Development and Evaluation of Mouth Dissolving Film of Clomipramine Hydrochloride

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ABSTRACT
Over 90% of drugs produced in recent years are in oral dosage forms, highlighting their significance as a standard worldwide. Among these, fast-dissolving oral films (FDOFs) have emerged as a novel and patient-friendly drug delivery system. FDOFs are ultra-thin films containing an active ingredient that dissolves in saliva within seconds, eliminating the need for water or chewing. Clomipramine HCL, a tricyclic antidepressant used to treat obsessive-compulsive disorder (OCD), depression, and panic disorders, traditionally poses challenges for patients with difficulty swallowing tablets or capsules. The development of a clomipramine FDOF offers a promising alternative, enabling the drug to be quickly absorbed through the oral mucosa.The formulation of clomipramine FDOF includes key ingredients such as HPMC E15, sodium starch glycolate, PEG 400, methyl paraben, ascorbic acid, citric acid, and aspartame. The film was evaluated and found to have a weight of 29.8 ± 0.04 mg, a thickness of 0.16 mm, a folding endurance of 767 ± 5.0, and a surface pH of 6.64 ± 0.02. The disintegration time ranged from 1 minute to 1 minute and 20 seconds, with the F5 formulation showing the best performance at 1 minute and 2 seconds. In vitro studies demonstrated that 96.05 ± 2% of the drug was released within 15 minutes for the F5 formulation. A stability study revealed that 99.865% of the drug content remained after 3 months, indicating excellent stability of the optimized clomipramine HCl film.

Keywords: Clomipramine HCL, antidepressant, fast-dissolving oral film, HPMC E15, depression.

INTRODUCTION
Oral drug delivery is the most preferred route for administration due to its convenience, non-invasiveness, and high patient compliance.[1, 2] However, conventional oral dosage forms, such as tablets and capsules, often have limitations, particularly for patients who experience difficulty swallowing (dysphagia), such as pediatric, geriatric, and psychiatric patients.[3, 4] Furthermore, drugs that undergo significant first-pass metabolism, like clomipramine, can exhibit delayed therapeutic effects, reducing their efficacy for acute conditions such as anxiety or panic disorders.[5] In this context, fast-dissolving oral films (FDOFs) offer an innovative alternative, providing rapid drug release without the need for water or swallowing, improving both bioavailability and patient adherence.[6, 7]

Clomipramine, a tricyclic antidepressant primarily used to treat depression, obsessive-compulsive disorder (OCD), and panic disorders, suffers from extensive first-pass metabolism when administered orally in tablet or capsule form, leading to delayed onset of action and variable bioavailability.[8] The development of clomipramine-loaded fast-dissolving oral films presents a novel drug delivery system that could overcome these limitations by promoting faster absorption through the oral mucosa, bypassing the gastrointestinal tract.[9, 10]

This innovative approach has the potential to revolutionize the way clomipramine is administered, particularly for patients requiring rapid relief from anxiety or panic attacks. It addresses the limitations of conventional formulations while improving patient compliance and therapeutic outcomes.

REVIEW OF LITERATURE

Thakur N. *et. al.*, (2023) prepared „Overview "A novel approach of fast dissolving films and their patients". Fast dissolving drug delivery systems have started gaining fame and acceptance as new drug delivery systems. Which aim to enhance safety and efficacy of a drug molecule by formulating it into a conventional oral dosage form for administration and to achieve better patient compliance. Fast dissolving drug delivery the film is placed on the top or the floor of the tongue. When put on the tongue, this film dissolves instantaneously, releasing the drug which dissolves in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such case is enhancing drug bioavailability, no risk of chocking, provide good mouth feel. [11]

Desai P. *et. al.*, (2021) were formulated „Formulation and evaluation of fast dissolving film of Domperidone". Domperidone is a specific blocker of dopamine receptors solvent casting method was used for preparation of fast dissolving film. Various film forming polymers were evaluated for selection of suitable polymer. Different polymers like maltodextrin, PVA and different grades of HPMC like HPMCE5 LV, HPMC E15 LV and HPMC E3 LV were used in the study for selection of polymers. Amongst them HPMC E3 LV, HPMC E5 LV was selected as film forming polymers and propylene glycol was used as plasticizer. For solubility enhancement inclusion complex from β cyclodextrin was prepared by kneading method. Films were evaluated for physical and mechanical properties, drug content, disintegration time, in vitro dissolution study.[12]

Deepthi *et. al.*, (2019) was prepared „Formulation and evaluation of fast dissolving oral films of Zolmitriptan". The present study was aimed to formulate and evaluate fast dissolving oral films of Zolmitriptan using sodium alginate, xanthan gum and sodium starch glycolate, guar gum. The suitable plasticizer and its concentration were selected on the basic of flexibility, tensile strength and stickiness of the film. The films are prepared by solvent casting method and characterized by UV, FTIR studies. The films were evaluated for disintegration time, Folding endurance, Tensile strength, Mouth dissolving time, Thickness, content uniformity and *in-vitro* dissolution studies. The F5 formulation has given 98.5% drug release within 6 minutes and has a tensile strength of 1.80 MPa. [13]

Rana S. *et. al.*, (2016) was developed „Formulation and evaluation of Domperidone fast dissolving film by using different polymers. Developing a fast-dissolving delivery system releasing domperidone concomitantly in stomach for treating vomiting and motion sickness. Domperidone FDFS was prepared by solvent casting principle. Different concentration of film forming polymer i.e. domperidone with and without solubilizing agent tween 80 had better. Korsmeyer-peppas model was found to be fit kinetic in which all formulation showed good linearity (R^2: 0.906 to 0.989), with slope (n) values ranging from 0.655 to 0.981. In korsmeyer-peppas model, ‟n‟ is the release exponent indicative of mechanism of drug release. The „n‟ values ranged from 0.5-1.0 indicate anomalous transport (non-fickian) diffusion where drug release is both diffusion and swelling controlled.[14]

MATERIAL AND METHOD

Table 1 are representing the list of materials and their sources and table 2 are representing the List of equipment.

Table.1: List of materials and their sources are shown in the below table

MATERIALS	SOURCES
Clomipramie Hydrochloride	Biophore India Pharmaceuticals Pvt. Ltd.
HPMC E15	SD Fine
PEG 400	SD Fine
Methyl Paraben	SD Fine
Ascorbic Acid	SD Fine
Citric acid (mg)	Loba chemie
Aspartam (mg)	Loba chemie

EQUIPMENTS

Table 2. List of equipments are shown in the below table

EQUIPMENT	MODEL/COMPANY
UV Visible Spectrometer	Shimadzu UV -1800
Analytic Weight Balance	Wensar
Digital PH Meter	Labtech
Magnetic Stirrer with Hot Plate	Rolex India
Sonicator	Pci Analytics

Determination of λmax of Clomipramin Hydrochloride in Phosphate Buffer pH 6.8

Accurately weigh 100 mg of Clomipramine hydrochloride and transfer it into a 100 mL volumetric flask. Dissolve the substance in phosphate buffer with pH 6.8 and adjust the volume to 100 mL to achieve a concentration of 1 mg/mL (1000 µg/mL). Next, take 10 mL of this solution (equivalent to 10 mg of Clomipramine hydrochloride) and transfer it into a

new 100 mL volumetric flask. Dilute with phosphate buffer pH 6.8 to reach a final volume of 100 mL, resulting in a stock solution of 0.1 mg/mL (100 µg/mL). Subsequently, prepare a 10 ppm (parts per million) solution by using this stock solution and analyze it using a UV spectrophotometer. Scan the solution across the wavelength range of 200 nm to 400 nm, using phosphate buffer pH 6.8 as a blank.

Preparation of Calibration Curve of Clomipramin Hydrochloride

The above stock solution was used to prepare several dilutions (2, 4, 6, 8, 10, 12, 16, and 18 µg/mL) in phosphate buffer with pH 6.8. The absorbances of these dilutions were then measured using a UV-spectrophotometer at the wavelength of maximum absorbance (λmax), with phosphate buffer pH 6.8 serving as the blank solution. The experiment was conducted in triplicate, and the average absorbance values along with the standard deviation were calculated. These values were used to construct a calibration curve plotting Concentration in µg/mL against Absorbance at λmax. Additionally, the equation for the line of best fit was determined from the calibration curve.

Solubility Determination of Clomipramin Hydrochloride

The solubility of Clomipramine hydrochloride was determined in different medium using the equilibrium solubility method. For this, 5 ml of each solvent was placed into separate vials, and an excess of Clomipramine hydrochloride was added to the vials containing distilled water and phosphate buffer (pH 6.8). The vials were stirred with a magnetic stirrer at 37±2°C for 12 hours. Following this, the solutions were left to equilibrate for an additional 24 hours. The equilibrated solutions were then transferred to Eppendorf tubes and centrifuged for 5 minutes at 2000 rpm. The supernatants from each vial were filtered through a 0.45-micron membrane filter, diluted as needed, and analyzed using a UV-visible spectrophotometer at 252 nm. The study was conducted in triplicate.

Melting Point Determination

The melting point of a Clomipramin Hydrochloride was determined by the capillary tube method. First, finely grind the substance and packed a small amount into a thin-walled glass capillary tube, ensured the sample occupies about 2-3 mm at the closed end. Attached the tube to the melting point apparatus, positioned it next to the bulb. The temperature was gradually increased and observed the sample closely, noted the temperature at which it begins to melt and when it is completely liquefied. Recorded the melting point range, which is typically narrow for pure substances.

FORMULATION STUDY

Preparation of Fast Dissoving Film of Clomipramin Hydrochloride Selection of Procedure for Film Preparation

The solvent casting method was employed to prepare the film. Initially, the polymer was soaked in three-fourths of the solvent overnight. The polymer solution was then mixed using a magnetic stirrer for approximately 30 minutes until a uniform dispersion was achieved. Subsequently, a plasticizer, film modifier, and sweetening agent were added, each followed by 10 minutes of stirring. The polymer solution was further mixed on the magnetic stirrer for

60 minutes. To remove any air bubbles, the solution was sonicated for 30 minutes. The polymer solution was then poured into a previously lubricated circular glass petri plate with a diameter of 9.0 cm, lubricated with glycerin. The films were dried at room temperature, then peeled off, cut into 2 cm x 2 cm pieces, wrapped in butter paper, and stored in a desiccator. The critical quality attributes considered for the formulation included the film's clarity, peelability, stiffness, and disintegration time. Table 3 representing a formulation of Clomipramine Hydrochloride Fast Dissolving Film

Table 3. Formulation Development of Clomipramine Hydrochloride Fast Dissolving Film

S.No.	Ingredients	F1	F2	F3	F4	F5	F6
1.	Clomipramie Hydrochloride (mg)	10	10	10	10	**10**	10
2.	HPMC E 15 (mg)	200	300	400	200	**300**	400
3.	Sodium Starch Glycolate (mg)	40	40	40	50	**50**	50
4.	PEG 400 (ml)	0.1	0.1	0.1	0.1	**0.1**	0.1
5.	Methyl Paraben	0.01	0.01	0.01	0.01	**0.01**	0.01
6.	Ascorbic Acid	10	10	10	10	**10**	10
7.	Citric acid (mg)	10	10	10	10	**10**	10
8.	Aspartam (mg)	5	5	5	5	**5**	5
9.	Distilled water (ml)	10	10	10	10	**10**	10

Evaluation of the Films

The prepared films were evaluated for physical appearance, microscopy, weight, thickness, surface pH, folding endurance, disintegration time, tensile strength, drug release and stability.

1. **Physical Appearance**

   The prepared mouth dissolving films were checked visually for uniformity, clarity and tackiness.

2. **Weight and thickness**

   The films prepared were cut into 2cm X 2cm size and then weighed on a Sartorius electronic balance. Three films were weighed individually and their average weight and standard deviation recorded. The thickness of the film was measured using micrometer at three different places and an average of three readings of three films and standard deviation was recorded.

3. **Surface pH**

   The film was placed in a glass petri plate then it was moistened with 0.5ml of phosphate buffer and kept for 30s and pH was noted after bringing the electrode of pH meter in contact with surface. An average of three readings of three films and standard deviation was recorded.

4. **Folding Endurance**

   This test was done by folding the individual film manually in the same plane till it produced visible crack. The number of times it is folded to produce visible crack is noted as the folding endurance of the film.

5. **Disintegration test**
   Disintegration test was done using disintegration test apparatus IP with phosphate buffer pH 6.8 as the medium and 37±2℃ temperature.
6. ***Invitro* Drug Release**
   The *Invitro* drug release was determined of Clomipramine hydrochloride mouth dissolving films using modified dissolution apparatus as used .The dissolution medium used was phosphate buffer pH 6.8. The films were placed in a 50 ml beaker containing 20ml of phosphate buffer pH 6.8 and suspended in dissolution flask. The dissolution apparatus II was used wherein the stirrer was used without the basket attachment and run at speed of 50rpm. The sample was drawn at the interval of 3,6,9,12,15, 18 and 21min and the content was measured spectrophotometrically at λmax 252 nm using UV Spectrophotometer.
7. **Assay**
   The Clomipramine hydrochloride film was dissolved in 10ml of phosphate buffer pH 6.8 and then the content of drug present was measured at λmax 252 nm using UV Spectrophotometer.
8. **Stability Study**
   The stability study was done for the optimized film formulation of Clomipramine hydrochloride. The prepared films of Clomipramine hydrochloride were wrapped in butter paper followed by aluminum foil and then placed in desiccator for period of 90 days at room temperature, ambient humidity and then evaluated for appearance weight, thickness, surface pH, folding endurance, disintegration time, drug release and assay.

RESULT AND DISCUSSION

1. **Determination of UV Spectra**
   The UV spectrum of Clomipramine Hydrochloride showed absorbance maxima at wavelength 252nm which is similar to the standard peaks therefore confirmed the identity of sample drug as Clomipramine Hydrochloride (figure 1). Reported absorbance maxima were Clomipramine Hydrochloride were λmax at 252 nm.

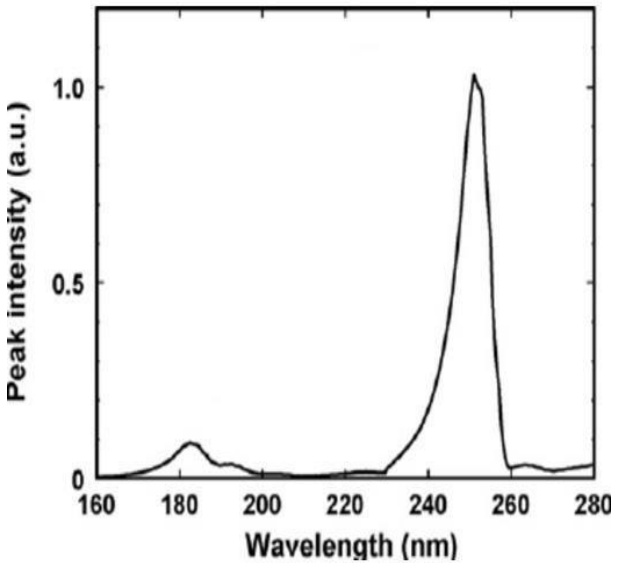

Figure 1 Spectra of Clomipramine Hydrochloride

2. Calibration Curve of Clomipramin Hydrochloride

The calibration curves of Clomipramine Hydrochloride in phosphate (6.8 pH) was prepared. Table 4 representing Absorbance of Clomipramine Hydrochloride in phosphate buffer at different concentration and figure 2 representing a calibration curve of Clomipramine Hcl in Phosphate buffer 6.8 pH

Table 4: Absorbance of Clomipramine Hydrochloride in phosphate buffer at different concentration

S.NO.	entration(µ g/ml)	Absorbance(nm)
1.	2	0.241
2.	4	0.397
3.	6	0.562
4.	8	0.699
5.	10	0.801
6.	12	0.895
7.	14	1.045
8.	16	1.196

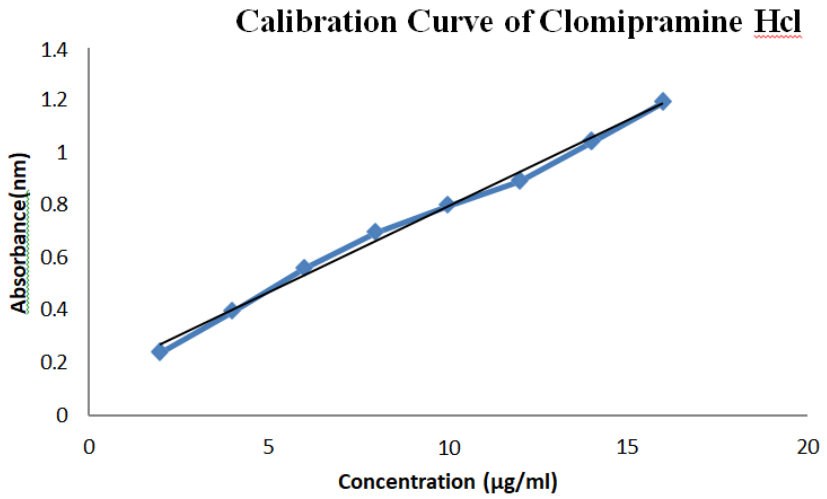

Figure 2 Calibration Curve of Clomipramine Hcl in Phosphate buffer 6.8 pH

3. Solubility Determination of ClomipraminHydrochlorid

The solubility of Clomipramine Hydrochloride in various medium was studied and the results of study are shown in table 5

Table 5: Solubility data of Clomipramine Hcl different medium

S.no.	Solvent	Solubility(mg/ml)
1.	Distilled water	125 mg/ml
2.	Phosphate Buffer 6.8	75 mg/ml
3.	Ethanol	70 g/ml

4. Melting Point Determination

Melting Point was measure by melting point apparatus, Recorded M.P. Shown in Table No. 6

Table 6: Melting Point of Clomipramine Hcl

S.no.	Standard	Observed
1.	191.5-192	190-192

5. Drug –Excipient Compatibility by FTIR

Figure 3 representing FTIR Spectra of pure drug Clomipramie Hcl and tsble 7 representing a FTIR Interpretation of pure drug Clomipramine HCL

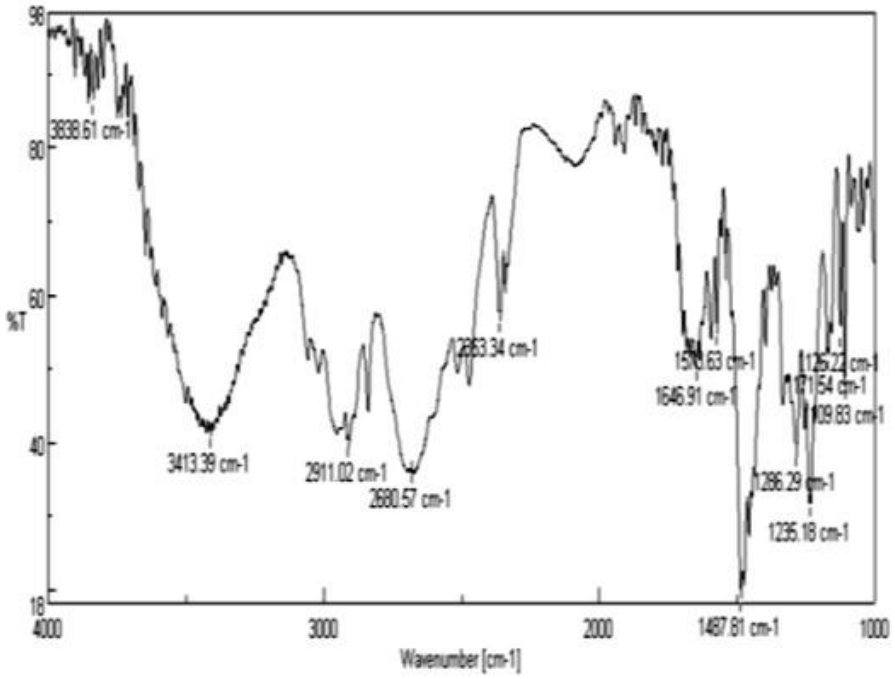

Figure 3 FTIR Spectra of pure drug Clomipramie Hcl

Table 7 representing FTIR Interpretation of pure drug Clomipramine HCL and figure 4 representing FTIR Spectra of Clomipramine HCl and HPMC E15. Table 8 representing FTIR Interpretation of Clomipramine HCl and HPMC E15 and figure 5 representing FTIR Spectra of Optimized batch. Table 9 representing FTIR Interpretation of Clomipramine HCl and HPMC E15.

Table 7: FTIR Interpretation of pure drug Clomipramine HCL

S.No.	Functional Group	Wave No.
1	C-H Stretching	2680.57,2911.02
2.	C=C Stretching	2663.34,1646.97
3.	C-N Stretching	1550.63

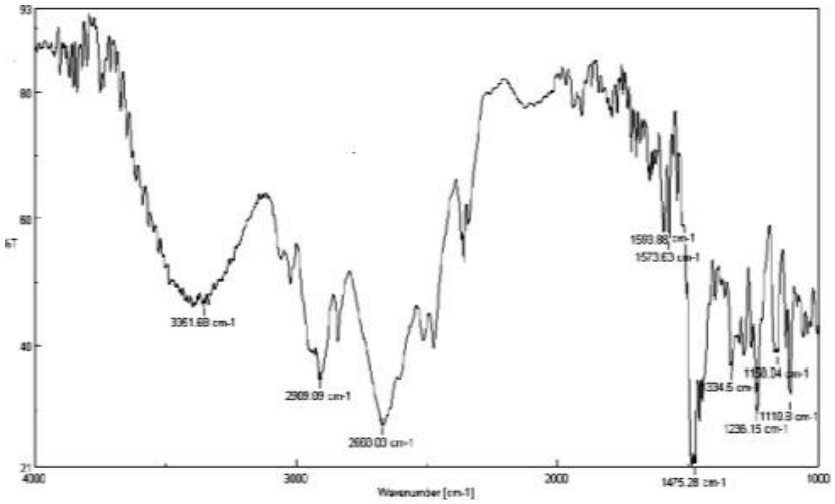

Figure 4: FTIR Spectra of Clomipramine HCl and HPMC E15

Table 8: FTIR Interpretation of Clomipramine HCl and HPMC E15

S.No.	Functional Group	Wave No.
1	O-H Stretching	3361.68
2.	O-H Bending	1334.50
3.	C-H Stretching	2509.09

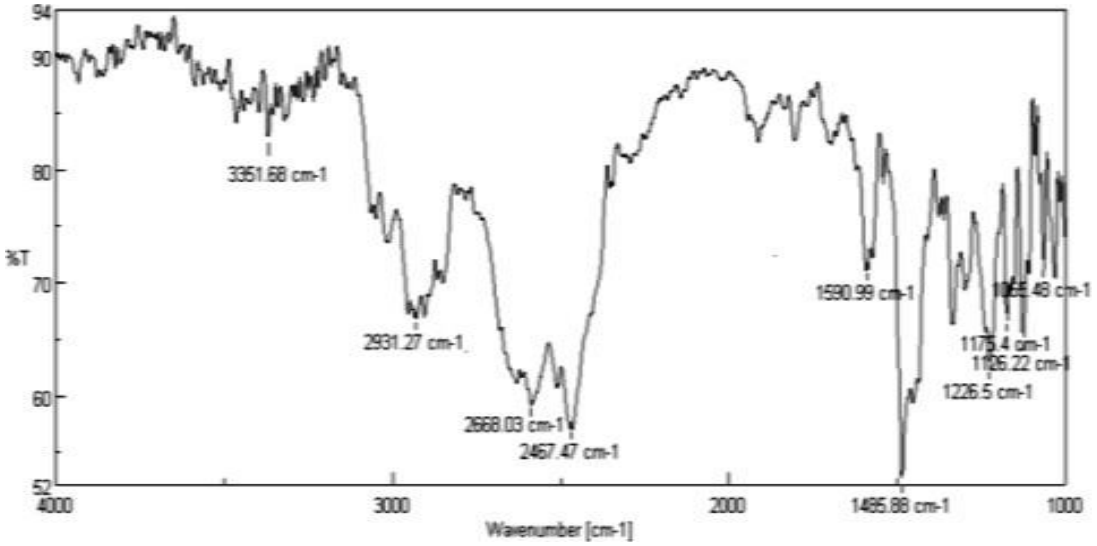

Figure 5 FTIR Spectra of Optimized batch

Table 9: FTIR Interpretation of Clomipramine HCl and HPMC E15

S.No.	Functional Group	Wave No.
1	C=N Stretching	1590.99
2.	O-H Bending	2931.27
3.	C=C Stretching	3351.68
4.	C=H Stretching	12265.0
5.	C=Cl Stretching	1175.04

6. Evaluation of Fast dissolving film of Clomipramine HCl

Table 10 representing Evaluation of optimized batches of selected excipients

Table 10: Evaluation of optimized batches of selected excipients

Code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Folding Endurance	720±5.0	735±5.0	755±5.0	785±5.0	**776 ±5.0**	789 ±5.0
Surface pH	6.67± 0.03	6.40±0.02	6.64±0.02	6.66±0.05	**6.67±0.05**	6.61±0.05
DT	1 mint. 7 sec.	1 mint. 12 sec.	1 mint. 20 sec.	1 mint.	**1 mint. 2 sec.**	1 mint. 17 sec.
Thickness(m m)	0.13 ±0.02	0.14 ± 0.01	0.17 ± 0.03	0.11 ± 0.01	**0.13 ± 0.01**	0.15 ± 0.01
Surface Texture	Not Smoot h	Smooth	Smooth	Not Smooth	**Smooth**	Smooth
Clarity	Not Clear	Clear	Clear	Not Clear	**Clear**	Clear

Results are expressed as mean ±SD (n=3)

7. In Vitro Drug Release

Table 10 representing In Vitro Drug Release of Optimized formulation and figure 6 representing Cumulative % drug release of optimized formulation

Table 11: *In Vitro* Drug Release of Optimized formulation

S.No.	Time (mint.)	Cumulative % Drug Release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	**0**	0
2	3	23.84	24.25	18.26	25.84	**25.51**	19.36
3	6	46.21	49.22	32.42	48.21	**40.03**	34.21
4	9	69.28	62.30	56..24	70.28	**62.24**	58.24
5	12	92.50	89.41	68.40	94.50	**79.89**	70.80
6	15		95.27	83.42		**96.05**	85.34

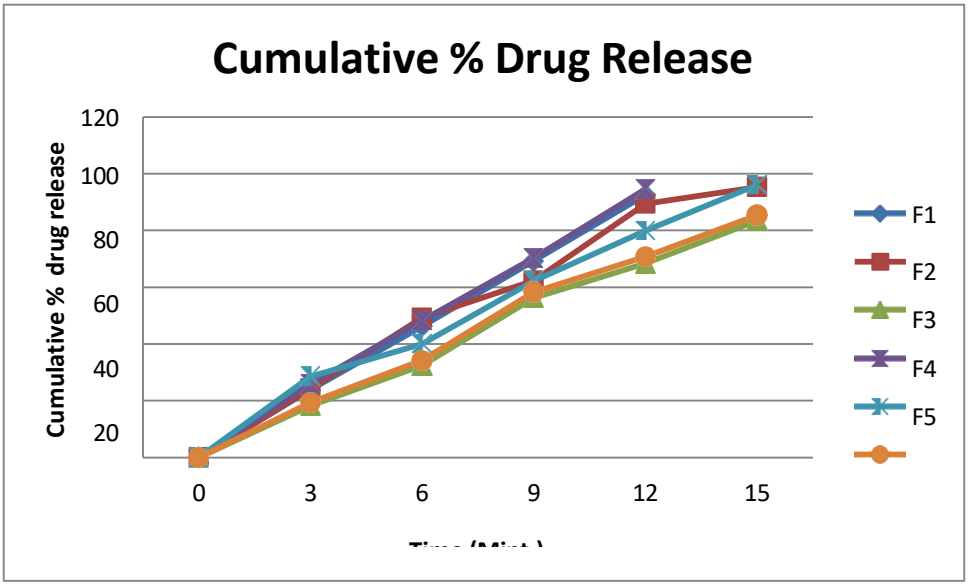

Figure 6 Cumulative % drug release of optimized formulation

In vitro drug release of all the formulation was performed. F5 considered as the best formulation on the basis of film property, texture. DT of the F5 formulation was 1mint. 2 sec. and the drug release was 96.05% in 15 mint.

8. Stability Studies

Table 12 representing Stability Studies of optimized film of clomipramine HCl

Table 12 Stability Studies of optimized film of clomipramine HCl

Time	0 day	15 days	1 Month	2 Months	3 Months
Assay	99.939%	99.924%	99.919%	99.879%	99.865%

CONCLUSION

The development of fast-dissolving oral films (FDOFs) containing clomipramine offers a promising and innovative approach to drug delivery, addressing several limitations associated with conventional oral dosage forms. This study successfully formulated and evaluated clomipramine-loaded FDOFs. The development of a clomipramine FDOF offers a promising alternative, enabling the drug to be quickly absorbed through the oral mucosa.The formulation of clomipramine FDOF includes key ingredients such as HPMC E15, sodium starch glycolate, PEG 400, methyl paraben, ascorbic acid, citric acid, and aspartame. The film was evaluated and found to have a weight of 29.8 ± 0.04 mg, a thickness of 0.16 mm, a folding endurance of 767 ± 5.0, and a surface pH of 6.64 ± 0.02. The disintegration time ranged from 1 minute to 1 minute and 20 seconds, with the F5 formulation showing the best performance at 1 minute and 2 seconds. In vitro studies demonstrated that 96.05 ± 2% of the drug was released within 15 minutes for the F5 formulation. A stability study revealed that 99.865% of the drug content remained after 3 months, indicating excellent stability of the optimized clomipramine HCl film.

The innovative FDOF formulation significantly enhances bioavailability and patient compliance, as it eliminates the need for swallowing or water, making it an ideal alternative for pediatric, geriatric, and psychiatric patients. Additionally, the solvent casting method used for formulation is cost-effective and scalable, enabling easy adaptation for large-scale production. This research highlights the potential of FDOFs as a novel and effective delivery method for clomipramine, contributing to advancements in the treatment of acute and chronic mental health conditions. Future studies focusing on in vivo assessments and clinical trials will further validate the therapeutic benefits of clomipramine FDOFs and support their development as a viable alternative to traditional oral formulations.

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REFERENCES

1. Harsha Kathpalia, Bhairavi Sule, Aasavari Gupte, Development and Evaluation of Orally Disintegrating Film of Tramadol Hydrochloride, Asian Journal of Biomedical and Pharmaceutical Sciences.3(24);2013:27-32.
2. Deepak Heer, Geeta Aggarwal and S. L. Hari Kumari, recent trends of fast dissolving drug delivery system - an overview of formulation technology, Pharmacophore. 2013, 4 (1):1-9.
3. Naryana Raju P, Sravan Kumar, Ch. Madhusudhan Reddy Ravi shanker K, Formulation and evaluation of fast dissolving films of Loratidine by solvent casting method.2;2013:31-35.
4. Pandya Ketul, Patel KR, Patel MR, Patel NM, Fast dissolving films A novel approach to oral drug delivery, Asian Journal of Pharmaceutical Science and Technology.3;2013:25- 31.
5. Prasanna P Ghodake, Kailas M. Karande, Riyaz Ali Osmani, Rohit R. Bhosale, Bhargav R. Harkare and Birudev B. Kale. Mouth Dissolving Films: Innovative Vehicle for Oral Drug

Delivery, International Journal of Pharma Research & Review. 2(10); 2013:41-47.
6. Bhupinder Bhyan, Sarita J, Manadeep Kaur, Harmanpreet Singh, Orally fast dissolving films: Innovations in formulation and technology. Int. Journal of Pharm Sci Rev & Res.9; 2011:2-9.
7. Arun Arya, Amrish Chandra, Vijay Sharma and Kamla Pathak. Fast Dissolving Oral Films: An Innovative Drug Delivery System and Dosage Form, International Journal of Chem Tech Research. 2(1);2010: 576-583.
8. B. Suresh, Halloran D, James L, Quick dissolving films: A Novel Approach to drug delivery, Drug delivery. Drug development technology. Pp; 2006: 1-7.
9. Gsnayub Rasool, Guidance for industry: Orally disintegrating tablets, center for drug Evaluation and Research (CDER), USFDA),International journal of innovative pharmaceutical sciences and research.2;2008:688-702.
10. Kulkarni P K, Dixit M, Gunashekara K, Shahnawaz A, Kulkarni A; Singh MN, Formulation and evaluation of mouth dissolving film containing Rofecoxib, International research journal of pharmacy. 2(3); 2011:273-278.
11. M J. Chein, Tirol G, Chien C, Schmitt R, Film Forming Polymers in Oral Films, Poster Presented at the Annual Meeting and Exposition of the American Association of Pharmaceutical Scientist, AAPS, PP;2006:1-5.
12. RP. Dixit and Puthli SP, Oral strip technology Overview and future potential, Journal of controlled release. 139; 2009:94- 107.
13. Vollmer U and Galfetti P, Rapid film Oral thin films as an innovative drug delivery system and dosage form, Drug development report. 2006:1-5.
14. http://www.bioprogress.com/pages/content/index.asp? PageID=50. www,drungbank,com