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FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILM LOADED WITH ANTIEPILEPTIC DRUG DIVALPROEX SODIUM

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ABSTRACT

The main objective of the present work was to formulate mouth dissolving films containing divalproex to attain its maximum drug release with a very short time and also to have an easy and compliant administration of the drug through oral route. Xantham gum was used as polymer for the preparation of the films. It was able to provide adequate thickness to the films and PEG-400 used as the plasticizer was able to impart excellent flexibility to the films. The folding endurance was used as the index of flexibility of the films. All the formulated batches exhibited quick drug release, rapid disintegration and optimal mechanical strength. The formulations neither exhibited much loss nor much uptake of moisture as observed from the results of the study. The folding endurance was found to increase with increasing concentration of the plasticizer whereas thickness was found to be related to the amount of the polymer in the formulation. The amount of drug loaded in the films was independent of the polymer concentration though it was found that level 0 of the variable X1, the drug uptake by the polymeric matrix was slightly lower. All the formulations had drug content of more than 90% with the highest content in formulation DF4 (96.7±4.42%) and the lowest in DF5 (90.8±7.26%). The disintegration time of all the formulations was less than 40 seconds suggesting that all the batches of the films were quick dissolving and would be able to release the drug, rapidly. All the formulations were found to disintegrate in less than 40 seconds thereby paving the way for quick release of divalproex from the films. The ratio of polymer content and plasticizer was found to have no significant role in the disintegration time of the films.

KEYWORDS: Mouth Dissolving Formulation, Epilepsy, Divalproex, Polymers, PEG 400.

1. INTRODUCTION

Amongst all the routes that have been explored for systemic delivery of drugs the oral route of administration has been the most widely utilized route. The primary reason for the popularity of the oral route is attributed to its ease of ease of ingestion and the common belief that the absorption of drug would be better via the oral ingestion.[1] Other factors that contribute to the popularity of the oral route are ease of manufacture and the ability to accommodate wide variety of drug candidates.

Over years it has been seen that all most 60-70 % of the patients are comfortable in taking the medication by swallowing through the oral route including pediatric, adult and geriatric patients. However around 30 % of the patients experience difficulty in swallowing coated or uncoated tablets or even the hard gelatin capsules.[2] Owing to the problem associated with swallowing the demand for a better patient friendly dosage form has increased over the last decades.[3] In view of the above demand, several mucoadhesive dosage forms have been studied and include adhesive tablets, mouth dissolving tablets, chewable tablets and recently polymeric films for buccal delivery of medicaments.[4]

These mucoadhesive systems were initially developed as fast dissolving delivery systems and were foreseen as a novel technology that will be able to disintegrate rapidly in the buccal cavity and will be able to release the drug quickly in the systemic circulation.[4]

1.1 Oral cavity

The buccal cavity or oral cavity (Figure 1.1) is considered to be consisting of the lips, cheek, tongue, floor of the mouth and the hard and soft palate. The internal lining of the oral cavity is called as the oral mucosa and is divided into buccal, gingival, palatal,

sublingual and the labial mucosa. The buccal, sublingual and the mucosal tissues on the lower surface of the tongue form about 60% of the oral mucosal surface area. The oral mucosa is protected against harmful agents and fluid loss by a layer of compact epithelial cells. The oral mucosa also contains several of the sensory receptors of the tongue including the taste receptors.

1.2 Barriers to transmucosal delivery

The environment of the oral cavity is known to present numerous challenges for systemic delivery of the drugs. The prime challenge is the passage of drug from the site of release (buccal/sublingual) through the mucosal layers in to the systemic circulation. The physiological aspects that affect this passage of the drug include pH, fluid volume, permeability of the oral mucosa and enzyme activity.[5] The volume of saliva secreted daily is around 0.5 to 2.0 L whereas the constantly available volume is just half of the total volume. This is a comparatively very low fluid volume for drug release as compared to the volume available in the gastro intestinal tract. The pH of saliva is weak as compared to the GI tract and this presents challenges in ionization of the drug molecules thereby limit the aqueous solubility.

1.3 Mouth Dissolving Films[6,7]

The mouth dissolving films (MDFs) or oral films are also called as oral wafers and consist of flat polymeric films that are administered in to the oral cavity. The MDFs are a highly proven and accepted technology for the systemic delivery of over the counter products and are widely investigated by the pharmaceutical industries for delivery of prescription drugs. These films possess some features which provide them an edge over the orally disintegrating tablet.

1. Thin and elegant film
2. Eliminates fear of choking and improves patient compliance
3. Available in various shapes and sizes
4. Fast disintegration and rapid release of medicament
5. High mucoadhesive property
6. Enhanced

1.4 MDF composition

MDF is a thin film containing drug and has an area of 1-20 cm2. A single of dose of up to 30 mg of drug can be loaded in to the film. The formulation considerations play a vital role in providing the mechanical strength to the films.[9,10] The drug to be loaded in to MDF should preferably be less bitter, potent and highly lipophilic in nature. The film forming polymer should be water soluble and can be used either alone or in combination to achieve the desired film properties. The plasticizers play a vital role in maintaining the flexibility of the film and reduce its brittleness. Natural as well as artificial sweetening agents have been used to improve the palatability of the MDFs.

1.5 Epilepsy

Epilepsies are a group of CNS disorders characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements(convulsions), sensory or psychiatric phenomena12. A seizure is a sudden surge of electrical activity in the brain. A convulsion is a condition in which body muscles contract and relax rapidly and repeatedly, results in an uncontrolled shaking of the body.[13]

Epilepsy is a chronic CNS disorder characterized by brief episodes of seizures and excessive EEG discharge. It is usually associated with loss of consciousness, violent spasmodic contractions of skeletal muscles (convulsions) and autonomic hyperactivity.[14] Epilepsy is one of the most common neurological disorders. Worldwide, the prevalence is estimated to be 0.5- 1%, and there is a life time incidence of 1- 3%. It has important medical, social and psychological consequences. Epilepsy is a heterogeneous symptom complex, a chronic disorder characterized by recurrent seizures. Seizures resulting from abnormal discharge of cerebral neurons and are finite episodes of brain dysfunction. It is estimated that in India (with population more than 1 billion), there will be 6- 10 million people with epilepsy, accounting for nearly 1/5 of global burden. The current treatment of epilepsy with modern antiepileptic agents is associated with side effects, dose-related and chronic toxicity, as well as teratogenic effects, and approximately 30% of the patients continue to have seizures with current antiepileptic drugs therapy. Therefore, there is a great need for the development of cheap, effective and safe anticonvulsant agents from plants and other sources.[15]

The term epilepsy is used to define a group of neurological disorders all of which exhibit periodic seizures. Not all seizures involve convulsions. Seizures are associated with episodic high-frequency discharge of impulses by a group of neurons (sometimes referred to as focus) in the brain. What starts as a local abnormal discharge may then spread to other areas of the brain. The site of the primary discharge and the extent of its spread determine the symptoms that are produced, which range from a brief lapse of attention to a full convulsive fit lasting for several minutes, as well as odd sensations or behaviours.

The particular symptoms produced depend on the function of the region of the brain that is affected. Thus, involvement of the motor cortex causes convulsions, involvement of the hypothalamus causes peripheral autonomic discharge, and involvement of the reticular formation in the upper brain stem lead to loss of consciousness.[16]

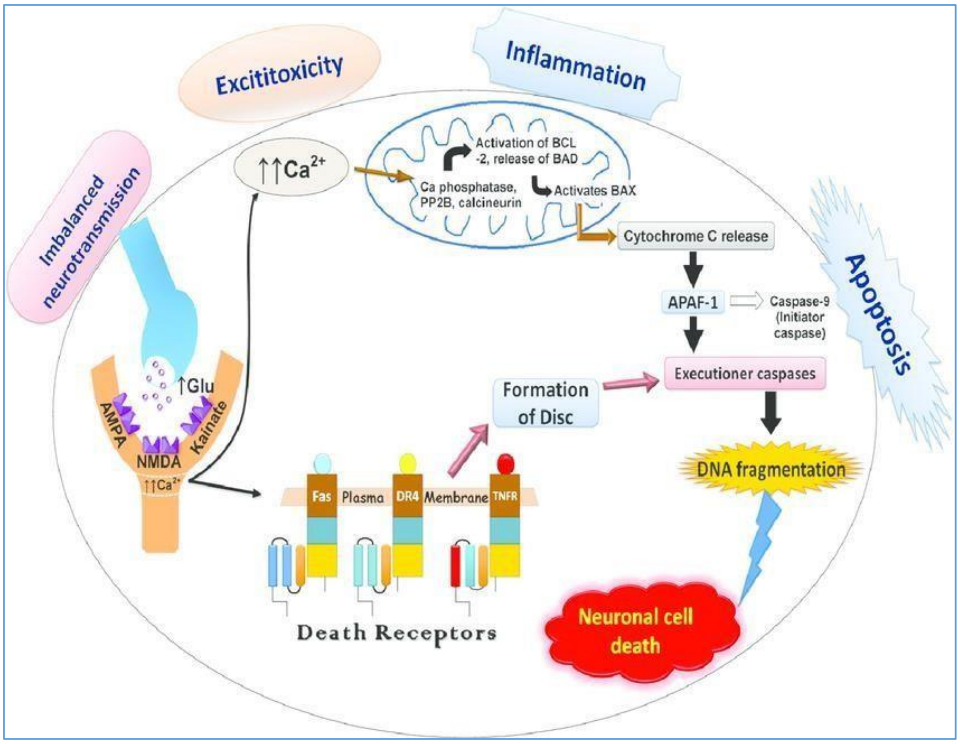

Figure 1.2: Sequence of actions in epileptic pathophysiology.

2. MATERIALS AND METHODS

2.1 Drug Profile

Divalproex

Chemical Formula: C8H15NaO2

Molecular Weight: 166.19

IUPAC Name: sodium 2-propylpentanoate Category: Anti-epileptic drug Description: Yellow crystalline powder

Solubility: Soluble in acetic acid, sparingly soluble in chloroform, practically insoluble in water

BCS Class: II

Dose: 250 mg to 750 mg daily in divided doses

2.2 Excipients Profile

2.2.1 Xanthan Gum[52]

Synonyms: Corn sugar gum; E415; Keltrol; merezan; polysaccharide B-1459; xanthan gum.

Functional category: Stabilizing agent; suspending agent; viscosity-increasing agent.

Typical properties

Acidity/alkalinity pH: 6-8 for a 1% w/v aqueous solution

Melting point: 270 °C

Heat of combustion: 14.6 J g

Specific gravity: 1.600 at 25°C

Viscosity: 1200-1600mPa.

Solubility: Practically insoluble in ethanol and ether. Soluble in cold or warm water

Description: Xanthan gum occurs as a cream or white – colored, odorless, free- flowing, fine powder.

Stability and storage conditions: Xanthan gum is a stable material. Aqueous solutions are over a wide pH range (pH 3-12) and temperatures between 60°C. Xanthan gum solutions less than1% w/v concentration may be adversely affected by higher than ambient temperatures.

Application: Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and food as a suspending and stabilizing agent. It is nontoxic, compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over a wide pH and temperature range. Although primarily used as a suspending agent Xanthan gum has also been used to prepare sustained release matrix tablets. Similarly optimum synergistic effects are obtained with Xanthan gum.

Safety: Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and food products and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient.

2.3 Materials

2.3.1 Chemicals

Divalproex was purchased from Yarrow Pharmaceuticals, Mumbai; Polyethylene Glycol (PEG 400) was purchased from Merck India Ltd. Xanthan Gum, sodium starch glycolate, Sucrose, citric acid, acetone, methanol, ethanol, hydrochloric acid, sodium hydroxide, potassium dihydrogen phosphate, sodium chloride and other chemicals and reagents required were obtained from Oxford Lab Fine Chemicals LLP, Mumbai. Distilled water was freshly prepared using glass distillation unit for the entire study.

2.3.2 Instruments and Equipments

- Magnetic Stirrer, Bio Technics India.
- Hot air oven, Bio-Technics India.

- UV Spectrophotometer, LT-2201, Labtronics, New Delhi.
- Digital pH Meter, Labtronics, NewDelhi
- Electronic Balance, Wensar

2.4 Methods

2.4.1 Preparation of Phosphate buffer (pH 6.8)[53]

0.4 g NaOH in 100 mL distilled water was taken to prepare 0.1M NaOH solution and 44.8 mL of this solution was mixed in 100 mL of 0.1 M KH2PO4 (prepared by dissolving 1.361 g in 100 mL distilled water) and the volume was made up to 200 mL using distilled water.

2.4.2 Preformulation Studies[54]

In order to perform the preformulation evaluation of the drug tests of identification such as physical appearance, melting point and FTIR spectroscopy were carried out. The solubility profile of drug in various solvent systems, incompatibility study by FTIR, partition coefficient and quantitative estimation of drug was also studied.

2.4.2.1 Physical Characterization

Color & physical state- A small quantity (unmeasured) of divalproex was taken in a clean watch glass and observed in well illuminated area.

Taste & Odor - A very small quantity of divalproex was placed on the tip of tongue to determine the taste and the odor was also determined by smelling the drug.

2.4.2.2 Solubility Profile of Drug

A solubility of divalproex was qualitatively determined by adding solvent in small and incremental amounts to test-tube containing fixed amount of drug. After each addition, the tube was shaken vigorously and visually examined for the presence of undissolved solute particles.

2.4.2.3 Melting Point

The melting point of the procured drug sample was determined by open capillary method and has been reported uncorrected.

2.4.2.4 Partition Coefficient[55]

The partition coefficient of divalproex was determined by using butanol as oil phase (10 mL) and water as aqueous phase (10 mL) in a separating funnel. 5 mg of drug was added and both the phases were mixed by shaking vigorously. The drug was allowed to dissolve and kept overnight undisturbed to separate the phases. The butanol and water were withdrawn in a conical flask and then analyzed by UV spectrophotometer against their respective blank solution and the partition coefficient was calculated by following formula.

Ko/w = Concentration of drug in butanol/ Concentration of drug in water

2.4.2.5 Calibration curve of divalproex[56]

A UV spectrophotometric method was utilized in the present study for the evaluation of divalproex content in the samples. The construction of calibration curve was done using the concentration range 10-50 µg/mL.

2.4.2.5.1 Standard curve in water

Divalproex 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 Divalproex 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. 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.

2.4.3 Preparation of divalproex MDFs[57,58]

The preparation of divalproex films was done using 32 factorial approach using xanthan gum as the variable X1 and PEG as variable X2. Both the variables were used at three different levels (+1, 0, -1) to obtain 9 different formulations. The design table for formulations has been presented as table 4.1.

Solvent casting method has been the most predominantly used method to prepare smooth films. The MDFs of divalproex were herein also prepared using the solvent casting method. An aqueous solution of the polymer was prepared by dissolving xanthan gum (table 4.2) in 5 mL of distilled water and kept aside to remove any trapped air bubbles. Divalproex was dissolved in very small quantity of solvent and stirred to dissolve in the polymer solution. All the other excipients of MDF such as plasticizer, sweetener, saliva secreting agent etc were dissolved separately in distilled water. The excipient solution was mixed with continuous stirring to the polymer solution and continued stirring at 1000 rpm for further 15 minutes. The mixture thus obtained was casted on petriplates as a film and dried in hot air oven at 50°C for 24h. After 24 h the films were cautiously peeled off from the petriplates using forceps and observed for any imperfections. The films were wrapped in aluminum foils and stored in desiccator until further use.

Table 2.1: Design table for formulation of MDFs of divalproex.

Formulation Code	DF1	DF2	DF3	DF4	DF5	DF6	DF7	DF8	DF9
X1	-1	0	+1	-1	0	+1	-1	0	+1
X2	-1	-1	-1	0	0	0	+1	+1	+1

Table 2.2: Composition of MDFs of divalproex.

S. No	Formulation	DF 1	DF 2	DF 3	DF 4	DF 5	DF 6	DF 7	DF 8	DF 9
1	Divalproex (mg)	96.2	96.2	96.2	96.2	96.2	96.2	96.2	96.2	96.2
2	Xanthan gum (mg)	150	200	250	150	200	250	150	200	250
3	Poly ethylene glycol (mg)	50	50	50	60	60	60	70	70	70
4	Sodium starch glycolate (mg)	10	10	10	10	10	10	10	10	10
5	Citric acid (mg)	5	5	5	5	5	5	5	5	5
6	Sucrose (mg)	10	10	10	10	10	10	10	10	10
7	Vanillin (mg)	5	5	5	5	5	5	5	5	5
8	Water (mL)	QS	QS	QS	QS	QS	QS	QS	QS	QS

Calculation of dose[59]

Area of petridish = 38.465 cm^2
No. of films of 2 cm^2 in whole plate = 19.23
Amount of drug in each film = 5 mg
Total amount of drug required = 96.16 mg
Label claim of films = 5 mg

2.4.4 Evaluation of MDFs[28,60,61]

2.4.4.1 Weight variation

The randomly selected films (10 nos.) from each formulation were weighted to calculate the average weight and then individually weighed using a high sensitivity electronic weighing balance. The percent variation in weight of the films from the average weight was recorded to calculated.

2.4.4.2 Thickness

The thickness of each film was measured at different positions by using Vernier calliper and the average thickness was calculated.

2.4.4.3 Folding endurance

Folding endurance was evaluated by folding repeatedly one film from the same place till it cracked or tore off. The number of times a film could be folded from the same place without breaking/ cracking provided the value of folding endurance.

2.4.4.4 Drug content test

The film was allowed to dissolve in 100mL of phosphate buffer pH 6.8 that has been enriched with 1% sodium lauryl sulfate. After the complete dissolution of the film, the amount of divalproex was estimated spectrophotometrically by measuring the absorbance at 254 nm.

2.4.4.5 Moisture Content

Films of 2 cm2 areas were cut out, accurately weighed and stored in desiccator over fused anhydrous calcium chloride. After 24 h the films were removed and reweighed. The percent moisture content of the films was calculated by the following formula

% Moisture content = (Initial weight – Final weight)/Initial weight x 100

2.4.4.6 Moisture uptake

The pre-weighed films were exposed to relative humidity of 84% at 28°C for three days using a saturated solution of sodium chloride in a closed desiccator. After 3 days the films were removed from the desiccator and reweighed. The amount of moisture absorbed by the films was computed using the following formula

% Moisture uptake = (Final weight – Initial weight)/Initial weight x 100

2.4.4.7 In-Vitro Disintegration time

In order to determine the disintegration time, the films were placed on glass petriplates containing 10 mL of distilled water. The time required for breaking of the film was recorded as the in vitro disintegration time of the film.

2.4.4.8 In-Vitro Dissolution Study

A film of 2 cm2 was placed in a glass petriplate and 25 mL of dissolution medium (phosphate buffer pH 6.8) was added to it. The solution was continuously stirred at 100 rpm for the entire period of the study. Aliquots of 2.5 mL were withdrawn at regular intervals of 1, 2, 3, 4, 5 and 10 minutes replenishing the medium with equal volume of fresh buffer. The collected samples were filtered and the concentration of divalproex in each sample was estimated by measuring its absorbance at 254 nm using UV spectrophotometer.

2.4.4.9 Stability Study[61,62]

The prepared formulations were kept for stability studies according to the International Conference on Harmonization (ICH) guidelines. The films were packed in aluminum foil and stored in stability chamber at accelerated conditions of testing, maintained at 40°C / 75 % RH for a period of 3 months and assessed for physical appearance, drug content, in vitro disintegration time and

drug release at monthly intervals and the results were reported.

3. RESULTS

The objective of the present investigation was to formulate mouth dissolving films of divalproex and evaluate it for various parameters. A 3^2 factorial approach with polymer concentration (X_1) and plasticizer concentration (X_2) as the independent variables and drug content in the films as the dependent variable was used for the formulation of different batches of the films. The results obtained from the study are presented in the following sections.

Preformulation Studies

Preformulation studies were carried out for divalproex for determination of its physical and chemical properties and also to confirm the specifications of the sample.

3.1.1 Physical Characterization

The results of the physical characterization of the pure drug are reported in table 3.1.

Table 3.1: Physical characteristics of divalproex.

S.No.	Test	Specification	Observation
1.	Appearance	White or off-white	White
2.	Taste	Tasteless	Not tested
3.	Odor	Odorless	Odorless
4.	State	Crystalline	Crystalline

The available literature and data confirm the physical characteristics of the drug.

3.1.2 Solubility profile of drug

The solubility of the pure drug was determined in various solvents and the result is reported in table 5.2.

Table 3.2: Solubility of divalproex.

S. No.	Solvent	Solubility
1.	Methanol	Slightly Soluble
2.	Acetonitrile	Soluble
3.	Water	Slightly Soluble
4.	Dimethyl formamide	Soluble

3.1.3 Melting Point

The melting point was determined using open capillary method and the result is reported in table 5.3. It was found to be equivalent to already reported results.[16]

Table 3.3: Melting Point of divalproex.

Test	Specification	Observation
Divalproex	222°C	220-225°C

3.1.4 Partition Coefficient

The partition coefficient study was performed and the log P value was found to be

The literature reveals the experimental log P value of 3.0 for the drug.[18]

3.1.5 Compatibility study

The FTIR spectrum of divalproex and a physical mixture of dialproex, xanthan gum and PEG suggested on interaction amongst the drug and the polymers. None of the characteristic peaks of divalproex were found to be affected by the physical mixture.

Table 3.4: Calibration data for divalproex.

S No	Concentration (µg/mL)	Absorbance at 254 nm
1	10	0.216
2	20	0.523
3	30	0.801
4	40	1.014
5	50	1.224

3.2 Evaluation of MDFs

3.2.1 Physical Parameters of films

The evaluation of the various physical properties of the formulated batches of films was performed as per the reported procedures and the results obtained are reported in table 5.5 and figure 5.5.

Table 3.5: Physiochemical Parameters of films.

Formulation Batch	Weight Variation* (%)	Thickness (µm)#	Folding Endurance#	% Moisture loss#	% Moisture uptake#
DF1	1.037±0.003	51.33±0.57	97.33±1.15	5.7±0.001	3.8±0.001
DF2	1.852±0.002	51.66±2.30	86.67±1.52	6.0±0.003	3.2±0.002
DF3	1.767±0.005	56.33±1.52	101.33±4.16	6.7±0.001	4.6±0.001
DF4	1.816±0.025	54.33±1.15	86.0±1.73	6.3±0.002	5.8±0.001
DF5	0.875±0.004	55.66±2.51	75.0±1.73	6.7±0.001	5.7±0.003
DF6	1.822±0.006	60.33±1.52	91.33±1.52	6.8±0.004	5.8±0.003
DF7	2.483±0.012	58.0±2	97.33±1.15	6.7±0.002	6.0±0.001
DF8	2.148±0.029	59.33±0.57	100.67±1.15	6.8±0.003	6.1±0.002
DF9	2.335±0.335	71.33±1.52	122.67±3.05	7.0±0.001	6.1±0.001

*Mean ± SD of 10 replicates; #Values are mean ± SD of 3 replicates

The thickness of the films was measured at three different locations to ensure the uniformity of the results. The weight variation was calculated as deviation from the average weight and is reported as the percentage weight variation obtained from 10 films. The folding endurance was found to increase with increasing concentration of the plasticizer whereas thickness was found to be related to the amount of the polymer in the formulation.

3.2.2. Drug content estimation in films

The evaluation of drug content in the prepared film formulations was performed as per the method reported by Velmurugan *et al*[55] and the amount of drug present in the formulations was calculated on the basis of absorbance of the sample at 254 nm in UV spectrophotometer. The results are reported in table 5.6 and figure 3.6.

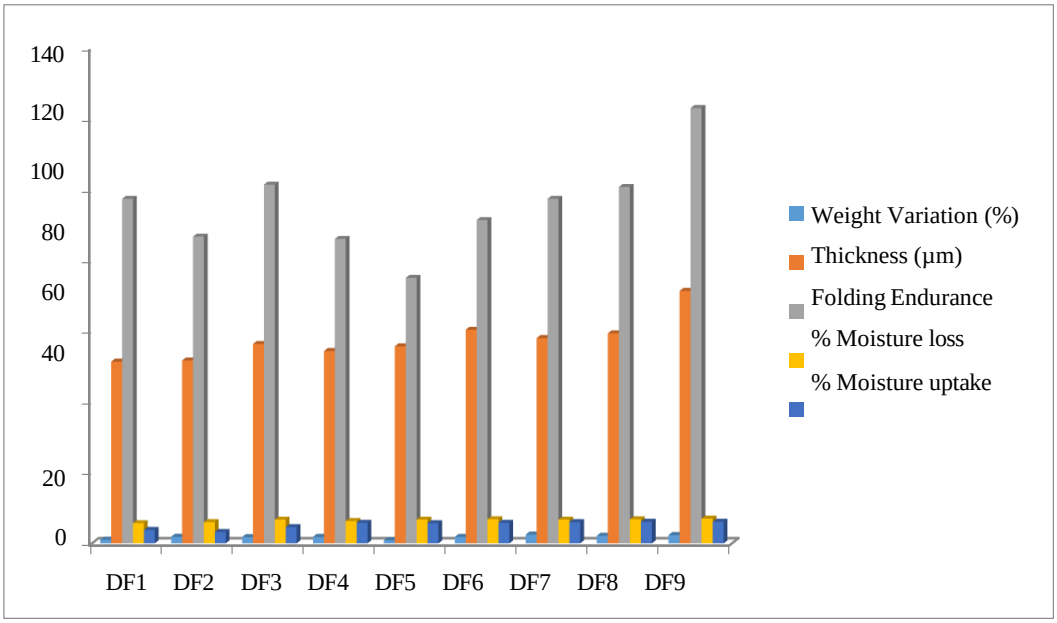

Figure 3.5: Physical characters of the prepared films.

Table 3.6: Drug content in the MDFs.

Formulation	% Drug Content
DF1	95.6±3.18
DF2	92.0±2.31
DF3	96.6±5.89
DF4	96.7±4.42
DF5	90.8±7.26
DF6	92.8±7.26
DF7	93.8±6.33
DF8	93.1±7.66
DF9	95.7±5.33

The results show that all the formulations had drug content of more than 90% with the highest content in formulation DF4 (96.7±4.42%). The amount of drug loaded in the films was independent of the polymer concentration though it was found that level 0 of the variable X1, the drug uptake by the polymeric matrix was slightly lower.

3.2.3 In vitro disintegration of MDFs

The *in vitro* disintegration of the films was performed using the petridish method in order to ascertain that the films will provide a rapid release of the divalproex. The results obtained for disintegration study of the films is shown in table 5.7.

Table 3.7: Disintegration time of the MDFs.

Formulation	Disintegration time (sec)
DF1	33
DF2	35
DF3	35
DF4	37
DF5	36
DF6	36
DF7	37
DF8	38
DF9	38

The disintegration time of all the formulations was less than 40 seconds suggesting that all the batches of the films were quick dissolving and would be able to release

the drug, rapidly. The amount of the disintegrating agent was therefore effective in maintaining the quick breakdown of the films.

3.2.4 In vitro release study

The release of divalproex from the prepared films using different concentration of xanthan gum is presented in table 5.8. All the formulations were found to disintegrate in less than 40 seconds thereby paving the way for quick release of divalproex from the films. The ratio of polymer content and plasticizer was found to have no significant role in the disintegration time of the films.

Table 3.8: *In vitro* drug release of formulations.

Time (minutes)	% Drug Released								
	DF1	DF2	DF3	DF4	DF5	DF6	DF7	DF8	DF9
0	0	0	0	0	0	0	0	0	0
1	24	26	23	24	21	20	24	19	24
2	33	34	31	30	33	29	35	31	30
3	40	45	34	38	41	38	46	44	41
4	52	56	48	49	52	51	54	55	53
5	68	70	64	61	66	64	68	64	66
10	92	91	88	94	87	91	93	92	89

The results reveal that all the film batches were able to release almost the whole quantity of drug within 10 minutes. The maximum amount of drug was released by DF4 (94%) while DF5 released the lowest amount of drug (87%) in the same period.

Table 3.9: Drug release kinetics.

Formulation Code	Zero order $_R2$	First order $_R2$	Higuchi's model $_R2$	Peppas model $_R2$
DF1	0.915	0.970	0.979	0.741
DF2	0.887	0.987	0.986	0.786
DF3	0.922	0.975	0.967	0.753
DF4	0.950	0.926	0.974	0.663
DF5	0.900	0.993	0.985	0.826
DF6	0.937	0.971	0.976	0.748
DF7	0.906	0.969	0.991	0.742
DF8	0.923	0.975	0.986	0.762
DF9	0.908	0.987	0.982	0.787

Rom the above table it can be concluded that the formulations are following mixed order kinetics. The best fitting model (First order and Higuchi's model) suggest that the drug release is concentration and time dependent and is a case II diffusion pattern.

Stability Study

Stability study has been performed on all the films for a short duration of time. The films were stored at 40°C at 75% relative humidity and tested at the end of 1 and 3 months. The results obtained were found to be in permissible limits and are shown in table 5.10 & 5.11. No significant difference was observed in the tested parameters at the end of the study.

Table 3.10: Results of stability study (DF1-DF5).

Parameter	DF1		DF2		DF3		DF4		DF5	
	1 mont h	3 mont h	1 mont h	3 mont h	1 mont h	3 mont h	1 mont h	3 mont h	1 mont h	3 mont h
Thickness (µm)	51	51	51	51	56	56	54	54	55	55
Folding endurance	97	97	86	85	101	99	86	85	75	75
***In vitro* disintegrat ion time (sec)**	33	33	35	36	35	36	37	37	36	36
Drug content (%)	95	94.8	91.5	91.4	96.2	96.2	96	96.1	90.4	90.2

Table 3.11: Results of stability study (DF6-DF9).

Parameter	DF6		DF7		DF8		DF9	
	1 month	3 month	1 month	3 month	1 month	3 month	1 month	3 month
Thickness (µm)	60	59	58	58	59	58	71	69
Folding endurance	91	89	97	94	100	97	102	100
***In vitro* disintegration time (sec)**	36	37	37	36	38	38	38	37
Drug content (%)	92.3	92.1	93.1	92.9	92.2	92.2	95.1	95

The films were found to be physically stable and also the disintegration time and drug content were not changed over the period of study. This suggests that the formulated films are suitable for storage and transport while retaining the efficacy of the formulation.

4. SUMMARY & CONCLUSION

SUMMARY

The main objective of the present work was to formulate mouth dissolving films containing divalproex to attain its maximum drug release with a very short time and also to have an easy and compliant administration of the drug through oral route.

Xantham gum was used as polymer for the preparation of the films. It was able to provide adequate thickness to the films and PEG-400 used as the plasticizer was able to impart excellent flexibility to the films. The folding endurance was used as the index of flexibility of the films.

All the formulated batches exhibited quick drug release, rapid disintegration and optimal mechanical strength. The formulations neither exhibited much loss nor much uptake of moisture as observed from the results of the study. The folding endurance was found to increase with increasing concentration of the plasticizer whereas thickness was found to be related to the amount of the polymer in the formulation.

The amount of drug loaded in the films was independent of the polymer concentration though it was found that level 0 of the variable X1, the drug uptake by the polymeric matrix was slightly lower. All the formulations had drug content of more than 90% with the highest content in formulation DF4 (96.7±4.42%) and the lowest in DF5 (90.8±7.26%).

The disintegration time of all the formulations was less than 40 seconds suggesting that all the batches of the films were quick dissolving and would be able to release the drug, rapidly. All the formulations were found to disintegrate in less than 40 seconds thereby paving the way for quick release of divalproex from the films. The ratio of polymer content and plasticizer was found to have no significant role in the disintegration time of the films.

The formulations were also found to be able to release almost complete drug content within a period of 10 minutes. The maximum amount of drug was released by DF4 (94%) while DF5 released the lowest amount of drug (87%) in the same period. The release kinetic modeling of the results showed a mixed kinetic obeying with first order kinetics and Higuchi model being the best fitting models for release. The best fitting model (First order and Higuchi's model) suggest that the drug release is concentration and time dependent and is a case II diffusion pattern.

The accelerated stability study of the films was performed for 3 month duration and the results show that the films were physically stable with no change in the disintegration time and drug content.

The formulation DF4 that contained the maximum drug content and was able to release the maximum amount of drug within a period of 10 minutes was suggested to be the best formulation of all the batches of the films formulated.

CONCLUSION

The objective of the present study was to formulate mouth dissolving films of divalproex for rapid release of the drug for quick relief from epilepsy along with improved patient compliance and ease of administration. The results of the study were able to rationalize the use of films for rapid release of the drug using xantham gum as the polymeric matrix of the film and PEG-400 as the plasticizer. The drug release pattern from the films suggests that the mouth dissolving films can be an excellent approach for quickening the onset of action divalproex and also might improve the patient adherence to the prescribed regimen owing to the ease of self-administration of the films.

5. REFERENCE

1. Dahiya M, Saha S, Shahiwala A. A Review on Mouth Dissolving Films. Curr Drug Del, 2009; 6: 469-476.
2. Patel AR, Prajapati DS, Raval JA. Fast dissolving films as a newer venture in fast dissolving formulations. Int J Drug Dev Res., 2010; 2(2): 232-246.
3. Gavaskar B, Kumar SV, Sharan G, Madhusudan Y. Overview on fast dissolving films. Int J Pharmacy Pharm Sci., 2010; 2(3): 29-33.
4. Squier C, Kremer M. Biology of oral mucosa and esophagus. J Natl Cancer Inst Monogr, 2001; 29: 7-15.

5. Hernden V, Sankar V. New developments and opportunities in oral mucosal drug delivery for local and systemic diseases. Adv Drug Del Rev., 2011; 64(1): 16-28.
6. Dixit R, Puthli S. Oral strip technology Overview and future potential. J Control Rel., 2009; 139: 94–107.
7. Mahajan A, Chhabra N, Aggarwal G. Formulation and Characterization of Fast Dissolving Buccal Films:A Review. Der Pharmacia Lettre, 2011; 3(1): 152-65.
8. Siddiqui MDN, Garg G, Sharma P. A Short Review on A Novel Approach in Oral Fast Dissolving Drug Delivery System and Their Patents. Adv Bio Res., 2011; 5(6): 291-303.
9. Saini S, Nanda A, Monika Hooda M. Fast dissolving films (fdf) , innovative drug delivery system. Pharmacology online, 2011; 2: 919-928
10. Suresh B, Halloran D, James L. Quick dissolving films: A novel approach to drug Delivery. Drug Dev Tech, 2006; 1-7.
11. Aggarwal J, Singh G, Saini S, Rana AC. Fast Dissolving Films: A Novel Approach To Oral Drug Delivery. Int Res J Pharm., 2011; 2(12): 69-74.
12. Tripathi KD. Essentials of medical pharmacology, Jaypee brothers medical publishers (P) Ltd, 6th edition, 401-402.
13. http://www.epilepsy.com; assessed on 16/01/2024
14. Gupta B. Medicinal plants as agent of anticonvulsant activity. Int. J. Res. Dev. Pharm. L. Sci., 2012; 1(3): 126-134
15. Sandeep Kumar K, Kota K, Tahashildar J, Tahashildar J, Ragavendhra P. Antiepileptic activity of ethanolic extract of Biophytum sensitivum (L.) DC. In Animal models. Int. J. Curr. Res. Aca. Rev., 2015; 3(7): 23-30.
16. Rang HP, Dale MM, Ritter JM, Flower RJ. In: Rang and Dale's pharmacology, Elsevier publications, 7th edition, 540-543.
17. Harvey RA, Champe PC. Pharmacology, Lipincott's illustrated review, 4th edition, 173.
18. Abdelhameed AA, Abdelhafez WA, Saleh KhI, Hamad AA, Mohamed MS. Formulation and optimization of oral fast dissolving films loaded with nanosuspension to enhance the oral bioavailability of Fexofenadine HCL. Journal of Drug Delivery Science and Technology., 2023; 85: 104578. Doi: 10.1016/j.jddst.2023.104578
19. Farghaly DA, Afifi SA, Aboelwafa AA, Mohamed MI. Oral Dissolving Film of Rivastigmine: Optimization Using Factorial Design. Journal of Pharmaceutical Innovation, 2023; 18: 1892–1907. Doi: 10.1007/s12247-023-09743-4.
20. Pawar R, Raj CN. Formulation and evaluation of mouth dissolving film of desloratadine 32 by factorial design. European Chemical Bulletin, 2023; 12(6): 2476-2500.
21. Chaudhari A, Tadavi S, Patil B, Pawar S. Formulation and In Vitro Characterization of Mouth Dissolving Film of Clopidogrel Hydrogen Sulphate. Engineering Proceedings., 2023; 56: 268. Doi: 10.3390/ASEC2023-16286.
22. Naga Sowjanya J, Raja Rao P. Development, optimization, and invitro evaluation of novel fast dissolving oral films (FDOF's) of Uncaria tomentosa extract to treat osteoarthritis. Heliyon., 2023; 9: e14292. Doi: 10.1016/j.heliyon.2023.e14292
23. Shirsat VA, Hukeri AA, Govind SB. Formulation development of oral fast- dissolving sublingual film of resveratrol. International Journal of Pharmaceutical Sciencs and Research, 2023; 14(5): 2447-2466.
24. Kamalakkannan V, Sangameswaran B, Subramanian V, Syed Irfan A, Tamilarasan V. Design and evaluation of mouth dissolving film of domperidone using synthetic and natural polymers. International Journal of Creative Research Thoughts, 2023; 11(2): d739-d750.
25. Dahmash EZ, Iyire A, Alyami HS. Development of orally dissolving films for pediatric-centric administration of anti-epileptic drug topiramate – A design of experiments (DoE) study. Saudi Pharmaceutical Journal, 2021; 29: 635-347.
26. Singh S. Formulation and invitro evaluation of mouth dissolving films of amlodipine besylate. World J Pharm Pharm Sci., 2020; 9(6): 974-997.
27. Badwar MR, Borse SL, Junagade MS, Jadhav AG. Formulation and evaluation of mouth dissolving tablet of amlodipine besylate. Int J Applied Pharmaceut, 2019; 11(4): 132-139.
28. Sharma PK, Sharma PK, Darwhekar GN, Shrivastava B. Development and evaluation of fast dissolving oral film of poorly water soluble drug Felodipine. Asian J Pharmaceut, 2018; 12(1): 256-267.
29. Pawar HA, Kamat SR. Development and Evaluation of Mouth Dissolving Film of Ondansetron Hydrochloride Using Hpmc E 5 in Combination with Taro Gum and Other Commercially Available Gums. J Mol Pharm Org Process Res, 2017; 5: 138. doi: 10.4172/2329-9053.1000138
30. Raghavendra HL, Prem Kumar G. Development and Evaluation of Polymer- bound Glibenclamide Oral Thin Film. J Bioequiv Availab, 2017; 9(1): 324-330.
31. Joshua JM, Hari R, Jyotish FK, Surendran SA. Formulation of propranolol hydrochloride oral thin films for migraine prophylaxis' Int J Pharm Sci Rev Res., 2017, 42(1): 8-14.
32. Pavani S, Goutham P. Formulation development of taste masked disintegrating films of Atenolol' Innovat Int J Medical Pharm Sci., 2017; 2(2): 1-3.
33. Thonte SS, Pentewar RS, Bhusnure OG, Gholve SB, Gaikwad WM, Pujdekar.
34. AA. Formulation and evaluation oral fast dissolving films of glipizide. World J Pharm Res., 2017; 6(7): 1279-1297.
35. Thonte SS, Bachipale RR, Pentewar RS, Gholve SB, Bhusnure OG. Formulation and evaluation of oral

fast dissolving film of glibenclamide. Int J Pharmacy Pharm Res., 2017; 10(4): 15-39.
36. Gorle A, Patil G. Design, Development and Evaluation of Fast Dissolving Film of Amlodipine Besylate. Int J ChemTech Res., 2017; 10(4): 334-344.
37. Ramya Deepthi P, Satish Kumar K. Formulation and evaluation of amlodipine besylate oral thin films. Int J Pharm Sci Res., 2016; 7(1): 199-205.
38. Mekapothula LSS, Kamarajugadda J, Nettum KJ, Mohammad G, Nadendla.
39. RR. Formulation and evaluation of glibenclamide oral fast dissolving films. Eur J Biomedical Pharm Sci., 2016; 3(5): 535-542.
40. Pathan A, Gupta MK, Jain NK, Dubey A, Agrawal A. Formulation and evaluation of fast dissolving oral film of Promethazine hydrochloride using different surfactant. J Innovat Pharm Biol Sci., 2016; 3(1): 74-84.
41. Raghavendra Rao NG, Kistayya C, Gampa VK. Design and development of fast dissolving thin films of Losartan potassium. Int J Pharm Sci Drug Res., 2016; 8(1): 1-6.
42. Ali MS, Vijendar C, Sudheer Kumar D, Krishnaveni J. Formulation and evaluation of fast dissolving oral films of Diazepam' J Pharmacovigil, 2016; 4(3): 1-5.
43. Padmawar PA, Phasate PP. Formulation and evaluation of fast dissolving oral film of bisoprolol fumarate. Int J Pharm Sci Res., 2015; 6(1): 135-142.
44. Talele SG, Harak Y, Bakliwal AA, Chaudhari GN. Formulation and evaluation of mouth dissolving films of Almotriptan malate' J Pharm Biosci, 2015; 3(3): 42-52.
45. Vasavi Geedi, Swagata Dutta Roy, P.Venkateshwar Reddy formulation and evaluation of fast dissolving oral films of Zolmitriptan by natural polymers, International journal of advanced pharmaceutics, 2014; 4(1): 57-63.
46. Nagendrakumar D, Keshavshetti GG, Mogale P, Swami S, Swami H. Formulation and evaluation of fast dissolving oral film of metoprolol succinate' Int J Engg Applied Sci., 2015; 6(4): 28-36.
47. Bhatt P, Patel M. Formulation and Evaluation of Fast Dissolving Film of Rizatriptan Benzoate. Int J Medical Pharm Res., 2015; 1(2): 58-77.
48. Bahri-Najafi R, Tavakoli N, Senemar M, Peikanpour M. Preparation and pharmaceutical evaluation of glibenclamide slow release mucoadhesive buccal film. Res Pharm Sci., 2014; 9(3): 213-223
49. Maheswari KM, Devineni PK, Deekonda S, Shaik S, Uppala NP, Nalluri BN. Development and Evaluation of Mouth Dissolving Films of Amlodipine Besylate for Enhanced Therapeutic Efficacy. J Pharmaceut, 2014; http://dx.doi.org/10.1155/2014/520949.
50. Nalluri BN, Sravani B, Saisri Anusha V, Sribramhini R, Maheswari KM. Development and evaluation of fast dissolving films of sumatriptan succinate for better therapeutic efficacy. J Applied Pharm Sci., 2013; 3(8): 161-166.
51. Raju PN, Kumar MS, Reddy Ch M, Ravishankar K. Formulation and evaluation of fast dissolving films of Loratidine by solvent casting method. The Pharm Innovat, 2013; 2(2): 31-34.
52. Mujib IY, Kumari SK. Mucoadhesive buccal films of glibenclamide: Development and evaluation. Int J Pharm Investig, 2011; 1(1): 42-47.
53. https://go.drugbank.com/salts/DBSALT001257; assessed on 11/12/2023
54. https://en.wikipedia.org/wiki/Xanthan_gum assessed on 12/12/2023
55. Appendix 13.1 Buffers, In: Indian Pharmacopoeia, 1996, The Indian Pharmacopoeia Commission, Ghaziabad
56. Chaurasia G. A review of pharmaceutical preformulation studies in formulation and development of new drug molecules. Int J Pharm Sci Res., 2016; 7(6): 2313-2320.
57. Hanson KB, Hoff DJ, Lahren TJ, Mount DR, Squillace AJ, Burkhard LP. Estimating n-octanol-water partition coefficients for neutral highly hydrophobic chemicals using measured n-butanol-water partition coefficients. Chemosphere, 2019; 218: 616-623.
58. Abualhasan M, Odeh NW, Younis GN, Zeidan OF. Analytical Method Development for Sodium Valproate through Chemical Derivatization. International Journal of Analytical Chemistry, 2020; 5672183. Doi: 10.1155/2020/5672183
59. Mashru R, Sutariya V, Sankalia M, and Parikh P. Development and Evaluation of Fast-Dissolving Film of Salbutamol Sulphate. Drug Dev Ind Pharm., 2005; 31: 25–34.
60. Gavaskar B, Kumar S, Sharan G, Rao Y. Overview on fast dissolving films. Int J Pharmacy Pharm Sci., 2010; 2(3): 29-33.
61. Maheshwari KM, Devineni PK, Deekonda S, Shaik S, Uppala NP, Nalluri BN. Development and Evaluation of Mouth Dissolving Films of Amlodipine Besylate for Enhanced Therapeutic Efficacy. J Pharmaceut, 2014; http://dx.doi.org/10.1155/2014/520949.
62. Bala R, Khanna S, Pawar P. Design Optimization and In Vitro-In Vivo Evaluation of Orally Dissolving Strips of Clobazam. J Drug Del., 2014; http://dx.doi.org/10.1155/2014/392783
63. Mushtaque M, Muhammad IN, Hassan SMF, Ali A, Masood R. Development and pharmaceutical evaluation of oral fast dissolving thin film of escitalopram: A patient friendly dosage form. Pak J Pharm Sci., 2020; 33(1): 183-189.
64. Rai A, Sharma S. Preparation and Evaluation of Oral Dispersible Formulations of Amlodipine Besylate. Asian J Pharm Res Dev. 2019; 7(5): 43-56.