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Formulation and Evaluation of Sublingual Films of Lumateperone Tosylate

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ABSTRACT:

The formulation of sublingual films of Lumateperone Tosylate a second-generation antipsychotic that works by modulating dopamine, serotonin, and glutamate neurotransmitters, was carried out in current research work. The prepared formulation evaluated through nine trial batches, with various parameters assessed for performance. The key components of the formulation included three types of film-forming polymers: Pullulan, HPMC E5 LV, and Lycagel, along with three types of plasticizers to improve flexibility and elasticity. Sucralose was used as a sweetener to enhance the taste. Additionally, a drug release study revealed that Lycagel batches demonstrated faster drug release compared to HPMC E5 LV and Pullulan, with over 90% of the drug released within 20 minutes. The T9 batch showed the highest drug release, achieving 95% in just 15 minutes. In conclusion, the T9 batch was considered the most promising formulation due to its combination of Lycagel as the film former, glycerin as the plasticizer, and its rapid disintegration and drug release characteristics. Further studies, including Design of Experiments (DoE), was conducted to optimize the formulation.

KEYWORDS: Lumateperone Tosylate, Lycagel, sublingual films, antipsychotic

INTRODUCTION

Lumateperone Tosylate is a second-generation antipsychotic that works by modulating dopamine, serotonin, and glutamate neurotransmitters, specifically indicated for the treatment of schizophrenia in adults. As a newly approved second-generation antipsychotic, Lumateperone offers a modern therapeutic option for managing this challenging mental health condition. The drug has a half-life of approximately 18 hours, allowing for convenient once-daily dosing. The available oral doses in capsules are 10.5 mg, 21 mg, and 42 mg, all taken once daily. However, it is important to note that Lumateperone has a relatively low bioavailability of 4.4%, primarily due to extensive first-pass metabolism, which can reduce its overall effectiveness when administered orally. Lumateperone is currently available in the market as an immediate-release capsule, specifically formulated for the treatment of schizophrenia. While this form is effective, it may present challenges for some patients, particularly those who have difficulty swallowing pills. To enhance

patient compliance, especially for individuals with schizophrenia who may struggle with swallowing, we propose the development of fast-dissolving Sublingual films containing Lumateperone Tosylate. This innovative delivery method would facilitate rapid absorption of the medication through the oral mucosa, bypassing the gastrointestinal tract and the first-pass metabolism. By providing an alternative administration route, these sublingual films could significantly improve the overall treatment experience for patients, reducing the frequency of dosing and addressing common swallowing difficulties. This formulation represents a promising advancement in the management of schizophrenia and gives a quick onset of action after taking with or without water, making treatment more accessible and user-friendly.

Sublingual Films

Sublingual films are a modern and innovative dosage form designed for the rapid delivery of therapeutic agents via the sublingual route, which involves placing the film under the tongue for absorption into the bloodstream.

This delivery method capitalizes on the rich vascular supply of the sublingual mucosa, enabling swift onset of action while bypassing the gastrointestinal tract and first-pass metabolism. As a result, sublingual films have garnered considerable interest in pharmaceutical development for various therapeutic applications.

Here are some types of sublingual film formulations:

- **Solid dispersion-based sublingual films**

These films can be evaluated for their folding endurance, which is the number of folds needed to break the film.

- **Fast dissolving buccal films**

These films can be characterized in vitro to determine their disintegration time. The high hydrophilicity of the excipients can indicate a fast dissolution of the film.

- **HPMC-based films**

Chitosan can be used as a mucoadhesive agent to enhance drug permeability in these films. HPMC polymer is commonly used in pharmaceutical applications due to its affordability, ease of manufacture, and widespread regulatory acceptance.

The sublingual and buccal routes of administration can be effective alternatives to the traditional oral route, especially when a rapid onset of action is required. Mucoadhesive films are a well-accepted dosage form among patients and prescribers, especially for paediatric and geriatric patients.

Sublingual film is a thin film with an area of 5-20 cm² containing an active ingredient. The immediate dissolution, in water or saliva, respectively, is reached through a special matrix from water-soluble polymers. A typical composition contains the following:

Table 1 Composition of film

Sr. No	Composition of strip	Quantity
1	Active pharmaceutical agent	1-25%
2	Film-forming polymer	40-50%
3	Plasticizer	0-20%
4	Saliva-stimulating agent	2-6%
5	Sweetening agent	3-6%
6	Flavoring agent	10%

Material and Methodology

All material required for the preparation of the formulation was procured either from the institute or as a gratis sample from pharma industries. The standard curve of Lumateperone tosylate in phosphate buffer pH 6.8 was prepared in UV-Visible spectrophotometer at λ_{max}

244nm. Using a concentration range 10 to 50 $\mu\text{g/ml}$, the linearity was observed as shown in the image.

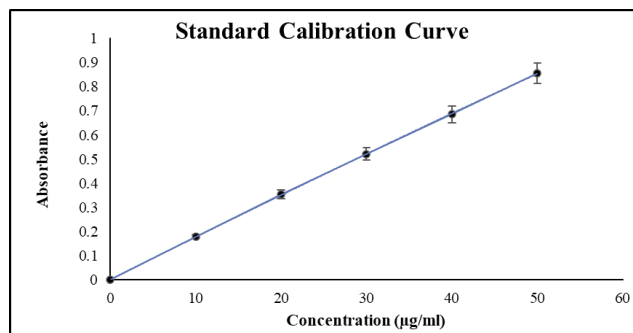


Figure 1 Calibration curve of Lumateperone tosylate at 244nm in Phosphate buffer pH 6.8

The characterization of the drug, including a drug excipient compatibility study, was done. The solvent evaporation method was selected, and a laboratory-sized 9 cm diameter petri dish was used. The dose was calculated accordingly.

Based on preliminary trials for Pullulan, HPMC E5LV, and Lycagel VS 720 as film-forming polymers, Lycagel VS 720 was selected for further study and optimization. Using 2 independent variables i.e., Lycagel VS 720 as film forming polymer and Glycerin as plasticizer at 3 levels, a 3² factorial design was selected for optimization of Sublingual Films. Total 9 batches were prepared and were evaluated for Weight Variation, Film Thickness, folding endurance film thickness, folding endurance, surface pH were evaluated.

Table 2 Trial batches with different polymers

Batch	Tensile Strength (kg/cm ²) (n=3)	Percentage Elongation (n=3)	Disintegration Time (Sec.) (n=3)	%Drug content (n=3)
T1	10.5±0.4	11±1.3	67±1	97.5±0.3
T2	11.6±0.2	12±2.1	71±3	98.1±0.5
T3	12.2±0.3	14±1.8	61±1.2	98.9±0.9
T4	15.6±0.7	22±1.2	78±5	97.2±0.8
T5	16.9±0.2	26±1.5	85±4	96.9±0.5
T6	18.4±0.4	27±2.5	80±1.8	97.4±0.7
T7	14.5±0.6	32±3.1	55±2	98.5±0.6
T8	15.1±0.2	34±2.3	54±3	98.8±0.8
T9	15.9±0.4	38±2.5	36±4	99.5±0.3

Weight Variation: All batches (T1-T9) were within an acceptable range, indicating consistency in manufacturing.

Film Thickness: Thickness ranged from 0.048 mm to 0.057 mm, which is typical for mouth-dissolving films.

Folding Endurance: The films exhibited satisfactory folding endurance, ensuring durability during handling.

Surface pH: The pH was found between 6.8 and 7.1, making the films close to neutral, which is ideal for oral mucosa contact.

Tensile Strength & Elongation:

Tensile strength and % elongation was higher in Lycagel compared to HPMC E5 and pullulan.

Pullulan showed even higher value than HPMCE5, which suggests better mechanical properties and flexibility.

Elasticity: The T9 batch, which used Lycagel as a film former and glycerin as a plasticizer, showed the best elasticity.

Drug Content: All batches showed drug content within an acceptable range.

Disintegration Time:

The T9 batch exhibited the lowest disintegration time at 36 seconds, the shortest across all formulations. Disintegration time is a crucial parameter for mouth-dissolving films, and T9 emerged as the most satisfactory formulation due to this characteristic.

T9 Batch was considered the most promising formulation based on its combination of lycagel as the film former, glycerin as the plasticizer, and the shortest disintegration time.

Drug release study: -

The drug release study conducted on T1-T9 batches revealed that Lycagel batches demonstrated faster drug release compared to HPMC E5LV and Pullulan batches. Specifically, Lycagel batches achieved over 90% drug release within 20 minutes, with the release occurring even faster (90% in 15 minutes). Among all the batches, T9 showed the highest drug release, reaching 95% in 15 minutes. As a result, the T9 batch is considered the optimized formulation, and further studies, including Design of Experiments (DoE), will be conducted to refine the formulation.

Factorial design: based on the obtained results, the Lycagel VS 720 was selected as variable X1 and Glycerin as variable X2, and factorial design was selected. With 2 factors and 3 levels total of 9 batches were prepared, and using statistical software, the data were evaluated.

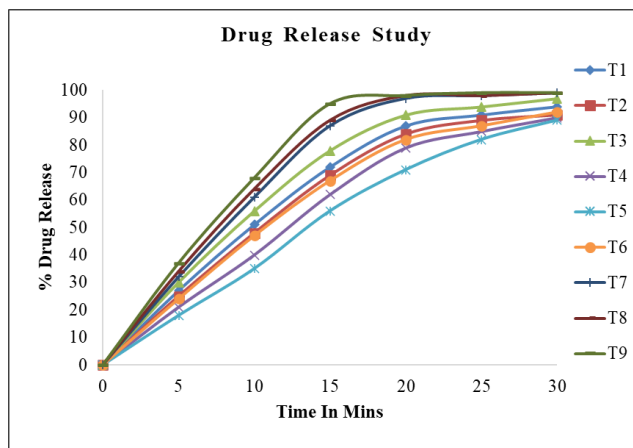


Figure 2 Drug release study of T1-T9 batches

Tensile Strength & Elongation:

Tensile strength and % elongation of F1-F9 batches were checked and found in the range of 9.1 to 26.8 and 19.2 to 39.8, respectively. The elongation was increasing with increased polymer concentration. As well as tensile strength was also affecting the variable concentration of polymer.

Elasticity: The F9 batch, which used lycagel as a film former and glycerin as a plasticizer, showed the best elasticity.

Drug Content: All batches showed drug content within an acceptable range.

Disintegration Time:

The F1 batch exhibited the lowest disintegration time at 14 seconds, the shortest across all formulations. Disintegration time is a crucial parameter for mouth-dissolving films, and F1 emerged as the most satisfactory formulation due to this characteristic.

F1 Batch was considered the most promising formulation based on its combination of lycagel as the film former, glycerin as the plasticizer, and the shortest disintegration time.

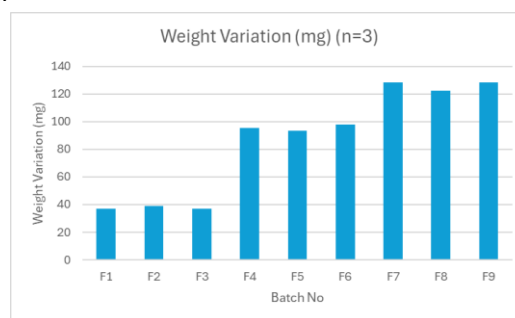


Figure 3 Weight variation data for batch F1 to F12

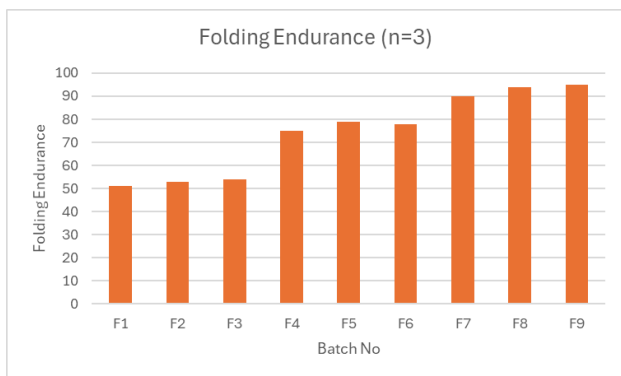


Figure 4 Folding endurance of batch F1 to F9

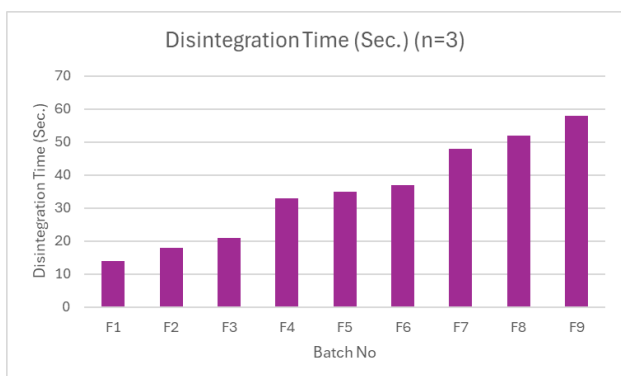


Figure 5 Disintegration time of of batch F1 to F9

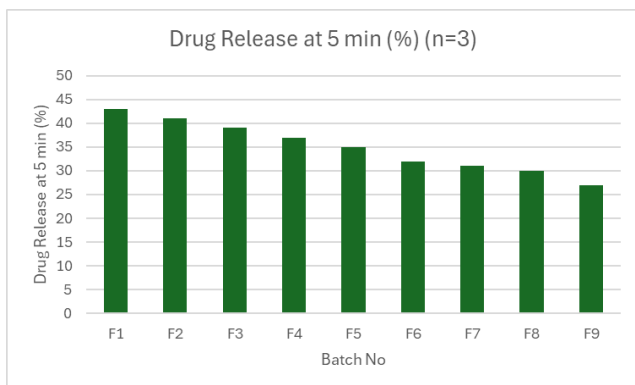


Figure 6 drug release data of batch F1 to F9

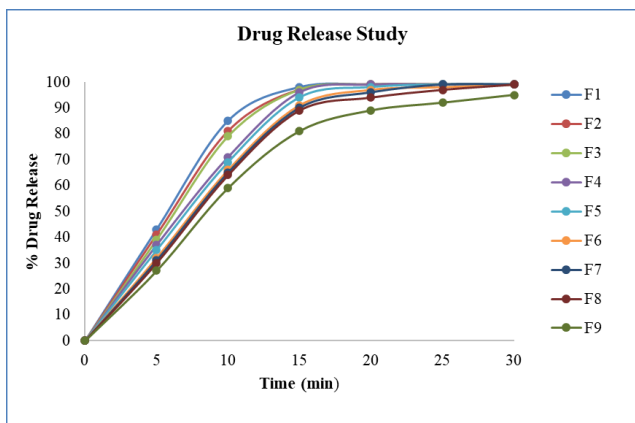


Figure 7 Drug Release study of factorial batches F1 to F9

Tensile Strength & Elongation:

Tensile strength and % elongation of F1-F9 batches were checked and found in the range of 9.1 to 26.8 and 19.2 to 39.8 respectively. The elongation was increase the with increased in polymer concentration. As well as tensile strength was also affect the variable concentration of polymer.

Elasticity: The F9 batch, which used lycagel as a film former and glycerin as a plasticizer, showed the best elasticity.

Drug Content: All batches showed drug content within an acceptable range.

Disintegration Time:

The F1 batch exhibited the lowest disintegration time at 14 seconds, the shortest across all formulations. Disintegration time is a crucial parameter for mouth-dissolving films, and F1 emerged as the most satisfactory formulation due to this characteristic.

F1 Batch was considered the most promising formulation based on its combination of lycagel as the film former, glycerin as the plasticizer, and the shortest disintegration time.

Statistical analysis of Response 1: Folding Endurance:

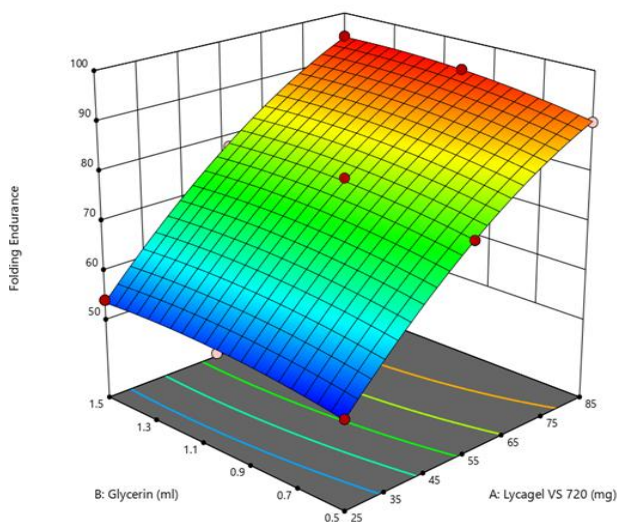


Figure 8 3D response surface graph for response 1

The statistical model for Response, Folding showed F-value of 902.28 implies the model is significant based on p value. There was only a 0.01% chance that an F-value this large could occur due to noise.

Statistical analysis of Response 2: Disintegration Time

The statistical analysis model for the disintegration time showed the F-value of 152.50 implies the model is significant. There is only a 0.08% chance that an F-value this large could occur due to noise.

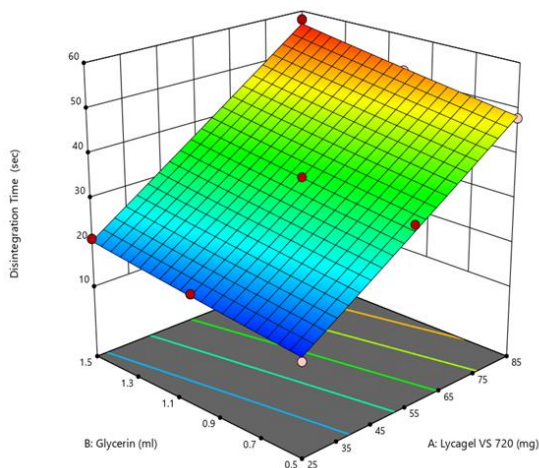


Figure 9 3D response surface graph for response 2

Statistical analysis of Response 3 Drug Release at 5 min

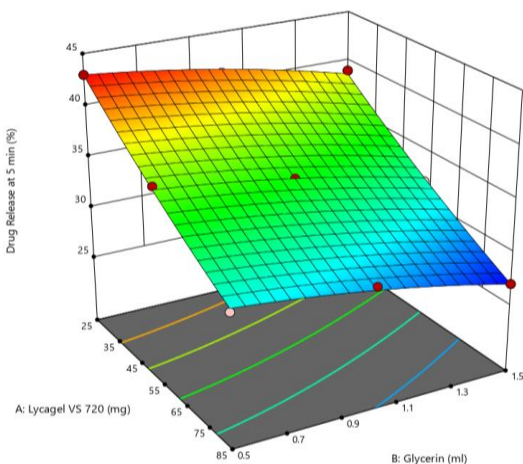


Figure 10 3D response surface graph for response 3

Statistical analysis of Response 3 Drug Release at 5 min showed Model F-value of 210.00 implies the model is significant. There is only a 0.05% chance that an F-value this large could occur due to noise.

The validation of all three-response model was done using batch preparation using software data. Batch preparation was done according to the data provided by design software data and all three responses were evaluated and compared with predicted data. The model thus was

validated based on minimal error. The errors found in all cases were less than 5%.

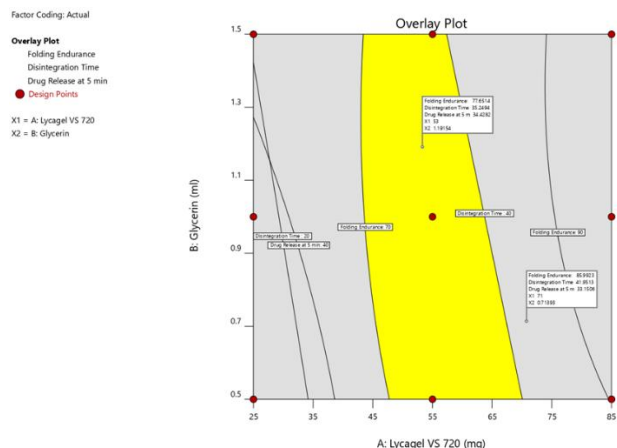


Figure 11 Overlay Plot after validation of the model

The overlay plot was prepared for best outcome output as shown in above image. The final batch was prepared as an optimized batch. All the evaluations were performed including a one month stability study.

CONCLUSION

The formulation of sublingual films of Lumateperone Tosylate was evaluated through nine trial batches (T1-T9), with various parameters assessed for performance. The key components of the formulation included three types of film-forming polymers: Pullulan, HPMC E5 LV, and Lycagel, along with three types of plasticizers to improve flexibility and elasticity. Sucralose was used as a sweetener to enhance the taste. Additionally, a drug release study revealed that Lycagel batches demonstrated faster drug release compared to HPMC E5 LV and Pullulan, with over 90% of the drug released within 20 minutes. The T9 batch showed the highest drug release, achieving 95% in just 15 minutes. In conclusion, the T9 batch was considered the most promising formulation due to its combination of Lycagel as the film former, glycerin as the plasticizer, and its rapid disintegration and drug release characteristics. Based on that factorial design was applied and analysis of Factorial design was done using DoE software. Validation of design was done. The optimized batch was subjected for Stability study and found stable for 1 month yet further stability study is yet to be performed and the formulation is yet to be tested for ex vivo and in vivo performance.

REFERENCES

1. Rajagopalan, S., D. Rajendhiran, I. A. Mohamed, and S. B. Sherbudeen. "Fast Dissolving Oral Thin Films: An Innovative Herbal Drug Delivery System". International

Journal of Research in Medical Sciences, vol. 12, no. 8, 2024, 3085-90.

2. Parmar D, Patel U. Orally Fast Dissolving Film as Dominant Dosage for Quick Releases. *Int J Pharm Res BioSci.* 2022;1(3):24-41.
3. Reddy MR. A Review an Introduction to Fast Dissolving Oral Thin Film Drug Delivery Systems. *J Pharm Sci Res.* 2020;12(7):925-40.
4. Niyaz USH, Elango K. Oral fast dissolving films: An innovative drug delivery system. *World J Pharm Pharm Sci.* 2018;7:881-907.
5. Giovanni Bocci, Tudor I. Oprea and Leslie Z. Benet. State of the Art and Uses for the Biopharmaceutics Drug Disposition Classification System (BDDCS): New Additions, Revisions, and Citation References. *The AAPS Journal.* 2022;24:37.
6. Murthy AV, Ayalasangam LU, Earle RR, Jyotsna P. Formulation and Evaluation of Tramadol Hydrochloride Oral Thin Films. *Int J Pharm Sci.* 2018;9:1692-8.
7. Hasanen Pinjari, Rehan Deshmukh, Khan Faizan, Dr. Gulam Javed. Fast Dissolving Oral Films: A Review. *IJPAS.* 2024; 3(1): 29-28.
8. Jain Priyanshi, Gupta Ashish, Darwhekar Gajanan. A Detailed Overview on Mouth Dissolving Film *Journal of Drug Delivery & Therapeutics.* 2023; 13(7):172-176.
9. Anjana I S, Sujith Varma K, Aparna George, Anupriya A B. Orodispersible Film, A new concept in Drug Delivery Technology. *RJPT.* 2024; 17(5):2391-7.
10. Adesh Yelave, Geeta Sameer Bhagwat, Adnan Rehmatullah Siddique. Incorporation of Antihypertensive Class IV Drug in Novel Buccal Film Formulation. *Asian Journal of Pharmaceutical Research.* 2024; 14(1):15-4.
11. Kawale, K. A., Neha B Autade, H. s Narhare, and R. L. Mhetre. "A Review on Fast-Dissolving Oral Film". *Asian Journal of Pharmaceutical and Clinical Research*, vol. 16, no. 10, 2023, 7-17.
12. Drug Information, September 2024, <https://go.drugbank.com/salts/DBSALT001873>.
13. Drug Information, September 2024, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209500s000lbl.pdf.
14. Drug Information, September 2024, <https://www.genome.jp/entry/D11170>.
15. Drug Information, September 2024, <https://www.capyta.com/schizophrenia>.
16. Drug Information, September 2024, <https://pubchem.ncbi.nlm.nih.gov/compound/Lumateperone-Tosylate>.
17. Shubham S, SheetalG,Ravindranath S, "Formulation and Evaluation of Sublingual Film of Nateglinide", *Int. Res. J. Pharm.* 2018, 9(7), 215-218.
18. YahyaAlhamhoom Y, Sharma A, Nanjappa SH, Kumar A, Alshishani A, Ahmed MM, Farhana SA, Rahamathulla M. Development and Evaluation of Solid Dispersion-Based Sublingual Films of Nisoldipine. *Pharmaceuticals.* 2023; 16(11):1589.
19. Husain M, Islam M, Razu M, Nabila Z, Tanoy S, Saiful M, "Preparation and evaluation of sublingual film of ketorolac tromethamine", *Drug Development and Industrial Pharmacy*, 2022, 48(9), 1-9.
20. Gondkar S.B, Tope U.C and Saudagar R.B, "Formulation And Evaluation Of Fast Dissolving Sublingual Film Of Aripiprazole", *International Journal of Current Advanced Research*, 2017, 6 (7), 4493-4499.
21. Rajni B, Shailesh S, "Formulation optimization and evaluation of fast dissolving film of aprepitant by using design of experiment", *Bulletin of Faculty of Pharmacy, Cairo University*, 2018, 1-10.
22. Londhe V, Shirsat R, "Formulation and Characterization of Fast-Dissolving Sublingual Film of Iloperidone Using Box-Behnken Design for Enhancement of Oral Bioavailability." *AAPS PharmSciTech.* 2018, 19(3), 1392-1400.
23. Pawandeep K and Vijay K, "Formulation Development and Evaluation of Fast Dissolving Bioadhesive Sublingual Film of Sumatriptan," *World Journal of Pharmaceutical Research*, 2017, 6 (14), 385-410.
24. Ayat A, Gihan F, "Sublingual fast dissolving niosomal films for enhanced bioavailability and prolonged effect of metoprolol tartrate," *Drug Design, Development and Therapy*, 2016, 10, 2421–2433.
25. Vani K, Tarun G, Gautam R, Amit K, "Development and evaluation of a sublingual film of the antiemetic Granisetron hydrochloride", *Taylor & Francis Online*, 2016,44(3), 1-12.
26. RamyaDeepthi and K. Satish Kumar, "Formulation And Evaluation of Amlodipine Besylate Oral Thin Films", *International Journal of Pharmaceutical Sciences and Research*, 2016, 7 (1), 199-205.
27. Maheswari K, PavanK, SravanthiD, Salma S, Naga P, and Buchi N., "Development and Evaluation of Mouth Dissolving Films of Amlodipine Besylate for Enhanced Therapeutic Efficacy", *Journal of Pharmaceutics*, 2014, 1-10.
28. Prachi P, Sonam C, "Fast Dissolving Sublingual Films of Zolmitriptan: A Novel treatment approach for

Migraine Attacks”, Indian Journal of Pharmaceutical Education and Research, 2014, 48, 67-72.

29. Deepali N. Tapre, Sachin P. Borikar, Shirish P. Jain, Sheelpriya R. Walde, Ganesh G. Tapadiya, Vishal C. Gurumukhi, “Development and evaluation of novel famotidine-loaded fast dissolving sublingual film using the quality-by-design approach,” Journal of Drug Delivery Science and Technology, 2023, 85, 1-18.

30. Ozgur E, Cansel K, Sevinc K, Alper A, Cetin T, AyhanSr, Sibel A &Yalcin O, “Development and In Vitro/In Vivo Evaluation of DihydroergotamineMesylate LoadedMaltodextrin-Pullulan Sublingual Films”, Drug Development and Industrial Pharmacy, 2019, 45 (6), 914-921.

31. SatyajitSahoo, Ami Makwana , AsitRanjanSahu , Asha Keshri and Vikash Dash, “Formulation And Evaluation Of Sublingual Film Of Enalapril Maleate By 32 Full Factorial Design”, Aegaeum Journal. 2020, 8 (4), 80-94.

32. Sachin G, Sonali S, Omprakash B, Sandeep S, Mahesh B, “Formulation and Evaluation of Oral Fast Dissolving Sublingual Film of Propranolol HCl”, Int J Pharma Res Health Sci. 2018, 6 (2), 2369-73.

33. Viviana D, Alessia A, Flavia M, Denise M, Maria Aand Clelia D, “Development and Characterization of an Amorphous Solid Dispersion of Furosemide in the Form of a Sublingual Bioadhesive Film to Enhance Bioavailability”, Pharmaceutics, 2017, 9 (3), 1-15.

34. Rakesh K, Chauhan C, “Design of Fast Dissolving Anti-Asthmatic Films Using 23 Factorial Designs,” The Pharmaceutical and Chemical Journal, 2016, 3(2), 145-157.

35. Prachi Pandey, Sonam Chauhan, “Fast Dissolving Sublingual Films of Zolmitriptan : A Novel treatment approach for Migraine Attacks”, Indian Journal of Pharmaceutical Education and Research, 2014, 14, 67-72.

36. Deepak Heer, Geeta Aggarwal and S.L. Hari Kumar, “Recent Trends Of Fast Dissolving Drug Delivery System - An Overview Of Formulation Technology”, International Research Journal, 2013, 4(1), 1-9.

37. Bradley G. Burk, Kyle Humphreys, Jim Waites, Bentley Adams, BadariBirur and Pamela E. Parker, “Sublingual asenapine for agitation in malabsorptive states: three patient cases”, TherAdvPsychopharmacol, 2024, 14,1-7.

38. BhyanBhupinder, JangraSarita, “Formulationand evaluation of fast dissolving sublingual films ofRizatriptan Benzoate.” International Journal of Drug Development & Research. 20124(1), 133-143.

39. SatyajitSahoo, Sohil Dal, Jagir Patel, DhartiDasadiya, “Formulation, Optimization And

Evaluation Of Fast Dissolving Sublingual Film Of Ziprasidone Using Statistical Design”, Indian Journal Of Applied Research, 2022, 12 (1), 4-9.

40. Manohar S. K. , Gowrav M. P. , D. V. Gowda, “Qbd-Based Development Of Orodispersible Films Of Antipsychotic Drugs,” Int J App Pharm, 2022, 14(5), 41-52.

41. Ali MS, Vijendar C, Sudheer Kumar D and Krishnaveni J, “Formulation and Evaluation of Fast Dissolving Oral Films of Diazepam”, Journal of Pharmacovigilance, 2016, 4 (3), 1-5.

42. Maryam M, Mahdieh R, Hamed G, Seyed H,Saieede S , Mitra A, Sara S, Mitra J, “Fast Dissolving Sublingual Films Containing Sumatriptan Alone and Combined with Methoclopramide: Evaluation in Vitro Drug Release and Mucosal Permeation”, Pharm Sci.2016, 22(3), 153-163.

43. Syed N, Aabid H, Taha U and Nisar A, “Formulation and Evaluation of Mouth Dissolving Films of Losartan Potassium Using 32 Factorial Design”, IJPSR, 2019, 10 (3), 1402-1411.

44. Lakshmi P, Malavika P, Vidya K, “Formulation and Evaluation of oral Films of Atomoxetine Hydrochloride”, Int. Res. J. Pharm. 2018, 9 (9), 105-109.

45. Vyas P, Hwang BJ, Brašić JR. An evaluation of lumateperonetosylate for the treatment of schizophrenia. Expert OpinPharmacother. 2020, 21(2):139-145.

46. Shradha S, Pravin W, Onkar S, Kanchan G, Shejal L, Bipin G, “Formulation Development and Evaluation of Immediate Release Dosage Form”, International Journal of Advanced Research in Science, Communication and Technology, 2023, 3(4),361-366.

47. Longo G, Cicolini A, Orsolini L, Volpe U. The Novel Antipsychotic Lumateperone (Iti-007) in the Treatment of Schizophrenia: A Systematic Review. Brain Sci. 2023, 26; 13(12):1641.

