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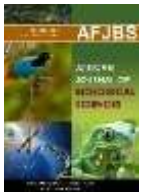

Fabrication and Characterization of Lacosamide Mouth Dissolving Films using Solvent Casting Technique

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Abstract

The pharmaceutical market is dominated by oral dosage forms, which constitute approximately 52% of total dosage forms. Traditional forms such as tablets and capsules present various challenges, including dosing inaccuracies and potential loss of active ingredients. Mouth dissolving films (MDF), have emerged as a promising alternative, enhancing compliance and ensuring precise dosing. This study focuses on the preparation and estimation of Lacosamide mouth dissolving films using the solvent casting technique. Lacosamide, an anticonvulsant with a unique dual mode of action, offers advantages in rapid onset of action and improved bioavailability when delivered through MDF. The films were prepared using hydroxypropyl methyl cellulose (HPMC) as the polymer matrix and polyethylene glycol (PEG 400) as plasticizer. Various formulations were developed and assessed for their physical and mechanical properties, drug content uniformity, disintegration time, in vitro release, and surface morphology. The optimized formulation (F3) demonstrated excellent results with rapid disintegration (within 24 seconds), high folding endurance, and nearly complete drug release i.e., 98% within three minutes. Accelerated stability studies confirmed the formulation's stability over three months. This innovative approach underscores the potential of MDF for efficient and effective Lacosamide delivery, enhancing patient compliance and therapeutic efficacy.

Keywords: Lacosamide, Mouth dissolving films, Solvent casting technique, Fast-dissolving drug delivery, Patient compliance

1. Introduction

Oral dosage forms dominate the pharmaceutical market, accounting for around 52% of the total drug delivery market (Vargason et al., 2021). However, traditional methods such as tablets and capsules pose several challenges. Issues such as the potential destruction of active components owing to crushing and imprecise liquid measurements can lead to dosing mistakes, leading to either overdose or ineffectiveness in pharmacological therapy (Bala et al., 2013). To overcome these issues, fast-dissolving drug delivery systems have emerged as a viable alternative, with oral film strips becoming particularly popular in recent years (Bala & Sharma, 2018). These gel-like wafers dissolve swiftly in the mouth, effectively releasing the

therapeutic compound and providing exact dosing (Scarpa et al., 2017). This technology is particularly beneficial for enhancing compliance among children. The advancement of transmucosal drug delivery routes has addressed many problems associated with traditional oral administration (Borges et al., 2015). The oral mucosa is highly vascularized, providing an excellent pathway for drug absorption into systemic circulation due to its high permeability. As a result, fast-dissolving films have become the preferred dose form for many drugs. Because of their vast surface area, they disintegrate quickly, which enhances adherence among patients (Bastos et al., 2022).

Lacosamide (LCM) is a personalized amino acid explored as an anticonvulsant therapeutic candidate (Beyreuther et al., 2007). LCM has a distinctive dual mechanism of action, boosting the slow ablation of voltage-gated sodium channels while not effecting fast suppression, which leads to its anticonvulsant and analgesic characteristics (Perucca et al., 2008). Clinical toxicological and pharmacological investigations in mammals such as rats, mice, rabbits, and dogs have indicated that LCM is acceptable, with a small impact on the central nervous, and respiratory, and no indication of abuse liability (Strzelczyk et al., 2017). Multiple dose toxicological investigations have demonstrated that negative consequences from both intravenous and oral ingestion of LCM are reversible, especially involving increased pharmacologic effects on the central nervous system (Beyreuther et al., 2007).

Using mouth dissolving films for Lacosamide delivery offers several benefits. These films enable a rapid onset of action by promoting quick absorption through the highly vascularized oral mucosa, bypassing the first-pass metabolism, which can otherwise reduce the drug's bioavailability (Pethe & Desai, 2016). This approach ensures precise dose, increases patient compliance, particularly for individuals who have trouble swallowing pills or capsules, and offers simplicity by removing the need for water or measurement devices (Chaudhary et al., 2013). The ease of administration and improved drug stability make mouth dissolving films a highly effective delivery system for Lacosamide (Han et al., 2019a). Given these advantages, the formulation and evaluation of Lacosamide mouth dissolving films (MDF) via the solvent casting technique represent an innovative approach to improving drug delivery and patient compliance. This study focuses on the development, optimization, and characterization of these films, aiming to leverage the benefits of fast-dissolving drug delivery systems for effective and efficient medication administration.

2. Material and Methods

2.1 Materials

Lacosamide was purchased from Hetero Labs Ltd in Baddi, India. Hydroxypropyl methyl cellulose (HPMC E5 and E15) was offered as a gift sample by BASF, Mumbai. All other substances were of analytical quality.

2.2 Preparation of Lacosamide loaded MDF

To prepare the polymeric solution (Solution A), the required amount of HPMC (E5 and E15) was dissolved in 70% distilled water. Solution B was formed by dissolving the medication, polyethylene glycol (PEG 400), and additional excipients in the remaining 30% water while swirling continuously. The solution B was then gradually incorporated into Solution A while continuously stirring. The completed mixture was kept uninterrupted for 30 minutes to allow for defoaming. Following this, the mixture was transferred to a petri dish and dried in a hot air oven at 60°C for 24 hours. The ensuing film was gently removed from a petri dish and cut into sections of the required dimensions and shape (Kumar et al., 2014). Various optimized film combinations containing HPMC and PEG 400 were prepared as detailed in **Table 1**.

Table 1: Formula composition of the MDF containing Lacosamide

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Lacosamide (gm)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
HPMC E5 (g)	-	-	-	1	1.5	1.75		1.5	1.5
HPMC E15 (g)	1	1.5	1.75				1.5		1.5
Propylene glycol (ml)	-	-	-	1.75	1.5	1	1.5	-	-
PEG 400 (g)	1.75	1.5	1					1.5	-
Citric acid (g)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sodium Saccharin (g)	0.110	0.110	0.110	0.110	0.110	0.110	0.110	0.110	0.110
Flavor (g)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Distilled water (ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

3. Evaluation of prepared Lacosamide loaded MDF

3.1 Fourier transform infrared spectroscopy (FTIR)

Lacosamide's FTIR absorption bands and the drug and excipients mixture were acquired in a region of 4000-400 cm^{-1} using the KBr disc method with an FTIR spectrophotometer (Pardeshi et al., 2022).

3.2 Thickness

The thickness of each oral film was measured at five distinct locations using a screw gauge. The mean thickness and variance for each oral film preparation were determined (ElMeshad & El Hagrasy, 2011).

3.3 Folding endurance

It was established by bending the film with an even cross-sectional area and width until it broke. The film's folding endurance score was determined by counting the number of times the film could be bent before breaking. This test confirms the film's tensile strength (R. Patel & Poddar, 2009).

3.4 Weight variation

Three films measuring 2 × 2 cm^2 were uniformly cut from each film composition. Films were separately measured on an electronic balance, and the average mass for each batch was computed (Han et al., 2019b).

3.5 Uniformity of drug content

The drug content was evaluated by dissolving a 4 cm^2 area film in 50 ml buffer solution with pH 6.8. The mixture was subsequently filtrated using Whatman filter paper and diluted to 100 mL using the same buffer. The resulting solution was subsequently analyzed using a UV spectrophotometer at 257 nm **(Figure 1)** (Aykaç & Başaran, 2022). Drug content was measured in triplicate using a straight-line equation with an R^2 value of 0.9992.

$$y = 0.0096x + 0.043 \quad \text{---------- (1)}$$

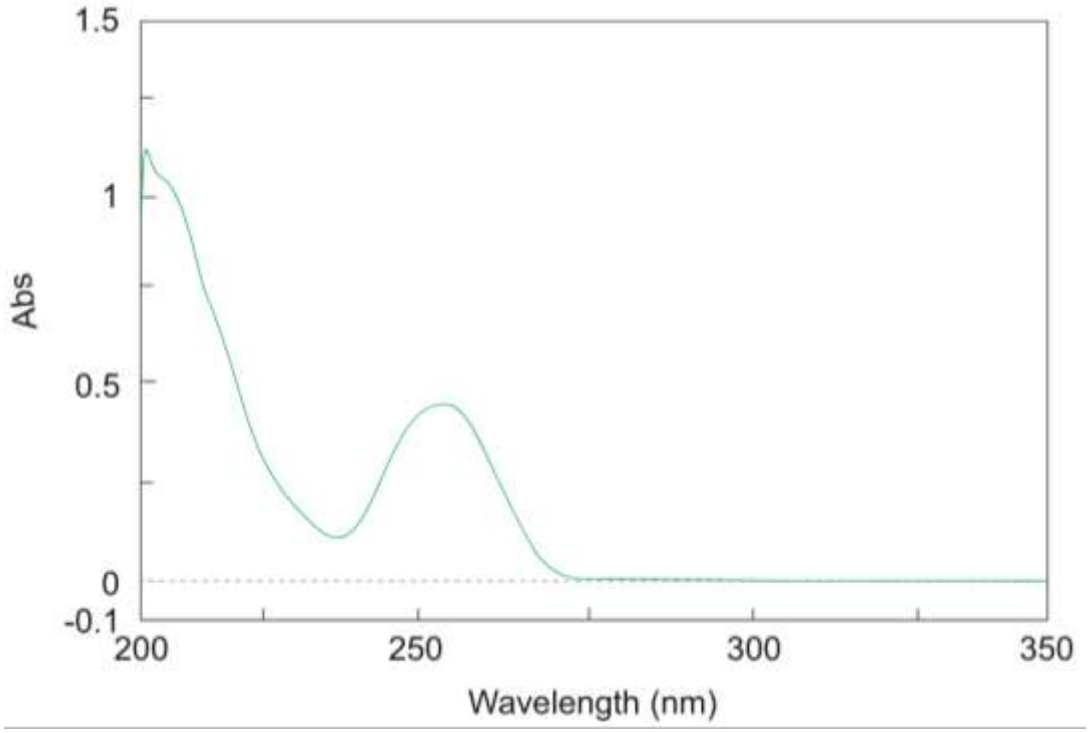

Figure 1: UV spectrum of Lacosamide

3.6 Tensile strength and % elongation

Tensile testing was employed to determine the strength and flexibility of the optimized composition. The casted film was cut into 10 mm pieces. The thickness of the samples was evaluated using a conventional micrometer screw gauge. Then five samples were tested on a tensile tester to evaluate their tensile attributes. The tensile stress is stated in terms of MPa, and strain in terms of percent elongation (Linku & Sijimol, 2018).

Tensile strength = (Load at failure×100) / (Strip thickness × Strip width) ……. (1)

% Elongation = (Increase in length of strip × 100) /Initial length of strip---------- (2)

3.7 Disintegration time

To evaluate disintegration time, a 2 x 2 cm^2 film strip was placed in a 6 cm Petri dish with 6 ml of pH 6.8 phosphate buffer. The duration necessary for the total breakdown of the film was recorded. Each measurement was performed in three separate experiments, and the mean values were presented (Saab & Mehanna, 2019).

3.8 In vitro release study

The dissolution characteristics of films were determined using a USP I apparatus using 900 ml of phosphate buffer (pH 6.8) at 37 ± 0.50 °C and 100 rpm. A sample aliquot (1.0 ml) was taken at various times and replenished with identical fresh media. Contents were filtered, dissolved with phosphate buffer (pH 6.8), and examined using a UV-spectrophotometer at 257 nm (Aykaç & Başaran, 2022).

3.9 Surface topography

Scanning electron microscopy (SEM, Jeol, JSM-7610F) is used at a specific resolution to examine the morphology of the oral adhesive strips. The study focuses on the differences among the film's upper and lower surfaces. It additionally serves to figure out API distribution (Ige et al., 2018).

3.10 Accelerated stability study

The optimized formulation (F3) was stored in a stability chamber (CHM-10S, REMI Instruments, Mumbai, India) at 40°C and 75% RH for three months, in accordance with ICH Q1A (R2) requirements. The specimens are assessed for its thickness, folding endurance, tensile strength, disintegration, and an in-vitro dissolution investigation (Pardeshi et al., 2023).

4. Results

4.1 FTIR analysis

Lacosamide displays unique peaks of absorption at 1,633 cm^{-1} and 3050 cm^{-1} which correlate to the vibrations of stretching of C=O and N-H, respectively **(Figure 2)** (Aykaç & Başaran, 2022). The distinctive peak absorption of Lacosamide was seen in the spectra of the physical mixture, and Lacosamide was compatible without any incompatibility with either of the formulation ingredients **(Figure 3)**. The distinctive peak at 3402 cm^{-1} relating to O-H (stretching) and at 1382.57 cm^{-1} because of -OH (bending vibration) relates to HPMC in the physical combination. **(Figure 3)** (van der Weerd & Kazarian, 2005).

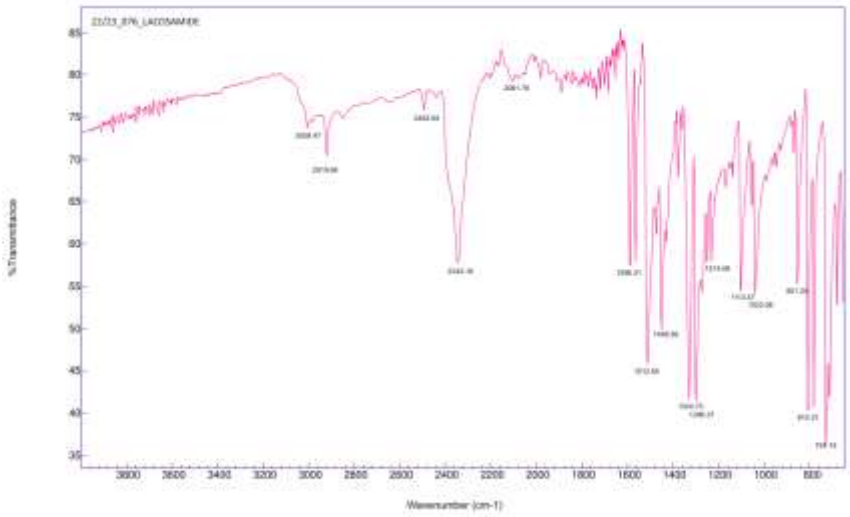

Figure 2: FTIR spectrum of Lacosamide

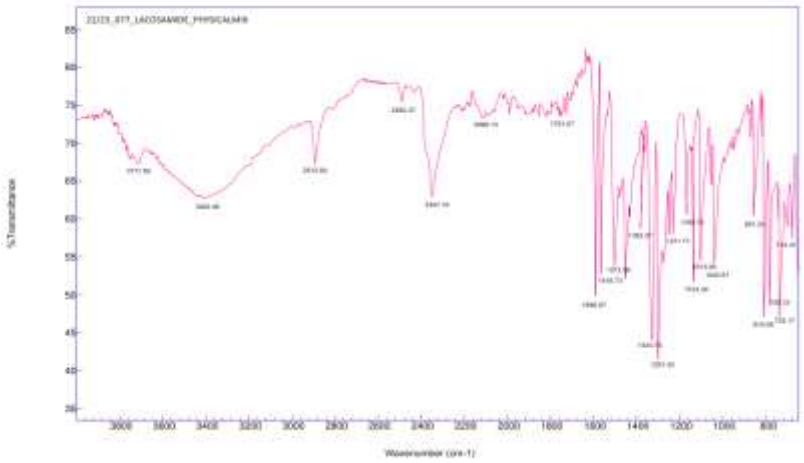

Figure 3: FTIR spectrum of physical mixture

4.2 Evaluation of mouth dissolving film

4.2.1 Thickness

The films' thickness was measured using a micrometer thread gauge. To guarantee uniformity, thickness measurements were done at five distinct places of each film. The acceptable variation in film thickness was set at less than 5% (Senthilkumar & Vijaya, 2015). The thickness of the films from batches F1 to F9 ranged between 0.50 mm and 0.60 mm. The detailed thickness measurements for all formulations are presented in **Table 2**.

Table 2: Assessment of Lacosamide loaded MDF

Formulation code	Thickness (mm)	Folding endurance	Tensile strength (g/cm^2)	% elongation	In-vitro disintegration time(sec)
F1	0.51	9	50.21	8	27
F2	0.53	7	48.34	9	28
F3	0.50	13	56.01	13	23
F4	0.54	11	57.04	11	25
F5	0.50	9	59.15	12	29
F6	0.52	9	49.91	7	25
F7	0.55	8	57.54	11	25
F8	0.57	10	48.08	11	30
F9	0.60	7	46.25	10	32

4.2.2 Folding endurance

To test the folding endurance, the film was folded continuously at the same point till it broke. Folding strength was defined as the number of instances the film was capable of being bent in the same place before breaking (Takeuchi et al., 2020). The folding endurance of the films from batches F1 to F9 was found to range between 7 and 13. Among all the batches, Batch F3 shows highest folding endurance. The detailed folding resistance measurements for all formulations are presented in **Table 2**.

4.2.3 Weight variation

Ten films were chosen at random, and their mean weight was calculated. The deviation was considered by weighing each film individually and comparing it to the average weight (D. M. Patel et al., 1970). The weight variation of the films from batches F1 to F9 ranged between 162.1 and 166.3 mg. The detailed weight variations for all formulations are presented in **Table 3**.

Table 3: Weight variation and content uniformity of mouth dissolving film

Formulations	Weight variation (mg)	Drug content (%)
F1	164.2	100.48
F2	162.5	101.64
F3	163.2	100.2
F4	165	101.7
F5	162.1	98.14
F6	166.3	101.82
F7	165.3	101.78
F8	163.6	100.04
F9	164.3	97.74

4.2.4 Uniformity of drug content

The drug concentration of the F1–F9 batches was determined to range from 97 and 101%. **Table 3** provides drug content results for each of the formulation.

4.2.5 Tensile strength and % elongation

Tensile strength is referred to as the highest stress put on a point where the film sample splits. The tensile force of the F1-F9 batches ranged from 46 to 59 gm/cm². The breaking strength values for all compositions are shown in **Table 2**. The percentage elongation, that specifies how far the film may stretch without breaking (ElMeshad & El Hagrasy, 2011), was also evaluated for the F1 to F9 batches and found to range between 8 and 13%. The results for all compositions are shown in **Table 2**.

4.2.6 Disintegration time

The quantity of HPMC enhanced the film's in-vitro disintegration time, but a higher concentration of plasticizer reduced it. Yet when the amount of polymers increased, the material became brittle, resulting in a slight reduction in time required for disintegration (Al-Mogherah et al., 2020). The in-vitro disintegration times for the F1-F9 batches varied between 23 to 32 seconds. The disintegration periods for all compositions are shown in **Table 2**.

4.2.7 *In-vitro release study*

The dissolution investigations of compositions F1 and F9 revealed approximately 93% and 98% release of drugs respectively. Nearly complete drug release was achieved from preparations F3 in 3 minutes in pH 6.8 phosphate buffer, and thus termed an optimum batch **(Figure 4)**. Rapid hydration and swelling properties of HPMC, the thin films large surface area allowing for quick drug-medium contact, and the optimized formulation ensuring efficient dissolution (Adrover et al., 2018). This pH is physiologically relevant and ideal for drug solubility, enhancing the release rate. Overall, these factors ensure quick disintegration and drug release in the tested conditions. In comparison, the in-vitro release data for the marketed formulation (Lacosam 50mg) shows 98% drug release at the end of 60 minutes **(Figure 4)**, with dissolution actually starting after 10 minutes, whereas the mouth dissolving film achieves complete drug release within 3 minutes.

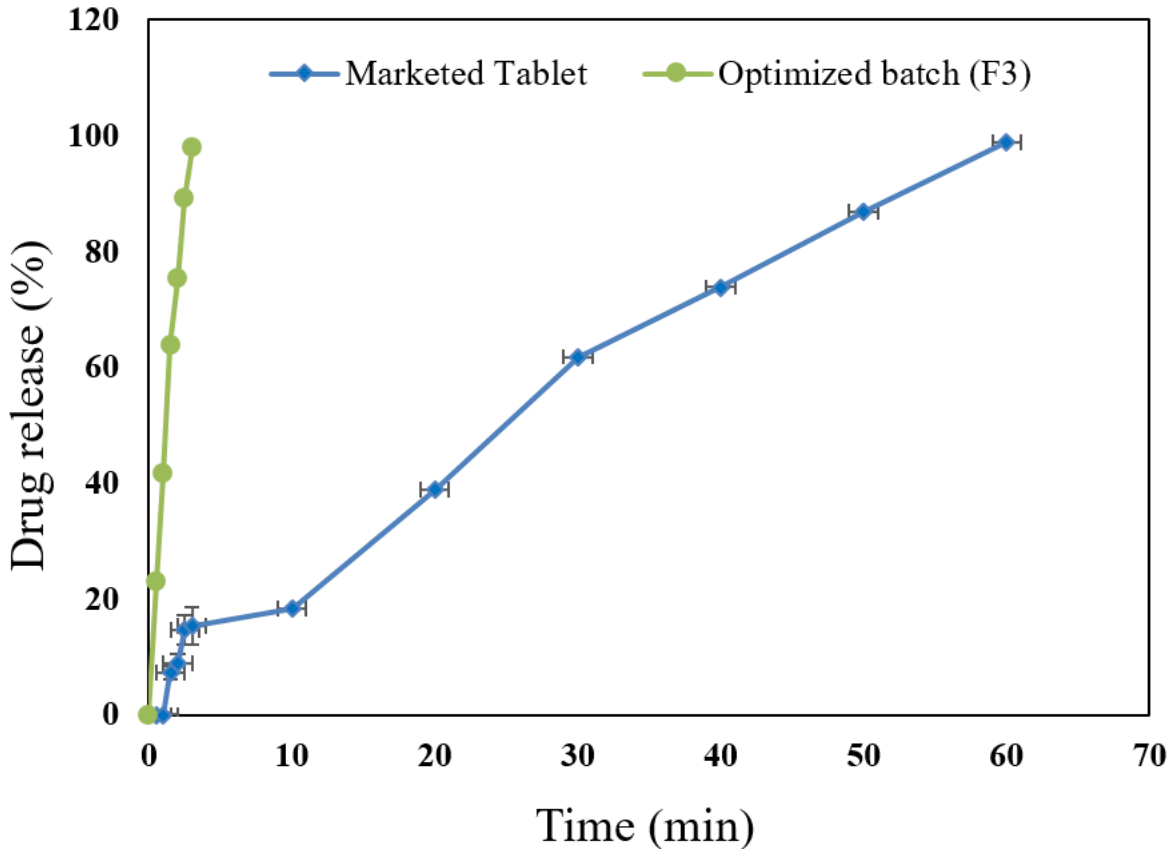

Figure 4: In-vitro release of Lacosamide loaded MDF (optimized formulation) and Marketed Lacosamide tablet formulation.

4.2.8 Surface morphology

The SEM analysis of formulation F3 reveals the surface is free of any scratches or striations, indicating that Lacosamide is uniformly distributed throughout the films. No drug crystals were observed on the surface of the mouth dissolving films. This uniform distribution contributes to the rapid drug release, facilitating immediate onset of action (Karki et al., 2016). The SEM surface photographs are shown in **Figure 5.**

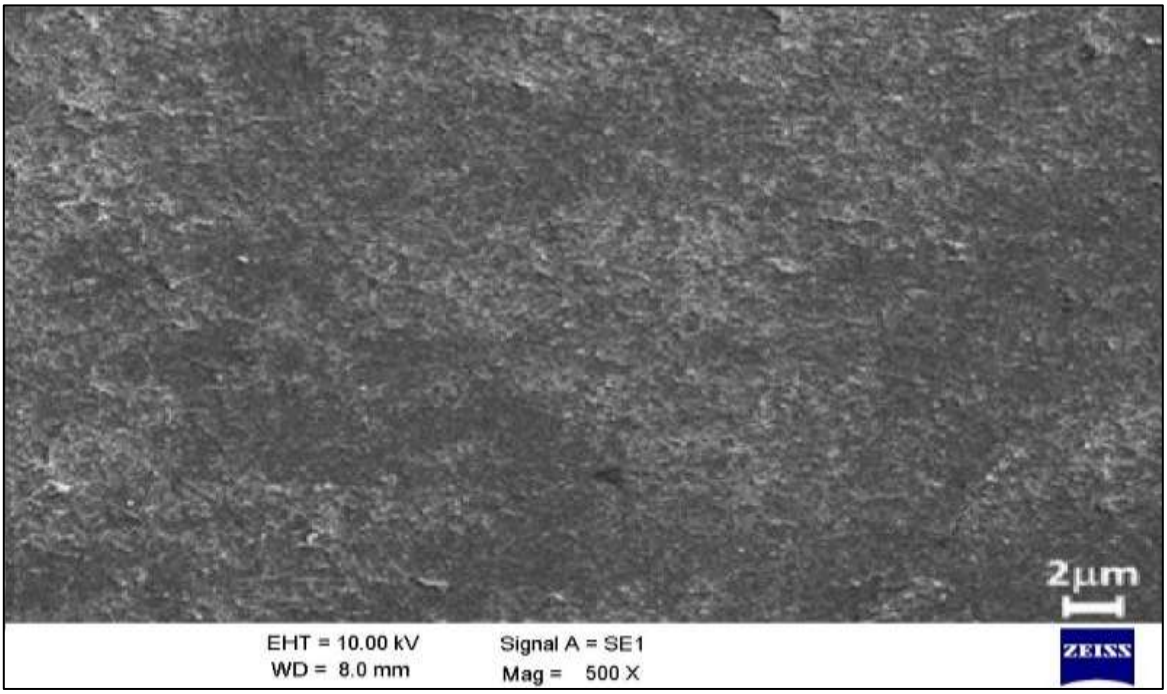

Figure 5: SEM image of Lacosamide loaded mouth dissolving film

4.2.9 Accelerated stability study

Investigations into stability were carried out on the Optimal Formulation (F3), which had the best thickness, folding endurance, breaking strength, disintegration, as well as in vitro drug release. The formulation was stored at 40ºC and 75% RH for three months. The formulation was tested every month (see Table 4). The findings demonstrated minor changes, implying that the medicine stayed inside the MDF, and the dosage form retained its consistency during the trial period (Li et al., 2019).

Table 4: Stability data of optimized batch at 40°C/75%RH)

Parameters	Initial	1 month	3 months
Thickness (mm)	0.50	0.50	0.49
Folding endurance	13	12	11
Tensile strength (gm/cm^2)	56.01	56.0	55.87
Disintegration time (sec)	23	23	22
Dissolution (%)	98.82	97.56	96.45

Conclusion

The formulation and evaluation of Lacosamide mouth dissolving films using the solvent casting technique have demonstrated significant potential in improving drug delivery and patient compliance. The optimized formulation (F3) showed favorable characteristics, including rapid disintegration, high folding endurance, tensile strength, and efficient drug release. The use of HPMC as a polymer matrix and PEG 400 as a plasticizer ensured the films' mechanical strength and quick disintegration, facilitating rapid drug absorption through the oral mucosa. The in vitro studies confirmed the superiority of the MDF over traditional tablet forms, achieving almost complete drug release within three minutes compared to 60 minutes for marketed tablets. SEM analysis indicated uniform distribution of Lacosamide within the films, contributing to the consistent release profile. Additionally, accelerated stability studies validated the formulation's stability over three months. This study highlights the advantages of MDF as a viable alternative for Lacosamide delivery, offering precise dosing, improved bioavailability, and enhanced patient compliance, particularly for individuals with difficulty swallowing conventional tablets or capsules.

Adrover, A., Varani, G., Paolicelli, P., Petralito, S., Di Muzio, L., Casadei, M. A., & Tho, I. (2018). Experimental and Modeling Study of Drug Release from HPMC-Based Erodible Oral Thin Films. *Pharmaceutics*, *10*(4), 222. https://doi.org/10.3390/pharmaceutics10040222

Al-Mogherah, A. I., Ibrahim, M. A., & Hassan, M. A. (2020). Optimization and evaluation of venlafaxine hydrochloride fast dissolving oral films. *Saudi Pharmaceutical Journal*, *28*(11), 1374–1382. https://doi.org/10.1016/j.jsps.2020.09.001

Aykaç, K., & Başaran, E. (2022). Formulation and Characterization of Lacosamide-loaded Polymeric Microneedles. *Journal of Exploratory Research in Pharmacology*, *7*(2), 61–75. https://doi.org/10.14218/JERP.2021.00051

Bala, R., Khanna, S., Pawar, P., & Arora, S. (2013). Orally dissolving strips: A new approach to oral drug delivery system. *International Journal of Pharmaceutical Investigation*, *3*(2), 67. https://doi.org/10.4103/2230-973X.114897

Bala, R., & Sharma, S. (2018). Formulation optimization and evaluation of fast dissolving film of aprepitant by using design of experiment. *Bulletin of Faculty of Pharmacy, Cairo University*, *56*(2), 159–168. https://doi.org/10.1016/j.bfopcu.2018.04.002

Bastos, F., Pinto, A. C., Nunes, A., & Simões, S. (2022). Oromucosal products – Market

landscape and innovative technologies: A review. *Journal of Controlled Release*, *348*, 305–320. https://doi.org/10.1016/j.jconrel.2022.05.053

Beyreuther, B. K., Freitag, J., Heers, C., Krebsfänger, N., Scharfenecker, U., & Stöhr, T. (2007). Lacosamide: A Review of Preclinical Properties. *CNS Drug Reviews*, *13*(1), 21–42. https://doi.org/10.1111/j.1527-3458.2007.00001.x

Borges, A. F., Silva, C., Coelho, J. F. J., & Simões, S. (2015). Oral films: Current status and future perspectives II — Intellectual property, technologies and market needs. *Journal of Controlled Release*, *206*, 108–121. https://doi.org/10.1016/j.jconrel.2015.03.012

Chaudhary, H., Gauri, S., Rathee, P., & Kumar, V. (2013). Development and optimization of fast dissolving oro-dispersible films of granisetron HCl using Box–Behnken statistical design. *Bulletin of Faculty of Pharmacy, Cairo University*, *51*(2), 193–201. https://doi.org/10.1016/j.bfopcu.2013.05.002

ElMeshad, A. N., & El Hagrasy, A. S. (2011). Characterization and Optimization of Orodispersible Mosapride Film Formulations. *AAPS PharmSciTech*, *12*(4), 1384–1392. https://doi.org/10.1208/s12249-011-9713-z

Han, C.-S., Kim, S., Oh, D.-W., Yoon, J., Park, E.-S., Rhee, Y.-S., Kim, J.-Y., Shin, D., Kim, D.-W., & Park, C.-W. (2019a). Preparation, Characterization, and Stability Evaluation of Taste-Masking Lacosamide Microparticles. *Materials*, *12*(6), 1000. https://doi.org/10.3390/ma12061000

Han, C.-S., Kim, S., Oh, D.-W., Yoon, J. Y., Park, E.-S., Rhee, Y.-S., Kim, J.-Y., Shin, D. H., Kim, D.-W., & Park, C.-W. (2019b). Preparation, Characterization, and Stability Evaluation of Taste-Masking Lacosamide Microparticles. *Materials (Basel, Switzerland)*, *12*(6). https://doi.org/10.3390/ma12061000

Ige, P. P., Pardeshi, S. R., Sonawane, R. O., Education, P., & Res, D. (2018). *Development of pH-Dependent Nanospheres for Nebulisation- In vitro Diffusion , Aerodynamic and Cytotoxicity Studies Authors*. 0–6.

Karki, S., Kim, H., Na, S.-J., Shin, D., Jo, K., & Lee, J. (2016). Thin films as an emerging platform for drug delivery. *Asian Journal of Pharmaceutical Sciences*, *11*(5), 559–574. https://doi.org/10.1016/j.ajps.2016.05.004

Kumar, G. P., Phani, A. R., Prasad, R. G. S. V., Sanganal, J. S., Manali, N., Gupta, R., Rashmi, N., Prabhakara, G. S., Salins, C. P., Sandeep, K., & Raju, D. B. (2014).

Polyvinylpyrrolidone oral films of enrofloxacin: Film characterization and drug release. *International Journal of Pharmaceutics*, *471*(1–2), 146–152. https://doi.org/10.1016/j.ijpharm.2014.05.033

Li, L., Hui Zhou, C., & Ping Xu, Z. (2019). Self-Nanoemulsifying Drug-Delivery System and Solidified Self-Nanoemulsifying Drug-Delivery System. *Nanocarriers for Drug Delivery*, 421–449. https://doi.org/10.1016/b978-0-12-814033-8.00014-x

Linku, A., & Sijimol, J. (2018). Formulation and Evaluation of Fast Dissolving Oral Film of Anti-Allergic Drug. *Asian Journal of Pharmaceutical Research and Development*, *6*(3), 5–16. https://doi.org/10.22270/ajprd.v6i3.374

Pardeshi, S. R., More, M. P., Pardeshi, C. V., Chaudhari, P. J., Gholap, A. D., Patil, A., Patil, P. B., & Naik, J. B. (2023). Novel crosslinked nanoparticles of chitosan oligosaccharide and dextran sulfate for ocular administration of dorzolamide against glaucoma. *Journal of Drug Delivery Science and Technology*, *86*, 104719. https://doi.org/10.1016/j.jddst.2023.104719

Pardeshi, S. R., More, M. P., Patil, P. B., Mujumdar, A., & Naik, J. B. (2022). Statistical optimization of voriconazole nanoparticles loaded carboxymethyl chitosan-poloxamer based in situ gel for ocular delivery: In vitro, ex vivo, and toxicity assessment. *Drug Delivery and Translational Research*, *12*(12), 3063–3082. https://doi.org/10.1007/s13346-022-01171-0

Patel, D. M., Patel, D. J., & Darji, P. J. (1970). Formulation and Evaluation of Fast-Dissolving Film of Cetirizine and Dextromethorphan. *International Journal of Pharmaceutical Sciences and Nanotechnology*, *9*(3), 3305–3311. https://doi.org/10.37285/ijpsn.2016.9.3.6

Patel, R., & Poddar, S. (2009). Development and Characterization of Mucoadhesive Buccal Patches of Salbutamol Sulphate. *Current Drug Delivery*, *6*(1), 140–144. https://doi.org/10.2174/156720109787048177

Perucca, E., Yasothan, U., Clincke, G., & Kirkpatrick, P. (2008). Lacosamide. *Nature Reviews Drug Discovery*, *7*(12), 973–974. https://doi.org/10.1038/nrd2764

Pethe, A. M., & Desai, R. B. (2016). Formulation, optimization and evaluation of mouth dissolving film of nifedipine by using design of experiment. *Asian Journal of Pharmaceutical Sciences*, *11*(1), 74–76. https://doi.org/10.1016/j.ajps.2015.10.059

Saab, M., & Mehanna, M. M. (2019). Disintegration time of orally dissolving films: various methodologies and in-vitro/in-vivo correlation. *Die Pharmazie*, *74*(4), 227–230. https://doi.org/10.1691/ph.2019.8231

Scarpa, M., Stegemann, S., Hsiao, W.-K., Pichler, H., Gaisford, S., Bresciani, M., Paudel, A., & Orlu, M. (2017). Orodispersible films: Towards drug delivery in special populations. *International Journal of Pharmaceutics*, *523*(1), 327–335. https://doi.org/10.1016/j.ijpharm.2017.03.018

Senthilkumar, K., & Vijaya, C. (2015). Formulation Development of Mouth Dissolving Film of Etoricoxib for Pain Management. *Advances in Pharmaceutics*, *2015*, 1–11. https://doi.org/10.1155/2015/702963

Strzelczyk, A., Zöllner, J. P., Willems, L. M., Jost, J., Paule, E., Schubert- Bast, S., Rosenow, F., & Bauer, S. (2017). Lacosamide in status epilepticus: Systematic review of current evidence. *Epilepsia*, *58*(6), 933–950. https://doi.org/10.1111/epi.13716

Takeuchi, Y., Ikeda, N., Tahara, K., & Takeuchi, H. (2020). Mechanical characteristics of orally disintegrating films: Comparison of folding endurance and tensile properties. *International Journal of Pharmaceutics*, *589*, 119876. https://doi.org/10.1016/j.ijpharm.2020.119876

van der Weerd, J., & Kazarian, S. G. (2005). Release of Poorly Soluble Drugs from HPMC Tablets Studied by FTIR Imaging and Flow-Through Dissolution Tests. *Journal of Pharmaceutical Sciences*, *94*(9), 2096–2109. https://doi.org/10.1002/jps.20428

Vargason, A. M., Anselmo, A. C., & Mitragotri, S. (2021). The evolution of commercial drug delivery technologies. *Nature Biomedical Engineering*, *5*(9), 951–967. https://doi.org/10.1038/s41551-021-00698-w