ISSN: 2306-6091

International Journal of Pharmaceuticals and Health care Research (IJPHR)

IJPHR |Vol.14 | Issue 1 | Jan - Mar -2026

www.ijphr.com

DOI : https://doi.org/10.61096/ijphr.v14.iss1.2026.50-61

Research

Development of Duloxetine hydrochloride Orodispersible Films for Rapid Onset of Antidepressant Action

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Published on: 27.02.2026

Published by: Futuristic Publications

Abstract

This study aimed to formulate fast-dissolving orodispersible films (ODFs) containing Duloxetine HCl to expedite beginning of action and augment patient adherence, especially in individuals with dysphagia. Films were fabricated by the solvent-casting method, employing HPMC E15 as the principal film-forming polymer, with sodium starch glycolate (SSG) and croscarmellose sodium (CCS) integrated as superdisintegrants to enhance wetting and disintegration. Seven formulations (DL1–DL7) were assessed for physicomechanical characteristics, content uniformity, FTIR compatibility, and in vitro dissolution. All films demonstrated sufficient flexibility, satisfactory surface pH, consistent thickness, and assay results within the range of 95–105%. Dissolution studies revealed swift drug release, with DL4 (9% SSG) and DL6 (4% CCS) attaining approximately 80–85% release in 10 minutes and nearly total release within 20 minutes. Kinetic modeling aligns most effectively with the Korsmeyer–Peppas model, suggesting the presence of anomalous diffusion. Stability testing verified the absence of substantial alterations in assay or performance. Ultimately, DL4 and DL6 were identified as optimal formulations.

Keywords: Duloxetine HCl, Orodispersible films, HPMC E15, Superdisintegrants, Rapid dissolving.

INTRODUCTION

Oral administration is the most favoured method for medication delivery due to its ease, non-invasiveness, and high patient adherence. Traditional solid-dose formulations, including tablets and capsules, provide obstacles such as dysphagia, delayed onset of action, and complications with first-pass metabolism.[1] Oral medicine distribution is thought to be the most

practical, economical, and secure drug delivery route because it has the highest compliance rate, particularly among paediatric and elderly patients. The successful delivery of the drug to the body is the ultimate goal of every medication delivery method. The oral disintegrating dose form is the most widely used commercial product among the various dosage forms[2]. Because it is the easiest to ingest, the oral cavity is the best location for the delivery of an oral disintegrating dosage form. Analgesics, neuroleptics, cardiovascular agents, antiallergic medications, and erectile dysfunction drugs are among the good drug possibilities for such a system. When applied on the tongue, a dose form like these dissolves rapidly, releasing the medication that dissolves in saliva. This is superior to a traditional dosage form in terms of absorption and quick beginning of action[3].

These characteristics often undermine therapy efficacy and patient compliance, particularly in at-risk populations such as children, the elderly, and individuals with psychiatric conditions. Oro-dispersible films (ODFs) provide an effective solution by swiftly disintegrating in the oral cavity without requiring water, hence improving patient convenience and accelerating therapeutic onset.[4] The development of thin Oro Dissolving Film Technology has addressed the shortcomings of traditional fast dispersion or dissolving tablet formulations. The film has convenient packaging, is easy to create, handle, and administer, and it raises the danger of choking and the anxiety of choking. It also reduces the disagreeable flavour. Other names for these thin polymer films are mouth dissolving films (ODF), fast dissolving films (QDF), rapidly dissolving films (RDF), melt-in-mouth dosage forms (MDF), and oral dissolving films (ODF)[5].

Duloxetine hydrochloride (DLX) is a serotonin-norepinephrine reuptake inhibitor (SNRI) commonly utilized for major depressive disorder, generalized anxiety disorder, neuropathic pain, and fibromyalgia. Notwithstanding its therapeutic significance, DLX encounters formulation difficulties attributed to its unpleasant taste, limited water solubility, and substantial first-pass metabolism, culminating in diminished oral bioavailability (about 50%).[6] The aforementioned disadvantages, along with the necessity for swift action in acute depressive or anxiety episodes, underscore the prospective clinical significance of an ODF formulation. While numerous studies have investigated orally disintegrating films (ODFs) for antidepressant medications, there is a paucity of literature regarding the formulation of Duloxetine ODFs, especially utilizing optimized concentrations of HPMC E15 in conjunction with effective superdisintegrants like sodium starch glycolate (SSG) and croscarmellose sodium (CCS). The current study seeks to develop and assess Duloxetine orodispersible films for the first time, utilizing HPMC E15 combined with SSG and CCS, intended to address solubility challenges, promote disintegration, mask bitterness, and improve patient compliance via a rapid-dissolving delivery strategy.

MATERIALS AND METHODS

Chemicals

Duloxetine HCl was obtained as a gift sample from UniChem laboratories Ltd., Mumbai, India. HPMC E15 was purchased from Shilex Chemicals Pvt. Ltd., Delhi. Glycerin, citric acid, starch glycolate and croscarmellose sodium were purchased from S.D. Fine-Chemical Ltd, Mumbai. All the used reagents and chemicals were of analytical grade.

Calibration of DLX

To a 100 millilitre volumetric flask, 100 milligrammes of carefully weighed DLX are introduced. The volume was raised to 100 ml using a stock solution of 1 mg/ml of 6.8 pH phosphate buffer. The stock solution was diluted to obtain solutions with concentrations of 1-6

µg/ml using 6.8 pH phosphate buffer. A UV-VIS spectrophotometer (EI 1372, Electronics India, Pune, India) phosphate buffer blank 6.8 pH was used to quantify these solution's absorbance using a standard graph at wavelength 288 nm.

Fourier Transform Infrared (FT-IR) Spectroscopy

Using a FTIR spectrophotometer (Shimadzu FTIR-8400S, Japan), the drug's FT-IR spectra were recorded. When using the diffuse reflectance technique, the mid-IR 4000-400 cm-1 spectral region was covered. The sample is first dispersed in KBr (100 mg) using a motor, and the materials are subsequently triturated into a fine powder bed inside the container using a compression gauge. Five tons of pressure was applied for five minutes. Following the light route, the film was placed, the spectrum was recorded twice, and the characteristic peaks associated with the functional groups were determined.

Formulation Design[7]:

DLX ODFs were created with HPMC E15, using the solvent casting method. DLX dose is 20 mg for each film.

Table 1: Formulation table of Duloxetine HCl ODF

Ingredients (mg)	**DL1**	**DL2**	**DL3**	**DL4**	**DL5**	**DL6**	**DL7**
Duloxetine HCl (For each film)	20	20	20	20	20	20	20
HPMC E15 (2.5%)	100	100	100	100	100	100	100
SSG (3%, 6%, 9%)	-	3	6	9			
CCS (2%, 4%, 6%)	-	-	-	-	2	4	6
Glycerin	20	20	20	20	20	20	20
Citric acid	2	2	2	2	2	2	2
Sod. Saccharine	1	1	1	1	1	1	1
Water	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S

*The above formulation was calculated for one film of 2x2 cm size.

Preparation of ODF

Duloxetine orally disintegrating films were fabricated using solvent casting. HPMC E15 was suspended in clean water and permitted to hydrate (≥2 hours; overnight is preferable for complete swelling). Duloxetine HCl was independently dissolved in a citric buffer at pH 6.0 ± 0.3 (a component of batch water). Glycerin (plasticizer), citric acid (saliva stimulant/buffer), and sodium saccharin (sweetener) were included into the polymer solution, then followed by SSG or CCS according to the formulation. The Duloxetine solution was amalgamated with the polymer phase under gentle agitation and blended on a cyclomixer for 15–20 minutes to achieve homogeneity; the dope was

thereafter de-aerated by resting and brief bath sonication. The solution was applied to a leveled 10×10 cm glass plate with a calibrated applicator to achieve a dry thickness of approximately 100–120 µm and then dried at 40°C until a consistent weight was attained (overnight). Dried films were examined, detached, and sectioned into 2×2 cm pieces. Defective samples, including those with bubbles, tears, and non-uniform thickness, were discarded.

Evaluation of oral dissolving films formulations:

For ODF formulations, various quality control tests were carried out. Different Performed in vitro examinations are: Measurement of thickness, Weight variation, Folding endurance, Drug content uniformity, Surface pH, Assay, In vitro disintegration time.

In Vitro Dissolution Test

The in-vitro dissolution of Candesartan ODFs was conducted utilizing a USP Type II (paddle) dissolution apparatus (EI-1916, Electronics India). Each film was immersed in 500 mL of pH 6.8 phosphate buffer, maintained at 37 ± 0.5 °C, and agitated at 50 rpm. At specified intervals (2–20 minutes), 5 mL samples were extracted and substituted with fresh medium. Samples were examined at 288 nm utilizing a UV-Visible spectrophotometer (EI-1372), and cumulative drug release was determined from the standard calibration curve. All tests were conducted in triplicate.

Release Kinetics[8]

Utilising the results of the in-vitro diffusion study, the order and mechanism of drug release kinetics of DLX films were examined. Plotting of the kinetic models included the zero order, first order, and Higuchi equations; the release was calculated using the Korsmeyer-Peppas equations.

Stability studies

The optimized DLX ODF formulations underwent expedited stability testing in accordance with ICH Q1A (R2) criteria. Films were encased in aluminum foil strips, situated in airtight containers, and maintained at 40 °C ± 2 °C / 75% RH ± 5% for a duration of 60 days. Samples were extracted at specified intervals (0, 30, 60 and 90 days) and analyzed for drug content to evaluate any physical or chemical alterations. All tests were conducted in triplicate, and average values were documented.

RESULTS & DISCUSSION

Calibration of DLX

Combine 50 mg of DLX in 100 ml of water to get the stock solution. To make 100 millilitres, 10 millilitres of the stock solution were removed and diluted with water. Using several concentrations (2–7 µg/ml) and the appropriate stock solution dilution, a calibration curve was produced. The absorbance was obtained at 288 nm. The curve that results from calibrating DLX in a pH 6.8 phosphate buffer is shown in Figure 1.

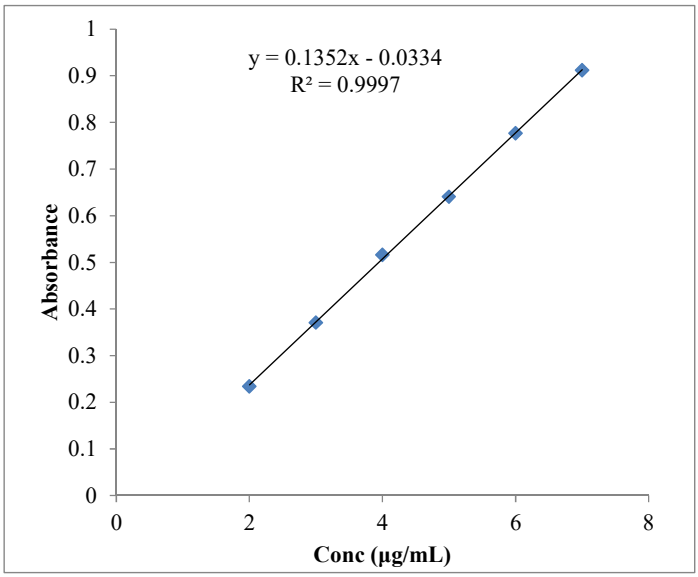

Figure 1: DLX standard calibration curve in phosphate buffer with a pH of 6.8

Drug – excipient Compatibility Studies

FTIR spectroscopy was used to determine the drug excipient compatibility, and the graphs were displayed figure 2 to 4. To find out if there is any interaction between the excipients and DLX, the physical mixture was put through FTIR analysis. The lack of a drug-carrier chemical interaction is confirmed by the absence of any drug-characteristic peak appearance or disappearance. Drug polymer and other excepient's physical mixtures all had their Fourier transform infrared spectra recorded and examined for chemical interactions. All samples, which were pure DLX, underwent FTIR analysis to determine the presence of the pure API in the mixtures and to describe it.

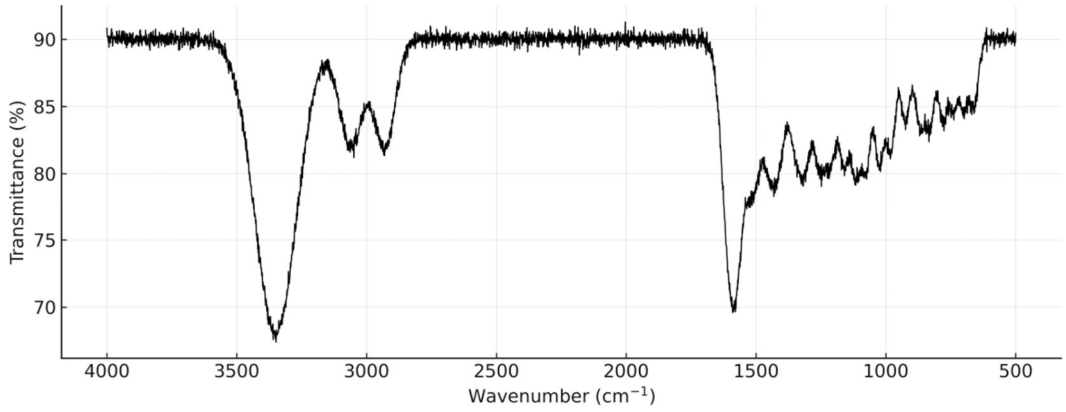

Figure 2: FTIR Spectral analysis of pure DLX.

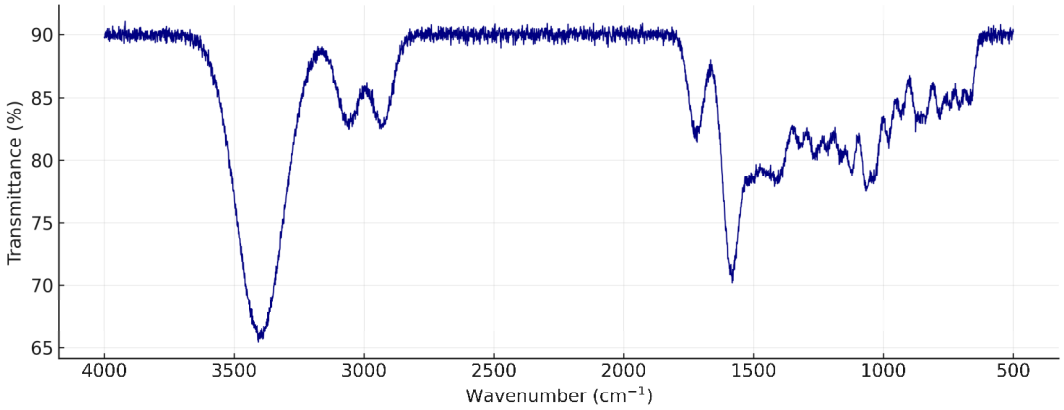

Figure 3: FTIR Spectral analysis of optimized formulation DL4

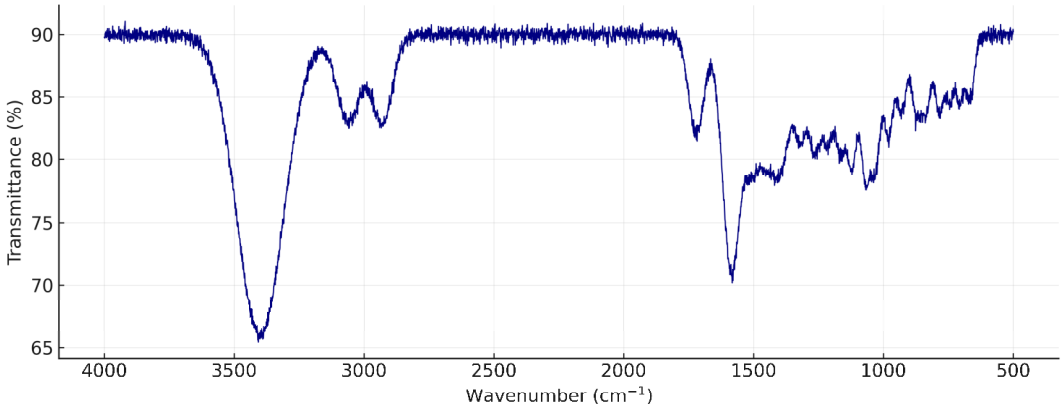

Figure 4: FTIR Spectral analysis of optimized formulation DL6

The acquired FTIR spectra are overlapped in the figure 2-4. The FTIR spectrum of pure duloxetine HCl exhibited characteristic bands in accordance with the literature, including aromatic and alkyl C–H stretching above and below 3000 cm^{-1}, peaks in the 1600–1575 cm^{-1} range attributed to aromatic C=C stretching, bands near 1460–1450 cm^{-1} corresponding to CH_2 bending and thiophene ring vibrations, and prominent C–O/C–N stretching bands around 1230–1235 cm^{-1} and 1090–1060 cm^{-1}, along with additional aromatic C–H bending bands in the 800–750 cm^{-1} region. The FTIR spectra of DL4 (duloxetine + HPMC + SSG) and DL6 (duloxetine + HPMC + CCS) exhibited all major duloxetine peaks, which had moderate broadening and mild shifts in the O–H / N–H and C–O regions, attributable to hydrogen bonding with HPMC and superdisintegrants. No novel peaks or loss of significant drug bands was seen, signifying the lack of chemical interaction or degradation. The preservation of distinctive duloxetine peaks in DL4 and DL6 verifies the drug's compatibility with HPMC, SSG, and CCS, maintaining its stable form inside the ODF formulations.

Evaluation of ODF:

Thickness

Each formulation's thickness (DL1–DL7) was examined; the findings are displayed in the table 13.

DL1–DL7 were determined to be 101.6 ± 0.5-103.9 ± 0.7µm thick. Based on the results of the aforementioned formulations, all of them demonstrated film thicknesses between 5 and 200 µm, which meets with the prior value's limit.

Table 2: Finding the thickness, folding endurance, and pH of the surface and disintegration time of all formulations

F. Code	Thickness (µm)± SD	Folding endurance (Folds)	Surface pH	In-vitro disintegration Time (sec)
DL 1	101.8 ± 0.6	140 ± 7	6.18 ± 0.06	28 ± 4
DL 2	102.0 ± 0.5	150 ± 6	6.20 ± 0.06	22 ± 3
DL 3	102.4 ± 0.6	155 ± 6	6.19 ± 0.07	17 ± 3
DL 4	103.9 ± 0.7	161 ± 7	6.18 ± 0.06	12 ± 2
DL 5	101.6 ± 0.5	145 ± 6	6.21 ± 0.06	21 ± 3
DL 6	102.3 ± 0.5	159 ± 7	6.20 ± 0.05	13 ± 2
DL 7	102.7 ± 0.6	155 ± 8	6.19 ± 0.05	16 ± 2

Folding Endurance:

The results are displayed in Table 2. It was discovered that the folding endurance value of DL1–DL7 was found to be 140±7-161±7.

Surface pH of Films:

For each formulation, the mean of the three findings was determined, and the standard deviation was also computed. It was found that the surface pH of each film ranged from 6-7.

In-vitro disintegration:

The findings are displayed in the table 2. The disintegration time for DL1–DL7 was found to be in between 12±2-28±4 seconds.

Weight variation:

Weighing each film, we compared its weight to the deviation's average. Table 3 demonstrates how each formulation's weight variance varies between 158.89±2.38-167.05±2.51.

Drug Content Uniformity:

Table 3 shows the results of calculating the percentage of DLX content for different formulations. DL4 and DL6 were found to be the best having a drug content percentage of 100.1±2.4and 100.0±2.3.

Assay: A UV spectrophotometer was used to analyse this solution. The assay findings for each formulation are shown in Table 3, ranging in between 98.4±2.8-100.3±2.3.

Table 3: Weight variation, drug content uniformity, and assay determination

F. Code	Weight variation (mg)	Drug Content Uniformity	Assay
DL 1	158.89 ± 2.38	97.8 ± 3.2	98.4 ± 2.8
DL 2	161.33 ± 2.42	98.9 ± 2.9	99.1 ± 2.6
DL 3	163.74 ± 2.46	99.6 ± 2.5	99.7 ± 2.4
DL 4	165.12 ± 2.49	100.1 ± 2.4	100.3 ± 2.3
DL 5	162.92 ± 2.44	98.8 ± 3.0	99.0 ± 2.7
DL 6	167.05 ± 2.51	100.0 ± 2.3	100.1 ± 2.2
DL 7	165.56 ± 2.48	99.4 ± 2.5	99.6 ± 2.4

In-vitro dissolution

For DL1 through DL7, figures 5 displays the cumulative medication release percentage. Utilizing a Type II USP paddel apparatus, the in vitro dissolution investigations were conducted in phosphate buffer with a 6.8 pH. In 20 minutes, DL1 with HPMC E15 released 95.36% of the drug; DL4 with HPMC E15 and SSG released 99.98% and DL6 with HPMC E15 and CCS released 99.92%. As a result, it is regarded as the ideal formulation.

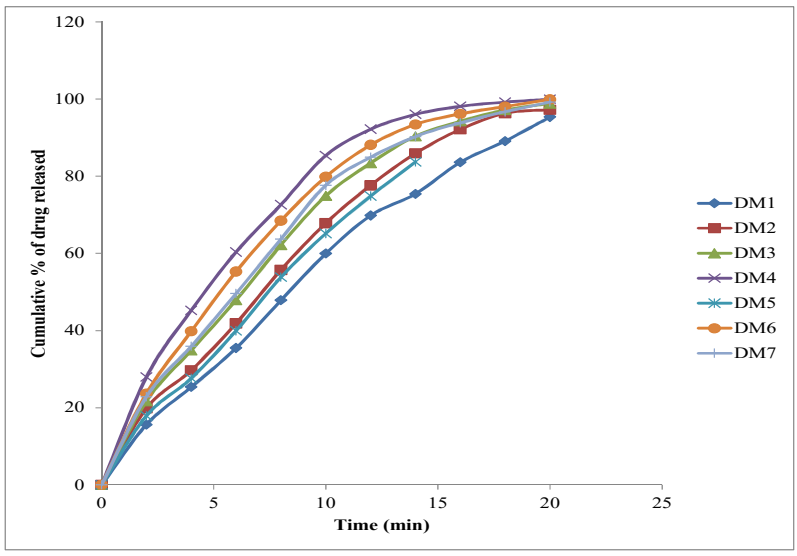

Figure 5: In-vitro dissolution studies of DLX formulations (DL1-DL7)

Application of Release Rate Kinetics to Dissolution Data:

The kinetics of drug release were investigated using a range of models. The drug release rate mechanism of the dose form kinetics was examined by fitting a variety of release models, such as first-order, zero-order, higuchi, and Korsmeyer-Peppas, to the collected data. The kinetics results were displayed in figures 6-9.

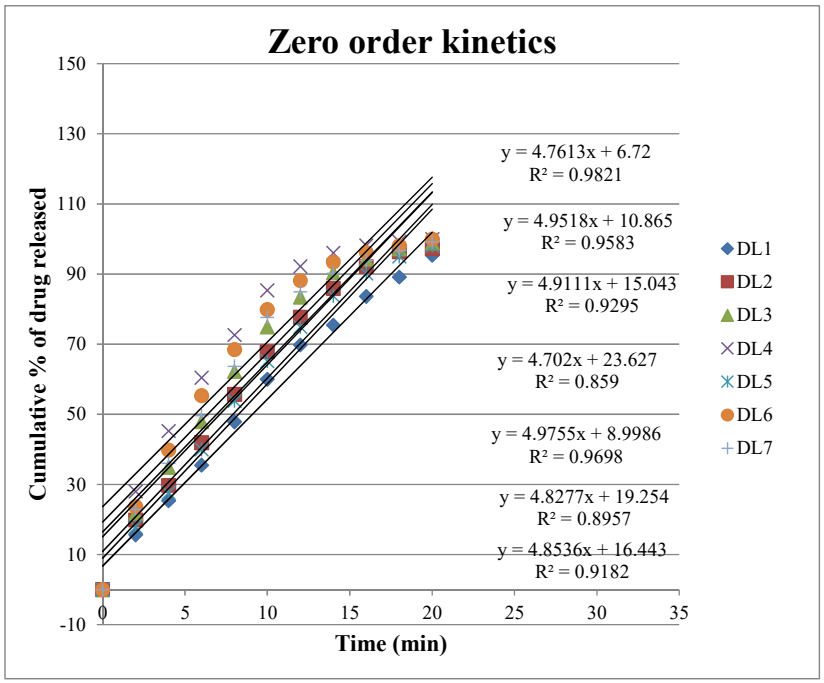

Figure 6: Zero order release kinetics graph of DLX formulations (DL1-DL7)

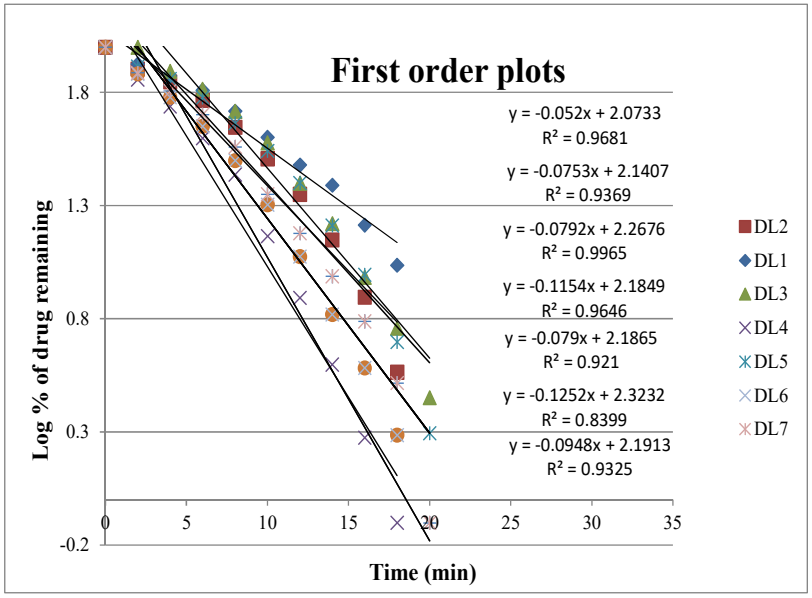

Figure 7: First order release kinetics graph of DLX formulations (DL1-DL7)

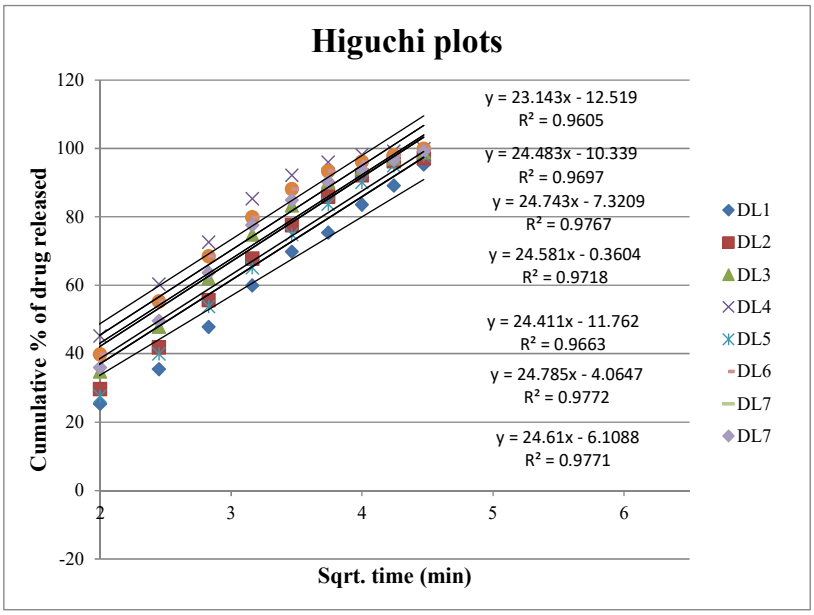

Figure 8: Higuchi release kinetics graph of DLX formulations (DL1-DL7)

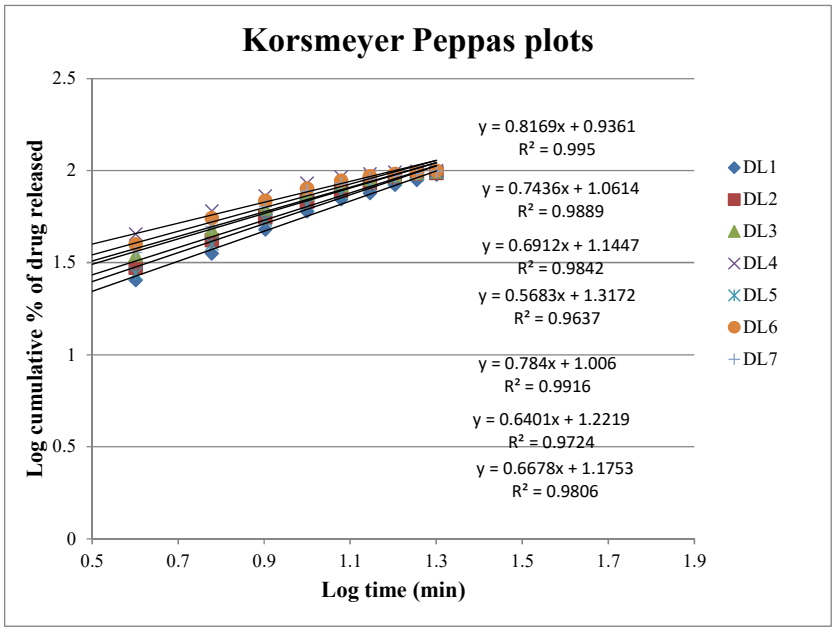

Figure 9: Korsmeyer-Peppas graph of DLX formulations (DL1-DL7)

The drug-release kinetics for Duloxetine ODFs (Figs. 6-9) exhibit robust linearity for zero-order in the majority of batches (R^2 = 0.859–0.9821), with optimal fits for DL1 (0.9821), DL5 (0.9698), and DL2 (0.9583), signifying nearly constant release from these matrices. DL3 was more well characterized by a first-order model (R^2 = 0.9965), indicating concentration-dependent release augmented by 6% SSG. The Higuchi model demonstrates a strong diffusion component across all formulations (R^2 = 0.9605–

0.9772), particularly in DL4 (0.9718) and DL7 (0.9771). The Korsmeyer–Peppas model exhibited the optimal fit (R^2 = 0.9637–0.995), with the release exponent n varying from 0.5683 to 0.8169, categorizing all batches within non-Fickian (anomalous) transport (0.45 < n < 0.89). Duloxetine release from HPMC E15 films is regulated by combined diffusion and polymer relaxation/erosion, with superdisintegrants enhancing early release while maintaining near-zero-order kinetics in specific matrices.

Stability Studies:

In compliance with ICH recommendations, stability experiments were carried out to assess the pharmaceutical formulation's stability. The optimised DL4 and DL6 formulation was packaged in aluminium with a polyethylene lamination. The Samples were stored for three months at 40°C and 75% relative humidity. The composition was examined for changes in color, drug content, physical appearance, and drug release characteristics at the conclusion of the study period. In accordance with ICH requirements, stability experiment was conducted for the optimal formulations of DL4 and DL6 at room temperature, 40^0C/75%RH. The drug content percentage was examined at 0, 30, 60, and 90 days, all of which fall within the 98–100% indicating minimal loss and robust matrix protection. It follows that the formulation is stable.

CONCLUSION

Duloxetine HCl orodispersible films formulated with HPMC E15 and superdisintegrants exhibited superior mechanical strength, rapid wetting properties, and expedited drug release, making them appropriate for patients in need of prompt antidepressant effects. Among all batches, DL4 (SSG 9%) and DL6 (CCS 4%) exhibited ideal disintegration (≤20 s), exceptional dissolving (80–85% in 10 min; 100% in 20 min), and uniform drug content nearing 100%. FTIR validated excipient compatibility, and 90-day stability studies demonstrated the preservation of important quality features. The films exhibited non-Fickian diffusion dynamics, characteristic of hydrated HPMC matrices. In summary, DL4 and DL6 were optimized as the most effective formulations, illustrating the viability of Duloxetine ODFs as a convenient, patient-centric option for swift therapeutic effects.

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