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Research Article

Formulation and Evaluation of Orally Dissolving Tablets of Sodium Valproate and Levetiracetam

Monika Sahu*, Dr. Kaushelendra Mishra, Dr. Parul Mehta

Lakshmi Narain College of Pharmacy, Raisen Road, Bhopal, Madhya Pradesh, India.

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ABSTRACT

The objective of the present work was to formulate orally disintegrating tablets of sodium valproate and levetiracetam for rapid onset of action with an intention of increasing its therapeutic efficacy and also increase the compliance amongst geriatric, pediatric and uncooperative patients. The integrity of the drug sample was confirmed by physical characterization, melting point, solubility. Precompression blends of the ODTs were prepared and evaluated for its micromeritic properties. The angle of repose, bulk and tapped density, Hausner's ratio and Carr's Index were determined and all indicated that the prepared blends have excellent flow characteristics. Total four formulations of ODTs were prepared using direct compression method. The concentration of the super-disintegrant was varied depending on the method. Mannitol was used as the binder as well as sweetener while saccharin sodium was used as the additional taste masking agent in the formulations. All the formulations were subjected to post compression evaluation test and the results indicate that the formulation had hardness of 4 Kg/cm2, thickness of 8 mm, weight variation in the range of 2.7-4.6 %, friability of less than 1 %, drug content in the range of 97.80 to 98.60 %, wetting time from 21 to 49 seconds with water absorption ratio of more than 75 %, disintegration time of less than 30 seconds and a drug release of more than 90 % over a period of 5 minutes. The formulations were found to be stable under accelerated conditions for a period of 3 months with almost negligible change in the critical parameters.

INTRODUCTION

Drug delivery systems have been a strategic tool for extending the life cycle of drugs products and expanding its market ratio. For decades oral drug delivery has been known as the most extensively utilized route of administration among the various routes that have been explored for the systemic delivery of drugs through different dosage forms due to ease of administration and the common belief that it will provide better absorption of the drugs as do the nutrients from the food that are ingested daily.[1] Amongst the dosage forms

***Corresponding Author:** Monika Sahu
Address: *Lakshmi Narain College of Pharmacy, Raisen Road, Bhopal, Madhya Pradesh, India*
Email : monikasahu818@gmail.com

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administered via the oral route solid dosage forms like tablet and capsules are quite popular and preferred dosage forms due to ease of production, ease of marketing, dosing accuracy, and physical and chemical stability.[1] The inherent constraints presented by the GI physiology, pharmacodynamics and pharmacokinetics of the drug molecule and the formulation design need to be understood comprehensively in order to optimize a oral dosage form for delivering regulated amount of drug in to the systemic circulation.[2] The oral dissolving tablets were initially intended for the delivery of drugs like steroids and analgesics that have very low bioavailability through the GI tract and are usually administered parenterally.[3] The idea of delivery of drug in the oral cavity or wet mucosa originated back when sublingual or buccal tablets were formulated for delivery of drugs. These sublingual or buccal tablets presented basic disadvantage as the patient's impulse to crunch and swallow the tablet. [4-7] The concept of orally dissolving tablets (ODTs) was tried and tested for several drugs but not all drugs but it was found that not all ODTs had sufficient buccal absorption but the relatively small tablet weight and the fast disintegration of the tablet helped in enhancing the buccal absorption of these drugs. The initial ODTs utilized effervescence as the technology of disintegration and were designed especially for children to take vitamin pills. The European Pharmacopoeia adopted the term orodispersible tablets for defining the tablets that need to be placed in the buccal cavity where it disperses before swallowing.[8,9] In order to cater the patient with better options, the melt in mouth or mouth dissolving tablet (MDTs) delivery system was innovated wherein the formulation gets dissolved in the saliva instead of dispersing.[10] These mouth dissolving tablets do not need water to swallow the disintegrated tablet instead the disintegrated formulation dissolves in the saliva and the pharmaceutically active agent is absorbed through the mucosa of the oral cavity.

MATERIAL AND METHODS

Preformulation Studies of sodium valproate[11]

Physical characterization, melting point and solubility

The procured sample of sodium valproate was observed for its appearance, odor and color in order to characterize the physical parameters. Melting point of the sample was determined by open capillary method. In order to check the solubility qualitative method was used. A small amount of the procured sample was taken in test tubes and 1 mL of different solvents was added to the tubes. The tubes were agitated to allow for solubilization of the drug and were physically observed for presence or absence of the sample particles in them.

Calibration curve of sodium valproate in water[12]

Sodium valproate 33.5mg (0.2mmol) was dissolved in 1ml acetonitrile. To this, 200µl of HCl was added and allowed to stir for 30 minutes. DMAP solution (30mg/0.5ml acetonitrile) and EDC (40mg/0.5ml acetonitrile) were added to the Na valproate solution and were mixed together. Trichlorophenol (40mg/0.5ml acetonitrile) was then added to the mixture and stirred for 2 hours. The mixture was allowed to dry to obtain powder which was used for UV spectroscopic analysis. An accurately weighed quantity of 10 mg of the above powder was taken in a 100 mL volumetric flask. To it was added 10 mL of acetonitirile shaken well until the drug completely dissolved. From this, 1 mL of the solution was pipetted out and made up to 10 mL with distilled water. From this 0.5, 1.0, 1.5, 2.0 and 2.5 mL of solutions are pipetted out in separate standard flasks and the volume was made up to 10 mL with distilled water. The absorbance is measured at 254 nm using UV-Spectrophotometer.

Preformulation Studies of levetiracetam

Physical characterization, melting point and solubility

The procured sample of levetiracetam was observed for its appearance, odor and color in order to characterize the physical parameters. Melting point of the sample was determined by open capillary method. In order to check the solubility qualitative method was used. A small amount of the procured sample was taken in test tubes and 1 mL of different solvents was added to the tubes. The tubes were agitated to allow for solubilization of the drug and were physically observed for presence or absence of the sample particles in them.

Calibration curve of levetiracetam in water[13]

An accurately weighed quantity of 10 mg levtiracetam pure drug was taken in a 10 mL volumetric flask. Sufficient quantity of distilled water was added to it and shaken well until the drug completely dissolved. From this, 1 mL of the solution was pipetted out and made up to 100 mL with distilled water. From this 0.5, 1.0, 1.5, 2.0 and 2.5 mL of solutions are pipetted out in separate standard flasks and the volume was made up to 10 mL with distilled water. The absorbance is measured at 220 nm uisng UV-Spectrophotometer.

Preparation of orally disintegrating tablets[14]

The ODTs of sodium valproate and levetiracetam were prepared by direct compression method according the batch formula given in Table 01. All the ingredients were separately sifted through 60 mesh sieve. The drug and microcrystalline cellulose were mixed in small portions of both and blending it to get a uniform mixture. This mixture was kept aside for blending. All the other ingredients were accurately weighed and mixed in geometrical order and tablets and blended in a double cone blender. The blend was compressed to tablets of 8 mm sizes using flat round punch using single punch tablet punching machine.

Table 01: Batch formula per tablet using direct compression method

Ingredient (mg)	Formulation code			
	F1	F2	F3	F4
Sodium valproate	5	5	5	5
Levetiracetam	5	5	5	5
Crospovidone	7	14	21	28
Saccharin Sodium	12	12	12	12
D-mannitol	109	102	95	88
Avicel PH-102	54	54	54	54
Methyl cellulose	3	3	3	3
Talc	3	3	3	3
Magnesium stearate	2	2	2	2

Precompression evaluation the formulation blends

Angle of Repose[15]

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose (θ) was then calculated by measuring the height and radius (r) of the heap of powder formed using the following formula:

$$\tan\theta = \frac{h}{r}$$

Bulk and Tapped Density

A weighed quantity of blend (10g) was taken into a graduated cylinder (50 mL) and measuring the volume of this weight. The bulk density (ρ bulk) was calculated by the formula:

ρ bulk = weight of the powder/initial volume

The above cylinder containing the powder blend was tapped until no further volume change occurs. The tapped density (ρ tap) was calculated by the formula:

ρ tap = weight of the powder/finial volume

Hausner's ratio and Carr's Index[16]

Hausner's ratio is the ratio of tapped density to bulk density and is calculated by the following formula

$$HR = \rho \text{ tap} / \rho \text{ bulk}$$

The Compressibility index is also known as Carr's Index and is calculated using the values of bulk and tapped density using the formula:

$$\text{Carrs Index} = \frac{\rho \text{ tap} - \rho \text{ bulk}}{\rho \text{ tap}} \text{ X } 100$$

Evaluation of ODTs[17]

The ODTs prepared using both the methods were subjected to evaluation of the post compression parameters (tablet evaluation) according to guidelines.

Hardness test and Friability test

The hardness of the formulated tablets was tested using Monsanto type hardness tester. Three tablets from each batch of formulation were randomly taken and the force required to break the tablets was measured using hardness tester. The friability test of the formulations was performed using a Roche type friability test apparatus. Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by the formula:

$$\% \text{ Friability} = \frac{W_{initial} - W_{final}}{W_{initial}} \text{X } 100$$

Weight variation test and Thickness

20 tablets were randomly taken and weighed to calculate the average weight of the tablets. Each of these tablets was individually weighed and the difference from average weight was calculated. The percent weight variation was calculated to determine the deviation from the average weight. The thickness of randomly selected tablets from each batch of formulation was measured using a digital vernier caliper.

Drug content

Five tablets from each formulation were weighed to determine the average weight. These tablets were crushed in a mortar then the amount of powder equivalent to 5 mg of each drug was transferred in a flask and 25 µL of HCl was added to it and the solution was allowed to stir for 30 minutes. DMAP solution (30mg/0.5mL acetonitrile) and EDC (40mg/0.5mL acetonitrile) were added to the solution and were mixed together. Trichlorophenol (40mg/0.5mL acetonitrile) was then added to the mixture and stirred for 2 hours. To this solution was added 10 mL distilled water and the absorbance of this solution was observed by UV spectrophotometery at 254 and 220 nm. The content of sodium valproate and levetiracetam was measured using the calibration curve.

Wetting time

A piece of tissue paper folded twice was placed in a small petri dish (i.d. = 6.5 cm) containing 10 mL of water, a tablet was placed on the paper, and the time for complete wetting was measured.

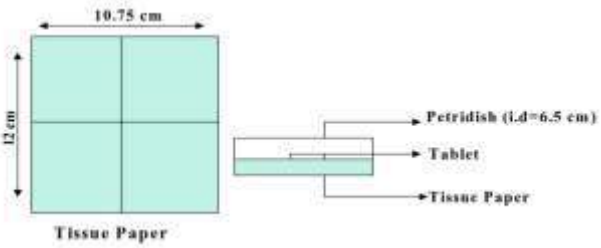

Figure 01: Diagrammatic representation of determination of wetting of tablet

Water Absorption ratio

A piece of tissue paper was folded twice and placed in a Petri dish containing 6 mL of 0.5% v/v amaranth solution (as a coloring agent) in water. A tablet was placed gently on the tissue paper, and the wetted tablet was reweighed. The water absorption ratio R was determined according the following equation

$$R = \frac{W_a - W_b}{W_b} \text{ X } 100$$

Where W_a is the weight of tablet after water absorption and W_b is the weight of tablet before water absorption.

***In vitro* disintegration time**

The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. One tablet was placed in each of the 6 tubes of the basket and a perforated disc was placed over each tablet. The assembly was raised and lowered at 30 cycles per minute in the pH 6.8 buffer maintained at 37±2°C.

***In-vitro* dissolution**

The USP type II paddle apparatus with a paddle speed of 50 rpm was used for dissolution testing for the formulated MDTs. The dissolution media used consisted of 900 mL of 0.1 N HCl and distilled water. 5 mL of samples were collected at time points of 5, 10, 15, and 30 min and the media was replenished with the same volume of fresh media.

Short term stability study

The formulated MDTs were randomly selected and subjected to three-month stability study at 25°C/ 60% and 40°C /75 % RH. After the end of the study period, some critical parameters were evaluated.

RESULTS AND DISCUSSION

Physical characterization, melting point and solubility of sodium valproate

The physical characterization of the procured sodium valproate sample was carried out in order to confirm the identity of the drug and the results of physical characterization, melting point and qualitative solubility studies are presented in Table 02.

Table 02: Physical characterization of sodium valproate

S. No	Test	Specification	Observation
1	Color	White or off-white	White
3	Appearance	Crystalline powder	Powder
4	Melting Point	>300°C	>300°C
5	Solubility	Slightly soluble in water, methanol, ethanol	Slightly soluble in water, and methanol, soluble in acetonitrile and DMF

Calibration curve of sodium valproate

The λmax of sodium valproate was determined by scanning a 10µg/mL solution of the drug using UV spectrophotometer from 200-400 nm. The λmax was found to be 254 nm (Figure 02) and was hereafter used for determination of the drug in solution. The absorbance of 5 to 25 µg/mL solutions was measured at 254 nm by UV spectrophotometer (Table 03). The linear regression correlation was found to be 0.998 for the calibration curve in water (Figure 03).

Table 03: Calibration data of sodium valproate in water

S. No	Concentration (mg/mL)	Absorbance at 254 nm
1	5	0.195
2	10	0.418
3	15	0.615
4	20	0.798
5	25	0.996

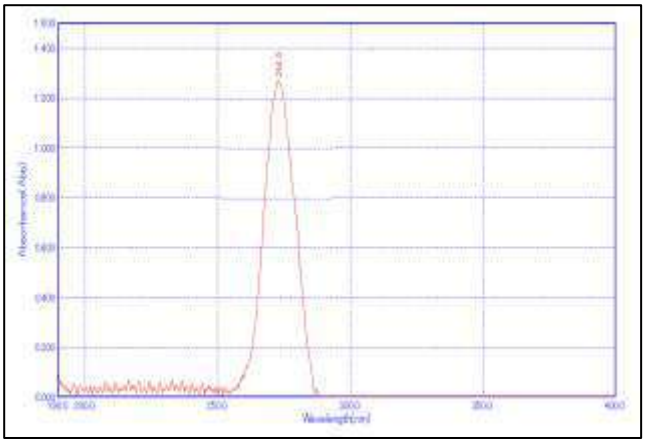

Figure 02: UV spectrum of sodium valproate after derivatization

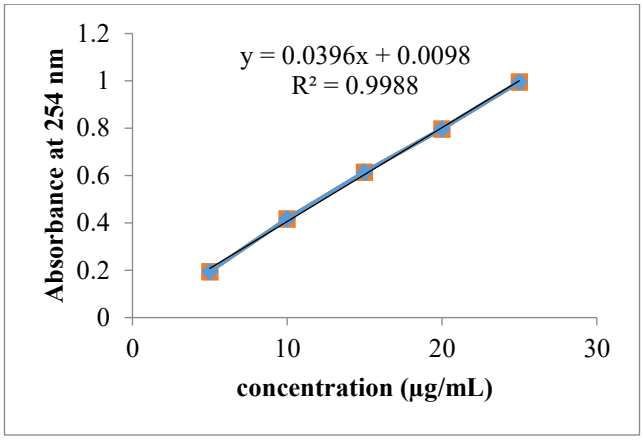

Figure 03: Calibration curve of sodium valproate

Physical characterization, melting point and solubility of levetiracetam

The physical characterization of the drug obtained was carried out in order to confirm the identity of the drug and the results of physical characterization, melting point and qualitative solubility studies are presented in Table 04.

Table 04: Physical characterization of levetiracetam

S. No	Test	Specification	Observation
1	Color	White or off-white	White
3	Appearance	Crystalline powder	Powder
4	Melting Point	>300°C	>300°C
5	Solubility	Slightly soluble in water, methanol, ethanol	Slightly soluble in water, and methanol, soluble in acetonitrile and DMF

Calibration curve of levetiracetam

The λmax of levetiracetam was determined by scanning a 10µg/mL solution of the drug using UV spectrophotometer from 200-400 nm. The λmax was found to be 220 nm and was hereafter used for determination of the drug in solution. The absorbance of 5 to 25 µg/mL solutions was measured at 254 nm by UV spectrophotometer (Table 05). The linear regression correlation was found to be 0.9979 for the calibration curve in water (Figure 04).

Table 05: Calibration data of levetiracetam in water

S. No	Concentration (mg/mL)	Absorbance at 220 nm
1	5	0.216
2	10	0.451
3	15	0.619
4	20	0.853
5	25	1.053

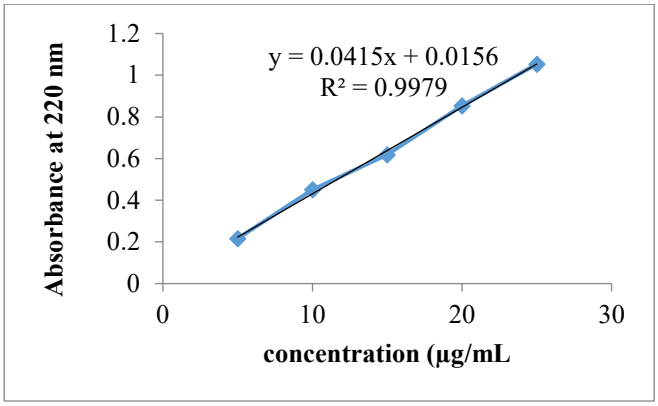

Figure 04: Calibration curve of levetiracetam

Precompression Parameters of the formulation blends

All the formulations were subjected to preformulation testing of the blends in order to ascertain their suitability for compression. The bulk and tapped density, angle of repose, Hausner's ratio and Carr's Index are used to determine the compressibility and flow properties of the blends. The angle of repose of all the formulation blends ranged from 29°49' to 30°18'. A θ value of less than 30° of powder or blends is known to exhibit excellent flow properties.[62] The results of precompression evaluation of the formulation blends are presented in Table 06.

Table 06: Precompression parameters of blends

Formulation Code	Bulk density (g/cm³)	Tap density (g/cm³)	Angle of repose (°)	Carr's Index (%)	Hausner's Ratio
F1	0.391	0.415	29°49'	5.78	1.06
F2	0.397	0.433	30°01'	8.31	1.09
F3	0.379	0.429	29°36'	11.66	1.13
F4	0.388	0.443	30°18'	12.42	1.14

Evaluation of ODTs

The tablets formulated after compression were evaluated for various quality control tests of solid dosage forms (tablets) in order to ensure that all the products meet the requirements of mouth dissolving tablets.

Hardness and Thickness

The hardness of tablets is an indicator of the resistance of the tablets to breakage under the condition of storage, transportation and handling immediately before use. The hardness of all the tablet formulations was less than 4 Kg/cm^2 indicating uniform hardness and sufficient mechanical strength. The thickness of all the tablets was found to be less than 8 mm and uniform. The thickness of tablets is an indicator of its appearance and exhibits the uniformity of flow of the blends in to the die cavity of the punching machine. A uniform thickness is also a requirement for design of packaging of the tablets.

Weight variation and Friability

The weight variation test was performed to ensure that the tablets of each formulation were of uniform weight, which in turn is an indicator of the uniform distribution of contents of the powder blends. The weight variation for all the formulations was found to be in the range of ±7.5% specified by the pharmacopoeias for tablets of average weight less than 324 mg. Friability testing provides an indicator of the mechanical strength of the tablets especially the external surface of the tablets which are liable to damage during packaging, handling, transit and storage of the tablets. All the formulations exhibited friability of less than 1 % indicating good mechanical strength in the tablets.

Drug content

The drug content of each formulation was determined by using the method described in experimental section and it was found that all the formulations contained drug content in the range of 97.80 to 98.60 %. The results of all the above physical parameters of the tablets formulation are presented in Table 07.

Table 07: Post compression parameters of ODT formulations

Formulation Code	Hardness (Kg/cm^2)	Thickness (mm)	Average Weight variation (%)	Friability (%)	Sodium Valproate content (%)	Levetiracetam content (%)
F1	4	8	4.6	0.61	97.80	98.30
F2	4	8	3.8	0.53	98.60	98.50
F3	4	8	2.7	0.63	98.30	98.40
F4	4	8	3.3	0.54	97.90	97.80

Wetting time and water absorption ratio

The wetting time and water absorption ratio are the indicator of the efficiency of the superdisintegrants. They exhibit the capacity of the disintegrants to absorb water and wet the tablet completely within the shortest time duration. The wetting time of the formulations ranged from 21 to 49 seconds with water absorption ratio of more than 75 % for the formulations. The results reveal that all the formulations possessed the ability to quickly disintegrate and dissolve.[64]

***In vitro* disintegration test**

The disintegration time is the minimum time that is needed by the tablets of break down in to smaller particles. The disintegration of the tablets reduces the particles size and in turn increases the total surface area that is available for dissolution of the particles in the site of disintegration. A quick disintegration implies that the drug will be absorbed quickly from the site of disintegration and dissolution thereby producing quick onset of action of the drug. It has been already discussed that the prescribed limit of disintegration for ODTs is 30 seconds and in certain cases for fast dissolving tablets it can be up to 3 minutes. All the formulations exhibited of less than 30 seconds in the *in vitro* test ranging from 18.1 to 27.2 seconds (Table 08).

***In vitro* dissolution test**

In vitro dissolution study was performed to evaluate the release profile of the drug from various formulated ODTs. The results of the study are used to relate the percentage of drug release from its dosage form as a function of time. All the formulations were found to release more than 90 % of the drug within a period of 5 minutes (Table 08). While F1 exhibited the lowest release of sodium valproate (91.20 %) as well as levetiracetam (89.70 %). On the other hand the highest amount of sodium valproate as well as levetiracetam were released from F4 (96.90 % and 97.10 %). The release rate was found to be higher in the formulations prepared by higher amount of crospovidone.

Table 08: Wetting, water absorption, disintegration and drug release of ODTs

Formulation Code	Wetting time (seconds)	Water absorption ratio	Disintegration time (seconds)	Sodium valproate release (%)	Levetiracetam release (%)
F1	49	76.8	27.2	91.20	89.70
F2	37	78.2	21.3	91.40	94.60
F3	28	83.6	18.9	96.30	96.30
F4	21	89.1	18.1	96.90	97.10

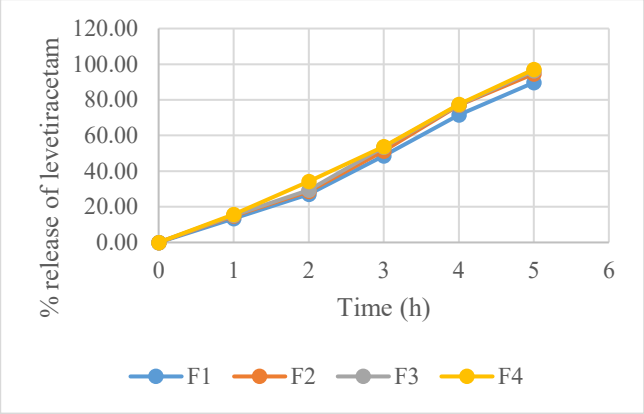

Figure 05: *In vitro* drug release levetiracetam from formulations

Stability Study

Accelarated stability testing was performed on 4 tablets of all formulations by storing them in amber colored stoppered vials at specified conditions of temperature and humidity for a period of 3 months. At intervals of one month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time. The results of stability study are presented in Table 09.

Table 09: Stability parameters at 40°C

Formulation Code	Time (days)	Hardness (Kg/cm^3)	Friability (%)	Sodium Valproate content (%)	Levetiracetam content (%)	Disintegration time (seconds)
F1	30	3	0.61	97.8	98.3	27.2
	60	3	0.62	97.8	98.3	27.3
	90	3	0.62	97.6	98.2	27.3
F2	30	3	0.52	98.6	98.6	18.9
	60	3	0.52	98.5	98.6	19
	90	3	0.52	98.5	98.5	19.1
F3	30	3	0.63	98.3	98.4	21.3
	60	3	0.63	98.3	98.4	21.3
	90	3	0.63	98.2	98.3	21.4
F4	30	3	0.54	97.9	97.9	18.1
	60	3	0.54	97.8	97.8	18.1
	90	3	0.54	97.8	97.8	18.1

DISCUSSION

The objective of the present work was to formulate orally disintegrating tablets of sodium valproate and levetiracetam for rapid onset of action with an intention of increasing its therapeutic efficacy and also increase the compliance amongst geriatric, pediatric and uncooperative patients.

Total four formulations of ODTs were prepared using direct compression method. The concentration of the super-disintegrant was varied depending on the method. Mannitol was used as the binder as well as sweetener while saccharin sodium was used as the additional taste masking agent in the formulations. All the formulations were subjected to post compression evaluation test and the results indicate that the formulation had hardness of 4 Kg/cm^2, thickness of 8 mm, weight variation in the range of 2.7-4.6 %, friability of less than 1 %, drug content in the range of 97.80 to 98.60 %, wetting time from 21 to 49 seconds with water absorption ratio of more than 75 %, disintegration time of less than 30 seconds and a drug release of more than 90 % over a period of 5 minutes.

CONCLUSION

It can be concluded from the study that orally disintegrating tablets of sodium valproate and levetiracetam could be easily formulated using super-disintegrants in order to achieve a rapid onset of drug action and peak plasma concentration over short period of time. The ODTs formulated using could be highly beneficial for the

management of epileptic seizures that require immediate attention.

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