DESIGN AND CHARACTERIZATION OF DULOXETINE HCl FAST DISSOLVING ORAL FILMS BY USING A PEARLITOL FLASH

K.Sudhamani,
Department of Pharmaceutics, Malla Reddy Institute of Pharmaceutical sciences,
Malla Reddy Vishwavidyapeeth, secunderabad, Telangana, India
Koramaina Akanksha

Department of Pharmaceutics,Malla Reddy Institute of Pharmaceutical sciences,

Malla Reddy Vishwavidyapeeth, secunderabad, Telangana, India

B. Rama

C.L.Baid metha college of pharmacy,Thoraipakkam,Chennai

P. Laxmimadhuri,

Department of Chemistry, Malla Reddy Institute of Pharmaceutical sciences,

Malla Reddy Vishwavidyapeeth, secunderabad, Telangana, India

Sunanda sabbithi

Department of pharmacology, Malla Reddy Institute of Pharmaceutical sciences,

Malla Reddy Vishwavidyapeeth, secunderabad, Telangana, India

Abstract: The present study focuses on the formulation and evaluation of fast dissolving oral films (FDOFs) of Duloxetine HCl, a widely used antidepressant, to enhance its patient compliance and onset of action.Till now no research work found on oral film of duloxetine. Fast dissolving films offer a promising alternative to conventional oral dosage forms, especially for patients with swallowing difficulties. In this study, Pearlitol Flash and Sodium Starch Glycolate (SSG) were employed as super disintegrating agents. The films were prepared using the solvent casting method, and various formulations were assessed for physical appearance, disintegration time, drug content uniformity, folding endurance, and in vitro drug release. Among the formulations, the one containing Pearlitol Flash as the primary polymer exhibited superior performance, demonstrating rapid disintegration and enhanced drug release profiles. The optimized formulation achieved desirable mechanical strength along with significantly improved dissolution, indicating the potential of Pearlitol Flash in developing effective FDOFs of Duloxetine HCl. This formulation strategy could be beneficial for improving therapeutic outcomes in depression management.

Keywords: Duloxetine HCl, Fast dissolving oral films, Solvent casting method, pearlitol flash

INTRODUCTION

Oral administration is the most commonly used route for drug delivery due to its ease of administration, cost-effectiveness, and high patient compliance [1,2]. However, conventional oral dosage forms such as tablets and capsules can be problematic for certain patient populations, including pediatric, geriatric, and mentally ill individuals, who may experience difficulty swallowing (dysphagia) [2,3]. To overcome these limitations and enhance therapeutic effectiveness, alternative dosage forms have been explored, among which fast dissolving oral films (FDOFs) have gained significant attention [1,4]. FDOFs are thin, flexible, and rapidly disintegrating polymeric films that dissolve quickly in the oral cavity without the need for water, offering a convenient and patient-friendly mode of drug delivery [1,5]. They provide a faster onset of action, improved bioavailability, and greater compliance, especially in acute conditions requiring immediate relief [5,6].

Duloxetine HCl, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), is widely used in the treatment of major depressive disorder, generalized anxiety disorder, and neuropathic pain [7,8]. Despite its effectiveness, its oral administration is associated with first-pass metabolism and delayed onset of action [6,9]. Formulating duloxetine into an FDOF could potentially bypass hepatic metabolism, offer rapid onset, and enhance therapeutic efficiency [4,9]. Till date no published data on Duloxetine HCl fast dissolving oral films. Hence the present study focuses on the development and evaluation of fast dissolving oral films of Duloxetine HCl using the solvent casting method, employing Pearlitol flash and sodium starch glycolate as key excipients. The objective is to optimize the formulation for rapid disintegration, adequate mechanical strength, and improved drug release profile, ultimately aiming to enhance patient compliance and treatment outcomes in depression management [4,10].

MATERIALS

Duloxetine HCl was obtained as gift sample from Mylan Laboratories Pvt Ltd. SSG was purchased from S D Fine chem limited (Mumbai), Pearliotl flash was obtaind from Signet excipients pvt.ltd (India), HPMC K15 was purchased from Yarrow chem products (Mumbai), Citric acid was purchased from Finar chemicals limited (Ahmedabad), Guar gum was obtained from Agro gums (Ahmedabad), Gelatin was purchased from Nitta gelatin India Ltd.

METHODOLOGY

Preparation of Duloxetine HCl Fast dissolving oral films

Duloxetine Fast dissolving oral films was prepared by using Solvent Casting method [11,12].

For the preparation of each of the six formulations (F1–F6), 15 mL of purified water was used individually as the dispersion medium. In each formulation, a specified amount of Duloxetine hydrochloride was first dissolved in water under continuous stirring. Based on the formulation design, Pearlitol® Flash was incorporated as the disintegrant in formulations F1 to F3, while sodium starch glycolate (SSG) was used in F4 to F6. The selected disintegrant was gradually added to the duloxetine solution with gentle stirring to ensure proper wetting and uniform dispersion. Separately, hydroxypropyl methylcellulose (HPMC) was dispersed in water and stirred until a clear solution was formed, then added to the main mixture. Guar gum and gelatin were each hydrated in a small volume of water until fully swollen and subsequently

incorporated into the formulation. Citric acid was added as it stimulates saliva, followed by the addition of sucrose as a sweetening and viscosity-enhancing agent. Each component was fully dissolved or uniformly dispersed before the final volume was adjusted to 15 mL with purified water.

After preparation, each of the six formulations was sonicated to remove entrapped air and obtain a bubble-free solution. The resulting clear solution was carefully poured into a petri dish and then placed in a hot air oven at a controlled temperature for 4–6 hours to allow complete drying. Once dried, the films were carefully peeled off and cut into the desired size. This entire process was repeated identically for all six formulations to ensure consistency and comparability during evaluation [11,12].

The compositions of the formulations are shown in Table-1

Table-1 Composition of different Fast dissolving oral films containing Duloxetine

S.NO	Ingredients	F1	F2	F3	F4	F5	F6
1.	Duloxetine HCl(gm)	0.24	0.12	0.12	0.12	0.12	0.12
2.	SSG (gm)	0.1	0.2	0.3	-	-	-
3.	Pearlitol flash (gm)	-	-	-	0.1	0.2	0.3
4.	HPMC K15 (gm)	0.6	0.3	0.3	0.3	0.3	0.3
5.	Gelatin (gm)	0.02	0.01	0.01	0.01	0.01	0.01
6.	Guar gum (gm)	0.02	0.01	0.01	0.01	0.01	0.01
7.	Citric acid (gm)	0.02	0.01	0.01	0.01	0.01	0.01
8.	PEG (ml)	5	2.5	2.5	2.5	2.5	2.5
9.	Water (ml)	15	15	15	15	15	15

Characterization of Fast dissolving oral films

Thickness: Thickness was measured at five different points of each film by using digital micrometre and mean value was reported [13].

Folding endurance: Film was repeatedly folded at the same place until it breaks. The number of the times the film is folded without breaking is taken as the folding endurance value and mean was reported [14].

***In vitro* disintegration time (DT):** In vitro disintegration time (DT),2 cm^2 film strip was placed in petri dish having 10 mL of USP phosphate buffer solution (PBS) (pH 6.8). DT was considered, when film was completely disintegrated after immersion in fluid and mean reported [14].

Drug content: FDOFs of 2 cm^2 was completely dissolved in 20 mL of PBS (pH 6.8) in beaker. Then solution was filtered through 0.45µm syringe filter. Filtrate was suitably diluted with PBS (pH 6.8) and scanned on UV/Vis Spectrophotometer (Shimadzu) at 290nm. The content of Duloxetine HCl was determined by using previously developed calibration curve [15].

Film moisture content: Moisture content tests were performed to ensure dryness. The prepared films were initially weighed and located in the desiccators containing calcium chloride. After 3 days the films were reweighed to obtain the percentage of moisture loss. Three films of each formula were used in this test [16].

Surface pH: The surface pH of the oral dissolving films is calculated in order to investigate the risk of any side effects *in vivo*. Since acidic or alkaline pH may cause irritation to the oral mucosa and it is measured to maintain the surface pH as close to neutral as possible. A combined pH electrode is used for this purpose. The film was slightly wet with the help of 1 ml of distilled water and kept for 30 seconds. The pH was measured by bringing the electrode in contact with the surface of the formulation and allowing it to equilibrate for 1 minute. The average of three determinations for each film was determined [17].

FTIR spectroscopy: FTIR studies are conducted to know drug-polymer compatibility. The spectra of Duloxetine HCl. and Duloxetine HCl loaded fast dissolving films were recorded on FTIR spectrophotometer by KBr. pellet method both the pellets were prepared by crushing the samples with KBr. The pellet was placed in a sample holder and spectral scanning was taken in a wavelength region between 4000-500cm^{-1} [18].

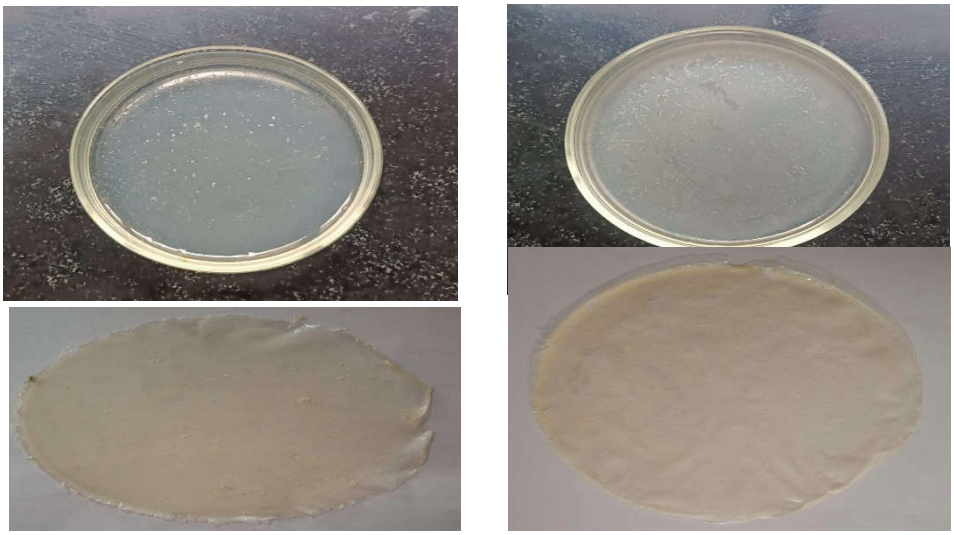
In vitro drug release: In vitro release of Duloxetine HCl loaded film was carried out in a beaker containing 200mL PBS having pH 6.8, maintained at 37±0.5˚C and stirred at 50 rpm. 5 mL of sample was withdrawn at specific time intervals (0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5 and 10 minutes) and substituted by 5mL of fresh prewarmed (at 37˚C) dissolution medium. The samples were passed through 0.45 µm syringe filters and analysed for drug content by measuring the absorbance at 290 nm [11]

RESULTS AND DISCUSSION

Preparation of Duloxetine HCl Fast dissolving oral films

Formulation i.e., F1 – F6 were prepared in formulation F1 the film formed was not transparent, hence in F2 the ratio of film forming agents were changed and F2 films was transparent, hence the same concentration of film forming agents was used from F3 to f6.

F1, F2, F3 were prepared by using SSG as super disintegrant whereas F3, F4, F5 were prepared by using Pearlitol flash as super disintegrant to optimize the disintegration time.



F1-Film F6- Film

Figure:1 Duloxetine HCl Fast dissolving oral films

Characterization of Fast dissolving oral films

Table-2: The physical parameters of the prepared oral films of Duloxetine HCl

Formulation code	Thickness (cm)	Folding endurance	Disintegration time(seconds)	Drug content	Moisture content(%)	Surface pH
F1	0.18	>200	45	93	4.8	6.1
F2	0.13	>200	37	91	2.7	6.4
F3	0.12	>200	31	96	2.3	6.8
F4	0.11	>200	28	97	3.1	6.6
F5	0.12	>200	22	96	2.6	6.7
F6	0.1	>200	10	98	2.4	6.9

Thickness: The Thickness films was in the range of 0.1 to 0.18cm.

Folding endurance: The results showed that all the formulations had folding endurance of >200 this indicates satisfactory folding endurance this may be due to the combination of film forming agents like Gelatin, HPMC K15, Guar gum.

Invitro disintegration time: The disintegration time for all the formulations were in the range of 10- 45 seconds. Formulation F6 shown the disintegration time of 10 seconds this may be due to the higher concentration of pearlitol flash.

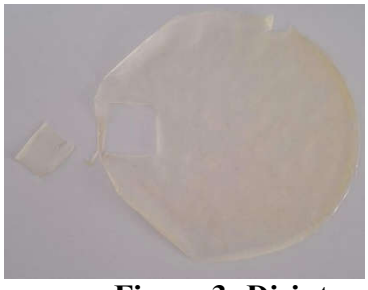


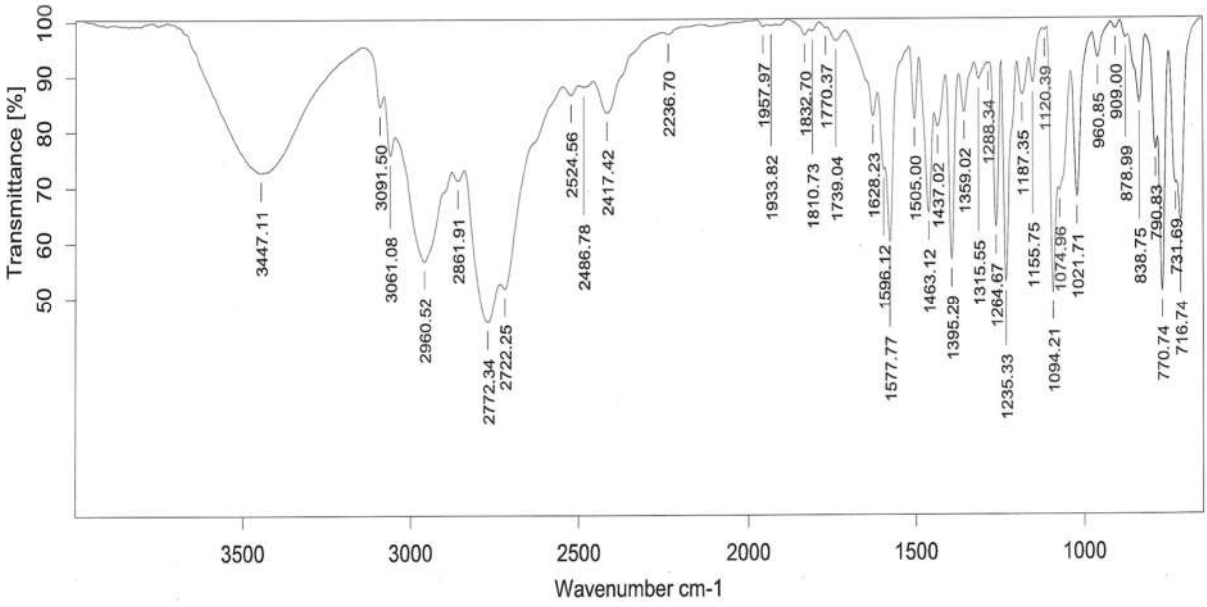
Figure 3: Disintegration of Duloxetine HCl Fast dissolving oral film (F6)

Drug content: The drug content was found to be in the range of 91- 98 % this indicates uniform distribution of drugs in the films**.**

Moisture content: The moisture content of all the formulations was in the range of 4.8-2.4 In formulation F1 increase in the moisture uptake by the film compare to other films may be due to the high concentration of film forming agents.

Surface pH: The surface pH of films were found to be in the range of 6- 6.9 which is within the salivary pH range this indicates the film does not cause any oromucosal irritation. The surface pH of all the films were slightly acidic in nature due to the use of salivary stimulating agent citric acid.

FTIR spectroscopy: The optimized formulation (F6) is investigated for FTIR analysis. FTIR spectra of Duloxetine HCL and optimized formulation were compared. In Duloxetine HCL spectrum Figure (3). The FTIR spectrum of Duloxetine showed principal bands at 1463.12cm^{-1} for thiophene ring, 1264.67cm^{-1} for ether C-O, 1505.00cm^{-1} for aromatic alkenes. FTIR bands of the drug remain intact in both the spectra of the drug and physical mixture, illustrating absence of interaction between drug and super disintegrating agent.



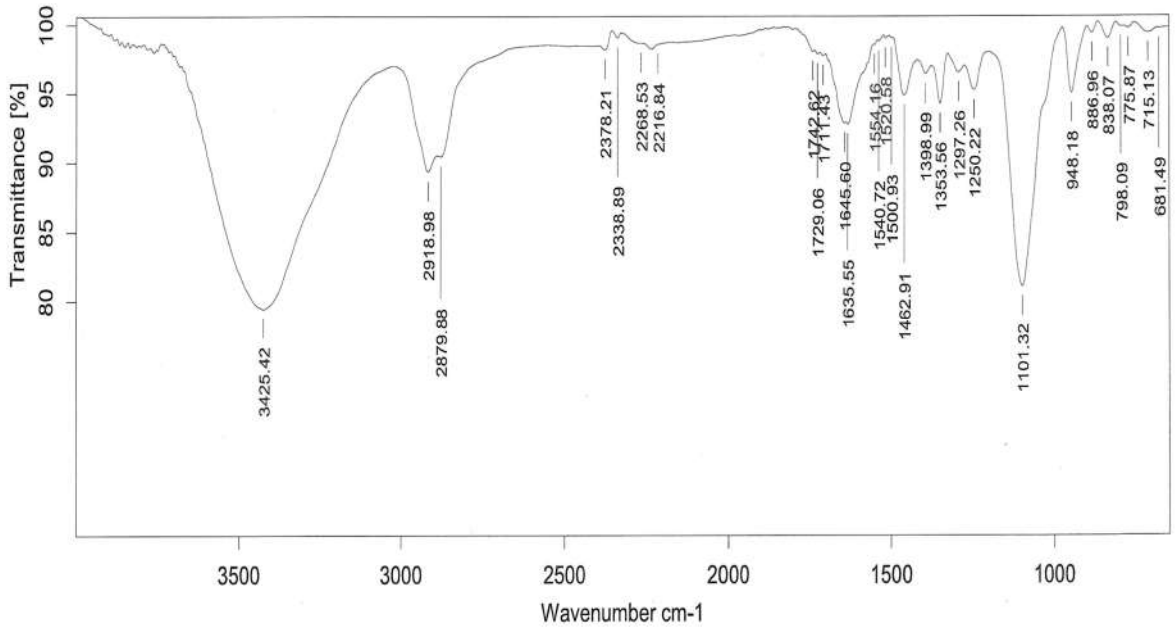
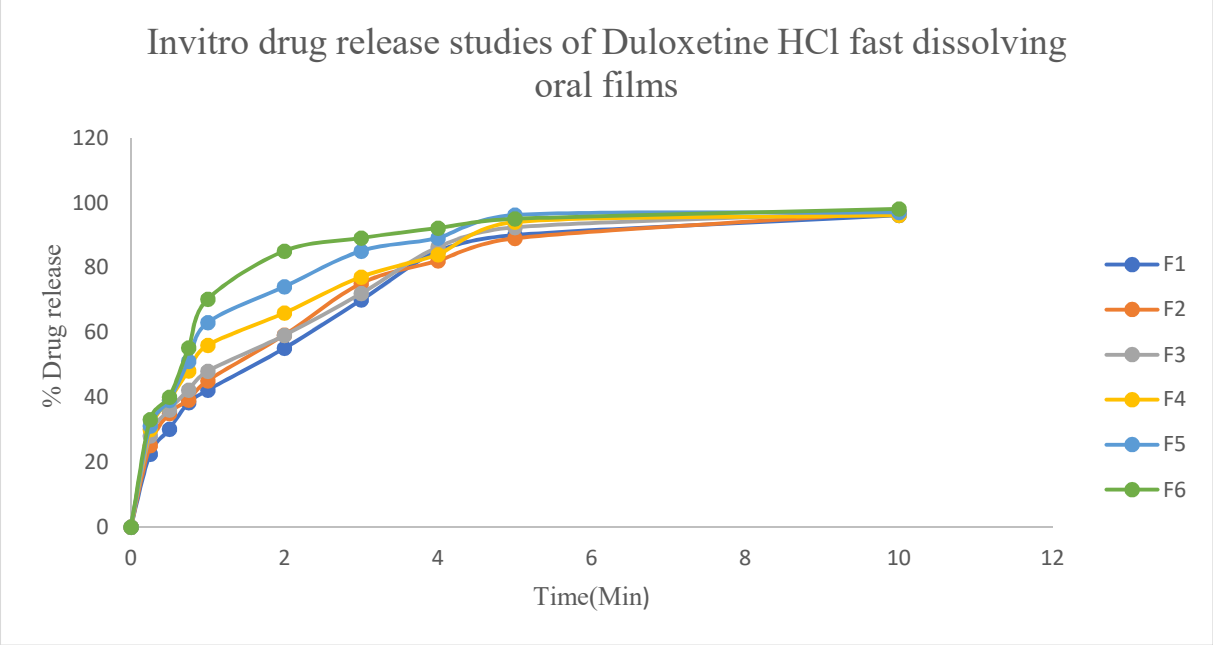


Figure 4: (a) FTIR Spectra of pure drug Duloxetine HCl (b) FTIR Spectra of Duloxetine HCl with Pearlitol flash loaded film

Invitro drug release studies



Formulation F6 showed maximum percent drug release of 98.2% within 3 minutes 85% of drug was released this could be due to higher rate and extent of swelling of large proportion of pearlitol flash.

CONCLUSION

Oral fast Dissolving films of Duloxetine HCl were formulated successfully by solvent casting method.

Formulation F6 showed maximum percent drug release of 98.2% within 3 minutes 85% of drug was released . Compared to the film prepared with sodium starch glycolate (F3), the film prepared with Pearlitol flash faster dissolution and drug release. These films offer an ideal platform for easier administration, particularly with patients with swallowing difficulties. The results from this formulation process indicate the films dissolve rapidly in the mouth without the need for water, which is a significant advantage for patient compliance.

REFERENCES

1. Arya, A., Chandra, A., Sharma, V., & Pathak, K. (2010). Fast dissolving oral films: an innovative drug delivery system and dosage form. *Int J ChemTech Res*, *2*(1), 576-83.
2. Bala, R., Pawar, P., Khanna, S., & Arora, S. (2013). Orally dissolving strips: A new approach to oral drug delivery system. *International journal of pharmaceutical investigation*, *3*(2), 67.
3. Bhyan, B., Jangra, S., Kaur, M., & Singh, H. (2011). Orally fast dissolving films: innovations in formulation and technology. *Int J Pharm Sci Rev Res*, *9*(2), 9-15.
4. Malke, S., Shidhaye, S., & Kadam, V. J. (2007). Formulation and evaluation of oxcarbazepine fast dissolve tablets. *Indian journal of Pharmaceutical sciences*, *69*(2).
5. Zhang, H., Zhang, J., & Streisand, J. B. (2002). Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. *Clinical pharmacokinetics*, *41*, 661-680.
6. Desai, K. G. H., & Pramod Kumar, T. M. (2004). Preparation and evaluation of a novel buccal adhesive system. *Aaps Pharmscitech*, *5*, 1-9.
7. Sc, S. (2009). Martindale: the complete drug reference.
8. Wohlreich, M. M., Mallinckrodt, C. H., Watkin, J. G., & Hay, D. P. (2004). Duloxetine for the long-term treatment of major depressive disorder in patients aged 65 and older: an open-label study. *BMC geriatrics*, *4*, 1-10.
9. Raju, P. N., Kumar, M. S., Reddy, C. M., & Ravishankar, K. (2013). Formulation and evaluation of fast dissolving films of loratidine by solvent casting method. *The pharma innovation*, *2*(2).
10. Alipour, S., Akbari, S., & Ahmadi, F. (2015). Development and in vitro evaluation of fast-dissolving oral films of ondansetron hydrochloride. *Trends in Pharmaceutical Sciences*, *1*(1), 25-30.
11. Rashid, A., Khan, I. U., Khalid, S. H., Asghar, S., & Munir, M. U. (2021). Development and evaluation of oral fast disintegrating film of ranitidine HCl by solvent casting method. *Pakistan Journal of Pharmaceutical Sciences*, *34*.
12. Samuel, A. J., Mulla, N. N., & Jagtap, P. C. (2020). Formulation and Evaluation of Oral Fast Dissolving Film of Simvastatin. *Journal of Emerging Technologies and Innovative Research*, *7*(6), 977-982.
13. Kumar, G. P., Phani, A. R., Prasad, R. G. S. V., Sanganal, J. S., Manali, N., Gupta, R., ... & Raju, D. B. (2014). Polyvinylpyrrolidone oral films of enrofloxacin: Film

characterization and drug release. *International journal of pharmaceutics*, *471*(1-2), 146-152.

14. Chandra, A., Chondkar, A. D., Shirodkar, R., & Lewis, S. A. (2018). Rapidly dissolving lacidipine nanoparticle strips for transbuccal administration. *Journal of Drug Delivery Science and Technology*, *47*, 259-267.
15. Brniak, W., Maślak, E., & Jachowicz, R. (2015). Orodispersible films and tablets with prednisolone microparticles. *European Journal of Pharmaceutical Sciences*, *75*, 81-90.
16. 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.
17. Salman, Z. D., Maraie, N. K., Alabbassi, M. G., & Ghareeb, M. M. (2014). In vitro/in vivo evaluation and bioavailability study of amitriptyline hydrochloride from the optimized oral fast dissolving films. *Pharmaceutical and Biosciences Journal*, 32-42.
18. Peddapalli, H., Chinnala, K. M., & Banala, N. (2017). Design and in vitro characterization of mucoadhesive buccal patches of duloxetine hydrochloride. *Int J Pharm Pharm Sci*, *9*, 52-9.