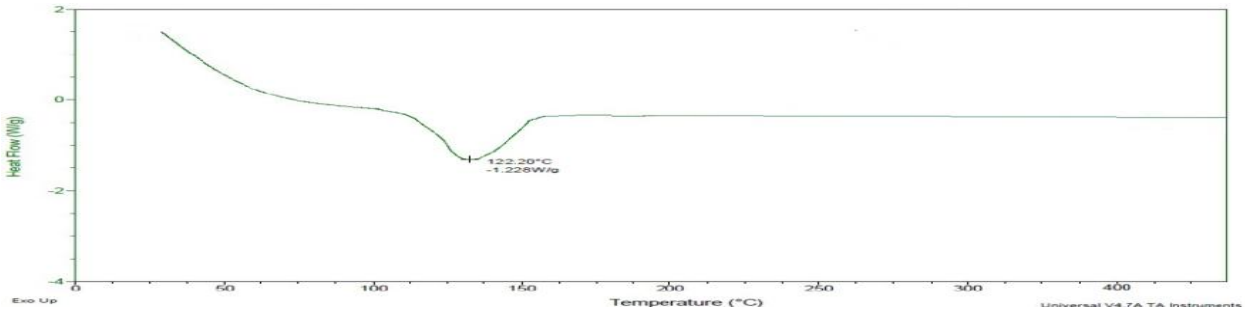

Fig. 2: (ii) DSC thermogram of β-Cyclodextrin

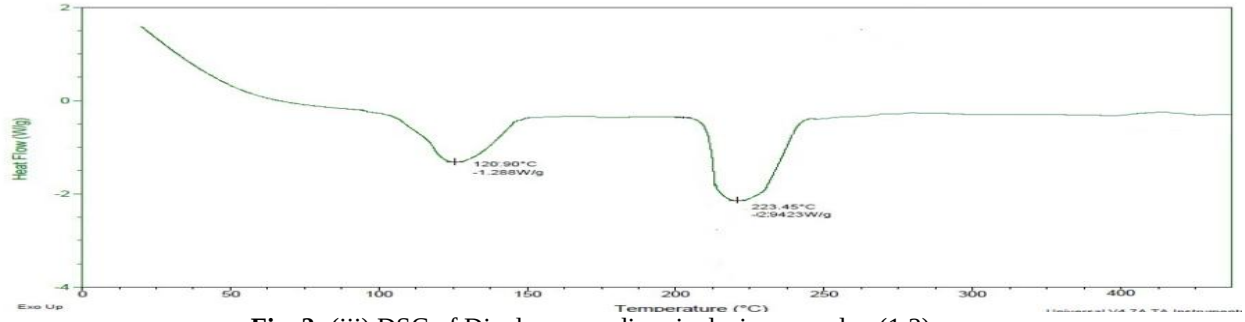

Fig. 2: (iii) DSC of Divalproex sodium inclusion complex (1:2)

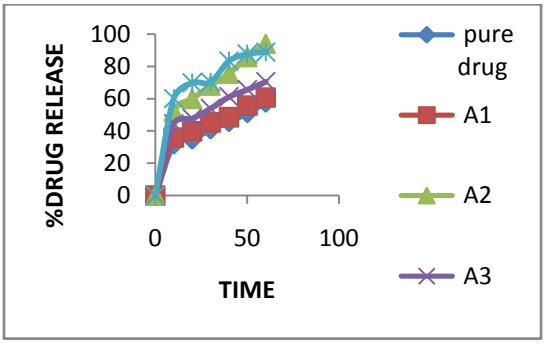

Fig 3: Dissolution Profiles of inclusion complex Batches A1, A2, A3, A4

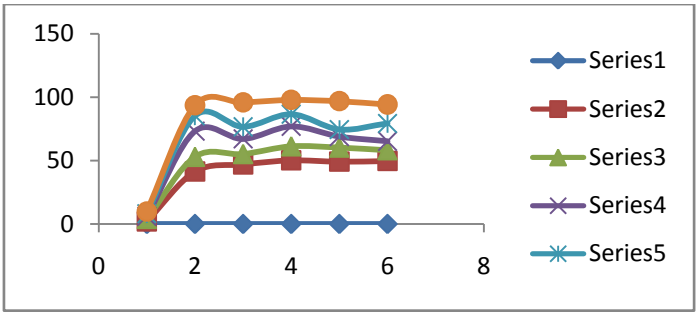

Fig 4: Comparison of *In-vitro* Drug Release Profile

CONCLUSION

Dissolution profile of Divalproex sodium was improved by complexation with β-CD by solvent evaporation method. This complex with the ratio of 1:2 (drug: carrier) has contributed for better drug release profile. The tablets were prepared by direct compression technique and evaluated for thickness, uniformity of weight, content uniformity, hardness, friability, wetting time,disintegration and *in-vitro* dissolution time and the formulations exhibited no alteration in the physical appearance or content of the tablet. The tablet prepared by direct compression method was found to be yield very reliable and best results. Result revealed that formulation F3 showed disintegration time 40sec, wetting time 26.83 sec and percent drug release was up to 97.8% % in 10 min.

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