Formulation and evaluation of mouth dissolving film loaded with antiepileptic drug divalproex sodium

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***Abstract*—The study aimed to formulate and evaluate mouth dissolving films (MDFs) of divalproex sodium to enhance drug release rate, provide rapid onset of action, and improve patient compliance, especially among individuals with swallowing difficulties. MDFs were prepared using xanthan gum as the film-forming polymer and polyethylene glycol (PEG-400) as the plasticizer through the solvent casting method. A 3^2 factorial design was employed to optimize polymer and plasticizer concentrations. The prepared films were evaluated for physical characteristics, folding endurance, drug content uniformity, moisture content, disintegration time, dissolution profile, and stability as per ICH guidelines. The results indicated that all formulations exhibited uniform thickness, good mechanical strength, and satisfactory folding endurance. Drug content across all films exceeded 90%, confirming uniform drug distribution. In vitro disintegration occurred within 40 seconds, and more than 90% of the drug was released within 10 minutes. Among all formulations, DF4 showed the best overall performance, with 96.7% drug content and 94% drug release following first order and Higuchi diffusion kinetics. Stability studies confirmed that the optimized film retained its physical integrity and efficacy over 3 months. The developed mouth dissolving film of divalproex sodium offers a promising, patient-friendly delivery system for rapid therapeutic action in epilepsy management.**

Keywords: Divalproex Sodium, Mouth Dissolving Film (MDF), Fast Drug Release, Epilepsy.

I. INTRODUCTION

Epilepsy continues to be one of the significant health challenges worldwide that affects all age groups, from adolescence to elderly. One of the biggest problems in the treatment of epileptic seizures is the rate at which clinical action takes place, a phenomenon that may take time with oral formulation [1]. In general, such formulations must have at least a 30 minute onset time for therapeutic effect and longer times when the formulations are controlled or sustained release. This delay may not be optimal, particularly for acute seizure management [2].

Furthermore, the dysphagia or difficulty in swallowing is one of the major constrains of conventional oral hard dosage forms. This problem is common in the pediatric and geriatric population due to physiological reasons profiled including decrease in salivary secretion, weak swallowing reflexes and disorientation of muscles movement. Also, patients who feel nauseous, vomit, suffer from motion sickness or mental disease or have an allergic reaction face difficulties of taking a commercial tablet as there way. It has been suggested that 35–50% of the general population have problems swallowing solid oral pharmaceuticals [3].

To counter these challenges, drug manufacturers are increasingly looking towards mouth dissolving films (MDFs) as a novel mode of oral drug delivery to promote patient compliance and achieve efficacy in shorter periods of time. MDFs are flexible thin polymeric films, which disintegrate or dissolve in the oral cavity without water. Dosage Saliva serves as the dissolving vehicle, and on administration the drug is rapidly dispersed for absorption via the mucosa of the mouth, pharynx and esophagus. This promotes not only ease of administration, but enhanced bioavailability by escaping first-pass hepatic metabolism to some extent [4][5].

Divalproex sodium, a known antiepileptic drug is also used to treat bipolar disorder and for migraine prophylaxis. Nonetheless, because it is slightly soluble in water and has a half-life of only about 2 hours, frequent administration is required to achieve therapeutic plasma levels. The low solubility of divalproex sodium results in absorption controlled by the rate of dissolution and thus the onset of action is delayed. The drug can have better dissolution rate by incorporating proper disintegrants or film forming polymers which can in turn enhance its pharmacokinetic profile [6[[7][8].

Hence, an attempt was made to develop and evaluate mouth dissolving film of divalproex sodium with the aim to mask the taste. The objective was a patient-friendly delivery system which offers rapid onset of action, better therapeutic effect and improved compliance compared with the reference dosage form. The aim of the study was to develop MDFs using water-soluble polymers, which would provide the right balance between a good mechanical strength, uniform drug distribution and clicker dissolution, to enable efficient and comfortable oral delivery of DS.

II. MATERIALS AND METHOD

2.1 Chemicals

Chemical / Reagent	Use in Formulation
Divalproex Sodium	Active pharmaceutical ingredient (API)
Polyethylene Glycol (PEG 400)	Plasticizer to enhance film flexibility
Xanthan Gum	Film-forming polymer
Sodium Starch Glycolate	Superdisintegrant to promote rapid dissolution
Sucrose	Sweetening agent to improve palatability
Citric Acid	Saliva-stimulating agent and pH adjuster
Acetone	Solvent for polymer and excipient dissolution
Methanol	Solvent for calibration and analysis
Ethanol	Solvent for formulation and analytical preparation
Hydrochloric Acid	pH adjustment and calibration curve preparation
Sodium Hydroxide	Buffer and pH adjustment
Potassium Dihydrogen Phosphate (KH_2PO_4)	Buffer component (phosphate buffer pH 6.8)
Distilled Water	Solvent and vehicle throughout formulation

2.2 Instruments and Equipment

Instrument / Equipment	Use / Purpose
Magnetic Stirrer	For uniform stirring and mixing of solutions
Hot Air Oven	For drying the films using controlled dry heat
UV–Visible Spectrophotometer	For measuring absorbance and constructing calibration curves
Digital pH Meter	For determining and adjusting pH of buffer and formulations
Electronic Balance	For accurately weighing drugs and excipients

2.3 Preparation of Phosphate Buffer pH 6.8

A 0.1 M of sodium hydroxide solution was prepared by adding 0.4g of NaOH in 100 mL distilled water. 0.1 M potassium dihydrogen phosphate solution (PDP) was also prepared by dissolving 1.361 g of KH 2 PO 4 in 100 mL of distilled water. Phosphate buffer (pH 6.8) was prepared by mixing 44.8 mL of the NaOH with 100 mL of the KH_2PO_4 solution and making up to a volume of 200 mL with distilled water.

2.4 Mouth Dissolving Films (MDFs) of Divalproex Sodium were prepared

The MDFs were fabricated according to 3^2 full factorial design by varying xanthan gum (X_1 reversible 3 levels -1, 0 and +1) and PEG 400 (X_2 in three concentrations -1, 0 and +1) resulting into nine formulations. Composition design. The solvent casting technique was used because of its reproducibility and ability to generate smooth, even films. An aqueous polymer solution (APS) was initially obtained by dissolving 1% (w/v) xanthan gum in 5 mL of distilled water and allowing to stand for about 24 h to remove air bubbles. Divalproex sodium was dissolved in a small amount of solvent and added to the polymer solution. Plasticizer, sweetener and saliva-stimulating agents were solubilized in distilled water and added to the polymer–drug mixture. The mixture was stirred at 1000 rpm during 15 min to get homogenization.

The solution obtained was poured on to the clean Petri-plates, spread evenly and dried in a hot air oven at 50°C for 24 h. Dried films were peeled by hand using tweezers and inspected for any surface irregularities. Film sheets were ultimately wrapped in aluminum foil and kept away in a desiccator until analysis was performed.

Design table for formulation of MDFs of divalproex

Formulation Code	DF 1	DF 2	DF 3	DF 4	DF 5	DF 6	DF 7	DF 8	DF9
X1	-1	0	+1	-1	0	+1	-1	0	+1
X2	-1	-1	-1	0	0	0	+1	+1	+1

Composition of MDFs of divalproex formulations

Formulation	DF1	DF2	DF3	DF4	DF5	DF6	DF7	DF8	DF9
Divalproex (mg)	96.2	96.2	96.2	96.2	96.2	96.2	96.2	96.2	96.2
Xanthan gum (mg)	150	200	250	150	200	250	150	200	250
Polyethylene glycol (mg)	50	50	50	60	60	60	70	70	70
Sodium starch glycolate (mg)	10	10	10	10	10	10	10	10	10
Citric acid (mg)	5	5	5	5	5	5	5	5	5
Sucrose (mg)	10	10	10	10	10	10	10	10	10
Vanillin (mg)	5	5	5	5	5	5	5	5	5
Water (mL)	QS	QS	QS	QS	QS	QS	QS	QS	QS

Calculation of dose

Area of petridish = 38.465 cm²

No. of films of 2 cm² 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

III. EVALUATION

The prepared mouth dissolving films (MDFs) of divalproex were evaluated for various physicochemical and performance parameters including weight variation, thickness, folding endurance, drug content, moisture content, moisture uptake, in vitro disintegration time, in vitro dissolution, and stability studies.

3.1 Weight Variation- Ten films were randomly selected from each formulation batch. Each film was weighed individually using a high-sensitivity electronic analytical balance, and the average weight was calculated. The percentage deviation of individual film weights from the mean was determined to evaluate uniformity.

3.2 Thickness- Film thickness was measured at three different points using a calibrated Vernier caliper, and the mean thickness for each formulation was recorded. *This ensured uniformity and reproducibility in film preparation.*

3.3 Folding Endurance Folding endurance was determined manually by repeatedly folding a film at the same location until it broke or cracked. The number of folds required to cause film breakage was noted as the folding endurance value, indicating the mechanical strength and flexibility of the film.

3.4 Drug Content Uniformity- Individual films were dissolved in 100 mL of phosphate buffer (pH 6.8) containing 1% sodium lauryl sulfate to ensure complete dissolution. The solution was analyzed spectrophotometrically at 254 nm to determine the amount of divalproex present. Drug content uniformity ensured accurate dosing across all films.

3.5 Moisture Content- Films with an area of 2 cm² were accurately weighed and stored in a desiccator containing fused anhydrous calcium chloride for 24 hours. After removal, the films were reweighed, and the percentage moisture content was calculated.

3.6 Moisture Uptake- Pre-weighed films were placed in a closed desiccator maintained at 84% relative humidity (using a saturated sodium chloride solution) at 28 ± 2°C for three days. The films were then reweighed, and the percentage moisture uptake was determined. This parameter indicated the hygroscopic nature and stability of the films under humid conditions.

3.7 In Vitro Disintegration Time- The in vitro disintegration time was measured by placing the film on a glass Petri dish containing 10 mL of distilled water at room temperature. The time required for complete breaking or disintegration of the film was recorded as the in vitro disintegration time.

3.8 In Vitro Dissolution Study- A film sample of 2 cm² was placed in a glass Petri dish containing 25 mL of phosphate buffer (pH 6.8) as the dissolution medium. The system was continuously stirred at 100 rpm. Aliquots of 2.5 mL were withdrawn at 1, 2, 3, 4, 5, and 10 minutes, replacing the withdrawn volume with an equal amount of fresh buffer each time. The samples were filtered, and the concentration of divalproex was analyzed spectrophotometrically at 254 nm to determine the drug release profile.

3.9 Stability Studies- The optimized formulations were subjected to stability studies in accordance with the ICH guidelines (Q1A R2). Films were packed in aluminum foil and stored in a stability chamber maintained at 40 ± 2°C / 75 ± 5 % RH for a period of three months. Samples were evaluated at one-month intervals for physical appearance, drug content, in vitro disintegration time, and drug release characteristics. The stability data were analyzed to assess any significant changes during the storage period.

IV. RESULTS & DISCUSSION

The thickness of the films was measured at three different locations to ensure uniformity. The weight variation among all formulations ranged from 0.875 ± 0.004% (DF5) to 2.483 ± 0.012% (DF7), indicating good uniformity of the solvent casting process. The slight variation observed may be attributed to minor differences in the amount of polymeric solution distributed during casting.

The thickness of the films varied between 51.33 ± 0.57 µm (DF1) and 71.33 ± 1.52 µm (DF9). This increase in thickness with higher polymer concentration demonstrates that xanthan gum directly influences the viscosity and solid content of the film-forming solution.

Folding endurance values ranged from 75.0 ± 1.73 (DF5) to 122.67 ± 3.05 (DF9), confirming that all films possessed sufficient flexibility and mechanical strength to withstand handling. The increase in folding endurance with higher plasticizer concentration (PEG-400) can be attributed to enhanced polymer chain mobility and film elasticity.

The percentage moisture loss ranged from 5.7 ± 0.001% (DF1) to 7.0 ± 0.001% (DF9). The low moisture loss observed indicates that all films were adequately dried and maintained physical stability under ambient conditions.

The percentage moisture uptake ranged from 3.2 ± 0.002% (DF2) to 6.1 ± 0.002% (DF8 and DF9). Moisture uptake increased proportionally with xanthan gum concentration due to its hydrophilic nature, which enables absorption of atmospheric moisture.

Overall, all formulations showed acceptable physical characteristics with minimal variations. The results confirm that xanthan gum and PEG-400 combinations produced smooth, flexible, and mechanically stable films suitable for rapid oral delivery of divalproex sodium. Among them, DF9 exhibited optimal mechanical strength and controlled moisture balance, suggesting a well-balanced polymer–plasticizer ratio.

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 ± 2.00	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

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 the formulation. whereas thickness was found to related to amount of polymer in formulation.

Drug content estimation in films

The evaluation of drug content in the prepared film formulations was performed 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.

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 result show that all the formulations had drug content of more than 90% with the highest content in formulation DF4 (96.7±4.42%).

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 drug.

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

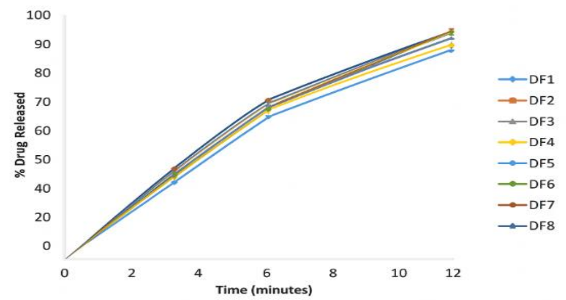
In vitro release study

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.

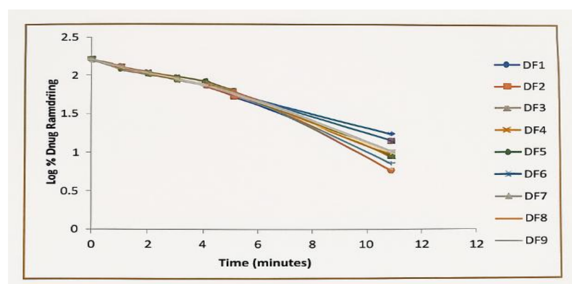
Time (minutes)	DF1	DF2	DF3	DF4	DF5	DF6	DF7	DF8	DF9
0	0	0	0	0	0	0	0	0	0
1	24	26	23	24	21	20	24	19	24
2	33	34	31	30	33	29	35	31	30
3	40	45	34	38	41	38	46	44	41
4	52	56	48	49	52	51	54	55	53
5	68	70	64	61	66	64	68	64	66
10	92	91	88	94	87	91	93	92	89

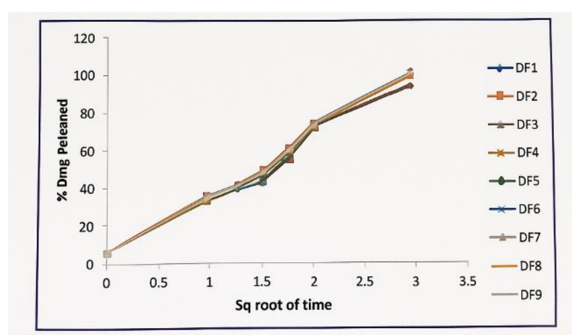
The results reveal that all the film batches were able to release almost the whole quantity of drug within 10 minutes. The maximum amount of drug was released by DF4 (94%) while DF5 released the lowest amount of drug (87%) in the same period.

Zero order plot of formulations



First order plot of formulations





Higuchi's plot of formulations

Drug Release Kinetics

Formulation Code	Zero Order (R^2)	First Order (R^2)	Higuchi's Model (R^2)	Peppas Model (R^2)
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

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.

Results of Stability Study (DF1–DF5)

Parameter	DF1 (1 month)	DF1 (3 month)	DF2 (1 month)	DF2 (3 month)	DF3 (1 month)	DF3 (3 month)	DF4 (1 month)	DF4 (3 month)	DF5 (1 month)	DF5 (3 month)
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 disintegration time (sec)	33	33	35	35	36	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 5.11: Results of Stability Study (DF6–DF9)

Parameter	DF6 (1 month)	DF6 (3 month)	DF7 (1 month)	DF7 (3 month)	DF8 (1 month)	DF8 (3 month)	DF9 (1 month)	DF9 (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.

V. CONCLUSION

The present study successfully developed mouth dissolving films (MDFs) of divalproex sodium using xanthan gum as the film-forming polymer and PEG-400 as the plasticizer. The films demonstrated desirable mechanical properties, rapid disintegration (within 40 seconds), and efficient drug release (over 90% within 10 minutes). The polymer concentration was found to influence film thickness, while plasticizer concentration improved folding endurance without significantly affecting disintegration time. Drug content across formulations remained above 90%, confirming uniformity and effective drug loading.

Among all batches, formulation DF4 exhibited the highest drug content (96.7 ± 4.42%) and maximum release (94% in 10 minutes), following first-order and Higuchi kinetics, indicating concentration- and time-dependent diffusion. Stability studies confirmed the physical and chemical stability of the optimized film over 3 months. Therefore, DF4 can be considered the most promising formulation for achieving rapid onset of action, improved patient compliance, and enhanced bioavailability of divalproex through the oral route.

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