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DESIGN, DEVELOPMENT AND EVALUATION OF NOVEL ORAL SOLUBLE FILMS OF LURASIDONE HYDROCHLORIDE

Ritesh Patel[1]*, G. Jagadish[2], Korlapalli Manasa[3], Ch. Mahalaxmi[4] and Sepuri Vijayalaxmi[5]

[1]Principal, Department of Quality Assurance, Keshari College of Pharmacy, Janjgir.
[2]Professor & Principal, Department of Pharmaceutics, DBM College of Pharmacy, Janjgir. Chattisgarh.
[3]Ms Pharmaceutics.
[4]Associate Professor, (Guest faculty), JNTUH.
[5]Associate Professor, Siddartha Institute of Pharmaceutical Sciences, Korremula Rd, Narepally, Ghatkesar, Hyderabad, Telangana 501301.

***Corresponding Author: Ritesh Patel**

Principal, Department of Quality Assurance, Keshari College of Pharmacy, Janjgir.

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ABSTRACT

Objective: The objective of the present work was to formulate and evaluate a fast-dissolving oral film of Lurasidone hydrochloride used as an atypical antipsychotic for the treatment of schizophrenia capable of providing faster onset of action. **Methods:** The fastdissolving films ofLurasidone hydrochloride were prepared by the solvent casting technique using different compositions and combinations of hydroxypropyl methylcellulose E-3, E-5, E-15, and K4M as fast-dissolving polymer bases. A set of seven formulations were prepared and evaluated for parameters like physical characterization, thickness, weight uniformity, mechanical characteristics (folding endurance, tensile strength), surface pH, *in vitro* disintegration time, drug content, and an *in vitro* drug release. **Results:** The prepared films exhibited uniform and a smooth surface with uniform weight, thicknessand 89-90% mg drug content. The formulation F7 Showed excellent elasticity and disintegration within seconds. Lurasidone hydrochloride was rapidly released *in vitro* from all formulations. The release was found to be rapid and maximum of 41.5% in Phosphate buffer pH 6.8 and 58.6% in 0.1 N hydrochloric acid over a period of 30 min. The further optimized formulation F7Adepicted a faster and maximum release of 78% as compared to the marketed tablet 74%.**Conclusion:** The developed formulation is a better alternative to tablets by its ability to produce good drug release.

KEYWORDS: Lurasidone hydrochloride, Hydroxyl propyl methylcellulose, Fastdissolving films, Solvent casting, *In vitro* drug release.

INTRODUCTION

Medication non-adherence and poor patient complianceis a significant concern in patients with schizophrenia and is closely linked to treatment failures and negative outcomes. Moreover, treating geriatrics, nauseous and non-compliance patients with solid dosage forms like tablets and capsule poses difficulties even after being the most preferred route due to ease of administration.[1,2]

The route of administration also plays an important role in patient medication compliance.[3] The orally dissolving films (ODF's) has recently become one of the most popular dosage forms of drug administration due to its excellent patient compliance.[4] The main advantage of the dosage form arises from rapid disintegration and their easy administration accomplished without the need for the water for swallowing.[5] Compared to conventional oral dosage forms, ODFs usually result in enhanced bioavailability with faster onset of action.[6]

Lurasidone hydrochloride (LH) is a psychotropic agent[7] reported to antagonize dopamine D2 receptors, also serotonin 5-HT2A and 5-HT7 receptors.[8] It is a partial agonist at 5-HT1A receptors.[9] Also, it antagonizes adrenergic alpha2A andalpha2C receptors but exhibits minimal affinity for histaminic (H1)and acetylcholinergic muscarinic (M1) receptors.[10] It is approved in October 2010 by the FDA in the treatment of schizophrenia and bipolar disorders.[8,11]

It is a lipophilic drug with a log P value of 5.6.[12] It is a poorly water-soluble drug belonging to BCS Class II.[13] It possesses a lower bioavailability of 9-19%, leading from its lower gastrointestinal absorption.[14] Its dose

varies according to the condition i.e. 20-80 mg/day.[15] It possesses a longer half-life of 18 h.[16]

The only marketed dosage form of Lurasidone is tablets of varied strengths. Thus, this work investigated the possibility of developing fast dissolving films of LH, allowing faster delivery through the saliva.

MATERIALS AND METHODS

Material, Chemicals and Equipment used in the experiment

All the chemicals used were of analytical grade. LH wasreceived as a gift sample from Unichem Laboratories, Goa. Hydroxypropylmethylcellulose (HPMC), E-3, E-5, E-15, and K-4M were provided by Colorcon Asia Pvt. Ltd. Propylene Glycol (LobaChem), Potassium Dihydrogen Phosphate (West Coast Laboratories), Sodium Hydroxide (Finar Ltd), Hydrochloric acid (Molychem), Methanol (Molychem), Ethanol (Changshu Hongsheng Fine Chemical Co, Ltd), Citric acid monohydrate (Molychem), Tween 80 (Molychem) were purchased locally.

Preformulation studies

Drug-polymer compatibility studies

Fourier transform infrared (FT-IR) spectroscopy

The compatibility of the drug and excipientsin the formulation was studied using IR spectra of pure drug and formulations. Drug-polymer interactions were studied by FT-IR spectroscopy. The spectrum was recorded for the drug, the physical mixture of polymer, and the drug in a ratio (1:1), and the selected formula. The mixtures were analyzed by FTIR spectroscopy from 4000-400 cm-1.[18]

Differential scanning calorimetry (DSC) studies

DSC studies were performed on individual excipients of the formulation and in the form of 1:1 physical mixture to check for any interaction and compatibility between drug and excipients. The thermal scans were carried out in a nitrogen gas purge and the temperature was raised at 20 °C/min. the overall temperature range applied for all the test samples was from 20 to 350 °C. The interaction between the drug substance and excipients was evaluated by comparing the spectra of the pure drug with the spectra of the drug mixtures. The influence of the presence of the excipient on the drug was analysed.[19,20]

Estimation of Lurasidone hydrochloride

Preparation of simulated saliva fluid (phosphate buffer pH 6.8) and LH standard plot

The phosphate buffer pH 6.8 was prepared by adding 0.2 M potassium dihydrogen phosphate and 112 ml of 0.2M Sodium dihydrogen phosphate in distilled water sufficient to produce 1000 ml.

The standard plot of LH was prepared in methanol, 0.1N HCl, and phosphate buffer pH 6.8.10mg of LH was weighed accurately and dissolved in methanol and the volume was made up to 100 mlin a volumetric flask. The stock solution resulted in a drug concentration of 100 µg/ml. The various concentrations ranging from 10µg/ml to 80µg/ml were made using the stock solutionand the absorbance was recorded. 20µg/ml solution was scanned in the UVrange of 200-400 nm. The wavelength at which maximum absorbance occurs was taken as the λ_{max} of LH. The calibration curve of LH was also performed with 0.1N HCl and phosphate buffer pH 6.8.[21]

Preparation of orally dissolving films

To overnight soaked polymer, in a mixture of ethanol and water (1:3 v/v), plasticizer was added and the solution was stirred for 30 min. The drug dissolved in ethanol was subjected to sonication until it was completely soluble. Other excipients were added to the drug solution and the resulting solution was finally added to the polymer solutionand was stirred continuously for 10 h. The resulting clear solution was cast on the flat petridish of 4.5 cm in diameter and was dried at a temperature of 40˚C for 24 h in a vacuum oven(Tempo). After 24 h, the film was slowly removed after ensuring that itwas completely dried and cut into 3×3 cm^2 and stored in the aluminumpouches.[22]

Different formulations were prepared as per table1. These films were stored in aluminum pouches under controlled storage conditions and were subjected to the various quality controltests.[23]

Table 1: Composition of fast dissolving films.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F7A	F7B
LH (mg)	42.6	42.6	42.6	42.6	42.6	42.6	42.6	42.6	42.6
HPMC E-15 (mg)	500	450	250	250	125	125	166	166	166
HPMC E-3 (mg)	-	-	250	-	175	-	166	166	166
HPMC E-5 (mg)	-	-	-	250	-	175	166	166	166
HPMC K-4M (mg)	-	50	-	-	-	-	-	-	-
Propylene glycol (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Tween 80 (ml)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Citric acid (mg)	20	20	20	20	20	20	20	20	20
Aspartame (mg)	40	40	40	40	40	40	40	40	40
Purified water (ml)	3	3	3	3	3	3	3	3	3
Ethanol (ml)	15	15	15	15	15	15	15	15	15

Sodium Starch Glycolate(SSG) (mg)	-	-	-	-	-	-	-	40	-
Crospovidone (mg)	-	-	-	-	-	-	-	-	40

Evaluation of ODFs
The prepared films were evaluated for the following parameters.

General appearance
The ODFwas examined visually for clarity, absence of any impurity or precipitation, or crystallization effects of the components involved.[24]

Drug content uniformity
The 3×3 cm^2 piece was first dissolved completely in 10 ml methanol. 1 ml of this solution was diluted to 25 ml using 0.1 N HCl. The drug concentration was determined by measuring the absorbance of the resulting solution at 315 nm against 0.1N HCl as blank using a UV visible spectrophotometer (LabIndia). Mean with SD was recorded.[13]

Weight variation
The 3×3 cm^2 pieces were cut from three different places of the cast film. Each film was weighed using a digital analytical balance (Mettler) and calculated for weight variation. Mean with SD was recorded.[25]

Thickness
It was carried out by measuring the thickness of the film at three different points using a digital vernier caliper. Mean with SD was recorded.[25,26]

Tensile strength
It was determined using a laboratory fabricated tensile strength tester. A 3×3 cm^2 film free from bubbles or physical imperfections was held longitudinally in the tensile grip on the tester. The test was performed at 6 mm of initial grip separation. Weights were added to the pan until the film breaks. All measurements were recorded in triplicate. Mean with standard deviation was calculated.[27] Tensilestrength was calculated by dividing the applied force at which the film is broken by the cross-section area of the strip and was expressed in force per unit area: mega Pascal (MPa) as shown in the following equation.

$$\text{Tensile strength} = (\text{Load at failure})/(\text{strip thickness} \times \text{strip width})$$

Folding endurance
The Folding endurance is measured by manual repeated folding of the film at the same place till it broke. The number of times the film is folded without breaking is known as the folding endurance value. A strip of 3 × 3 cm diameter was subjected to folding endurance by folding the film at the same place repeatedly several times until a visible crack was observed, and the average values were calculated and reported. Folding endurance of more than 300 indicates that the formulation is good, tough and flexible. Mean with standard deviation was calculated.[28]

***In vitro* disintegration time**
In vitro disintegration is the time at which the fast dissolving oral films start to break down or *invitro* disintegration time was determined visually in a Petridis containing 10 ml of pH 6.8 phosphate buffer, which is known to mimic the properties of saliva. The disintegration time was noted as soon as the film breaks and slowly disintegrates. The readings were measured along with Mean with standard deviation.[29,30]

Surface pH
An electrode pH meter (CONTECH) was employed for this purpose. The pH was measured by bringing the electrode into contact with the surface of the film. The procedure was performed in triplicate samples. Mean with standard deviation was reported.[31]

Surface morphology
Scanning electron microscopy (SEM) images of the prepared films were taken and the surface was analyzed for uniformity and absence of any pores.

***In vitro* dissolution test of ODFs**
These studies were carried out using USP type I (basket) dissolution apparatus (Lab India). The3×3 cm^2size film was placed in the basket of the dissolution apparatus. The test was carried out in two different dissolution mediums. Phosphate buffer pH 6.8 was selected as a dissolution medium for its properties to mimic the saliva, whereas 0.1N HCl was selected as a dissolution medium since LH has very low solubility in phosphate buffer pH 6.8; hence the unabsorbed drug will be ingested and will be released into HCl secreted in the stomach.

In both cases, 500 ml of dissolution medium was employed maintained at 37.5±0.5 °C at 50 rpm.5 ml samples were withdrawn at 2m interval until 10 m; after that, the samples were withdrawn at 15 m and 30 m until 180 m. Replenishing was done after every withdrawal with the fresh medium to maintain thesink condition. Contentwas then determined spectrophotometrically at λmax of 315 nm and the drug release was calculated.[32,33]

Comparison of an optimized formulation with the marketed formulation
LH is only available as tablets of strengths 20 mg, 40 mg, and 80 mg. The formulated film was compared against the tablet concerning its drug release profile. The Optimized formulation F7 was incorporated with super disintegrants and the release of both the formulations containing two different super disintegrants i. e. crospovidone and SSG was compared for percent drug release profile. The dissolution was carried out in 500 ml 0.1N HCl using USP I (basket) apparatus at 37±0.5 °C at 50rpm.

Stability studies of the optimized ODF

Stability studies of optimized formulations were carried out as per ICH guidelines by storing the formulations at 40 °C±2 °C/75% RH for 90 d. Samples were analyzed for drug content, weight variation, thickness, tensile strength, surface pH, disintegration time, and *in vitro* dissolution studies.[34,35]

RESULTS AND DISCUSSION

Fast dissolving films of LH were prepared using polymers HPMC E-3, E-5, E-15, and K4-M, alone or in combination.

Drug-polymer compatibility studies

The principal peaks of the FT-IR spectrum of LH are shown in(fig. 1), which is at the wavenumbers (cm^{-1}): 2935.66 of Ar-H stretch, 1681.93 of C = O stretch (Aryl ketone), 1504.48 of Ar C = C stretch, 1390.68 of C-H bending, 2250.93 of CN stretch. The IR spectra of LH did not show any significant difference from those obtained for their physical mixtures with the excipients. The results indicate that there was no positive evidence of interaction between LH and the polymers, more than if any hydrogen bonding, which may have occurred between the donating and accepting groups of both the drug and the polymers (fig. 1).

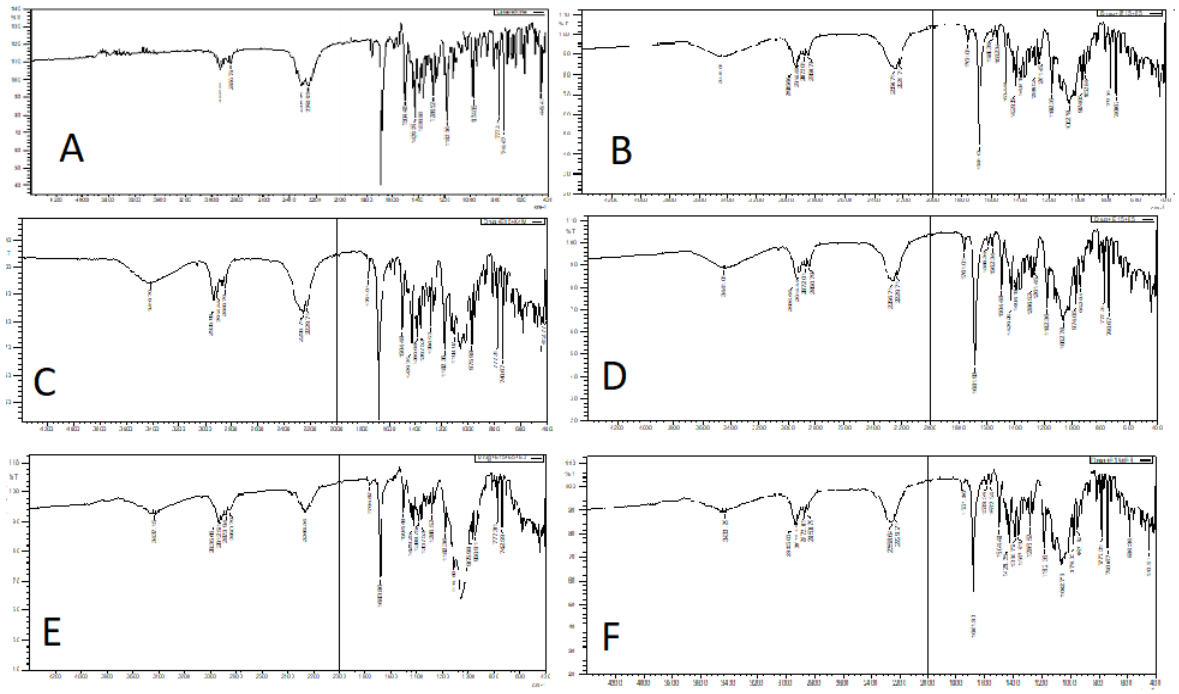

Fig. 1: FTIR spectra of [A] LH [B] 1:1 physical mixture of LH and HPMC E-15 [C] (1:1:1) physical mixture LH HPMC E-15 and HPMC K-4M. [D] (1:1:1) physical mixture of LH,HPMC E-15 and HPMC E-5 [E] (1:1:1:1) physical mixture of LH, HPMC E-15, HPMC E-5 and HPMC E-3 [F] (1:1:1) physical mixture of LH, HPMC E-15 and HPMC E-3, (mean±SD; n=3).

The DSC thermogram of LH showed a sharp endothermic peak at 268.93°C. A study has also reported a thermogram of pure LH, showing a melting endothermic peak at 286 °C.[36]

Upon comparison, the DSC scans displayed that the physical mixtures of the active and various excipients did not show any peaks before the main peak in the thermal scan of Lurasidone hydrochloride and no shift in endotherm. Any peaks seen before were inherent in the individual thermal scans of the excipients (fig. 2).

Determination of λ max

The scanning of diluted solutions of LH in 0.1N HCl and pH 6.8 phosphate buffers was performed by using UV spectrophotometer from 200-400 nm. The maximum absorption value of LH was found at 315 nm in 0.1N HCl and 6.8 pH phosphate buffer. Therefore 315 nm were recorded as λmax of the pure drug LH. 315 nm λ max was selected for calibration curve and further experiment. The UV spectrum of LH and calibration curve in 0.1 N HCl and 6.8 phosphate buffer is depicted in fig. 3A and 3B, respectively.

Evaluation of ODFs

The ODFs were found to be flat surfaces, translucent to opaque in color, square in shape 3×3 cm^2in area. They were examined visually and were found to possess a smooth texture and free of any imperfections including bubbles and cracks fig. 4 shows SEM image of the optimized formulation.

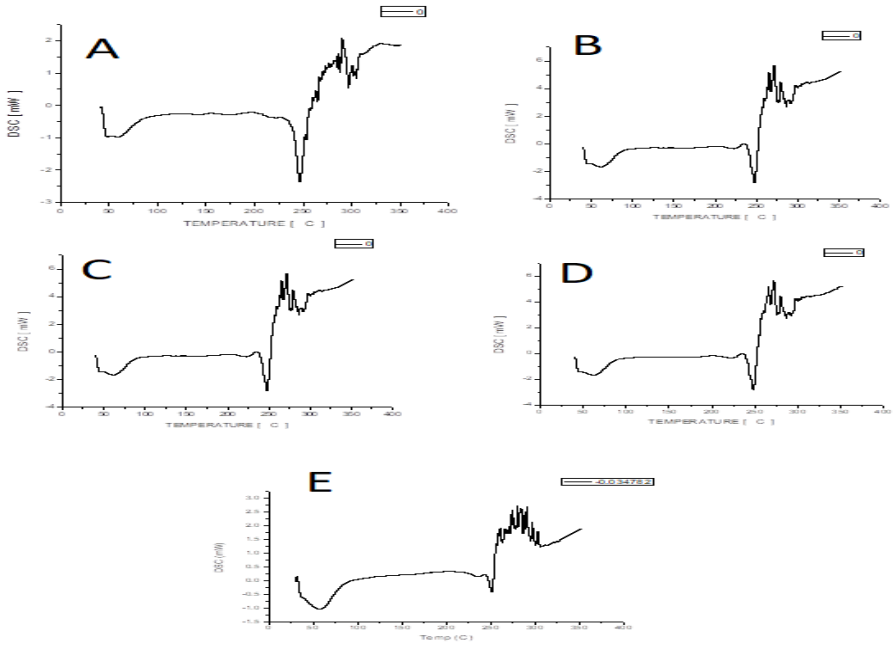

Fig. 2: DSC spectra of [A] LH. [B]1:1 physical mixture of LH and HPMC E-3 [C]1:1 physical mixture of LH and HPMC E-5 [D]1:1 physical mixture of LH and HPMC E-15 [E] 1:1 physical mixture of LH and HPMC K4M. (mean±SD; n=3).

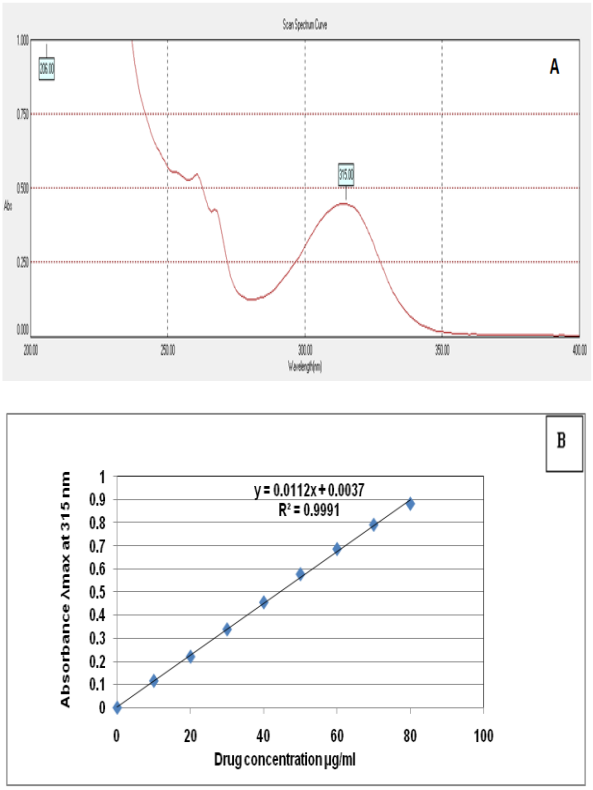

Fig. 3: [A] UV scan of LH (10 µg/ml) in methanol. [B] Calibration curve of LH in methanol (mean±SD; n=3).

The average percent drug content of all the formulations was from 89%-91% mg, within acceptable limits without any significant variation. All the batches were uniform in weight and thickness with no significant difference in the individual formulation. Formulations containing the combination of polymers HPMC E-3, E-5, and E-15 showed a higher tensile strength as compared to the formulations containing HPMC E-15 and a mixture of HPMC E-15 and E-5 and or HPMC E-3. Folding endurance of all the formulations showed variations depending upon the ratio and the type of polymers present.

All formulations showed a surface pH close to the neutral pH; hence the risk of irritation to oral mucosa due to extreme pH values was reduced. The results of these quality control tests are given in table 2.

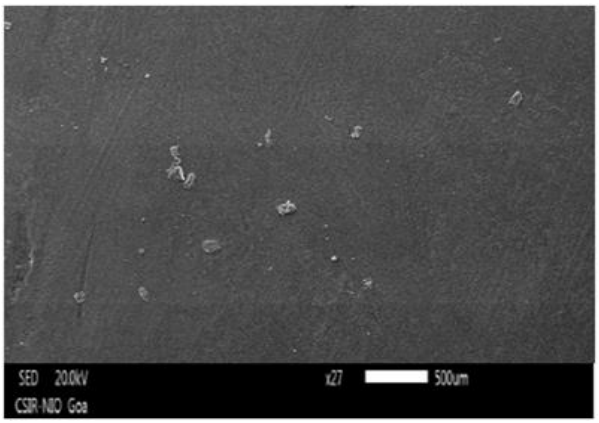

Fig. 4: SEM image of the optimized formulation (mean±SD; n=3).

Table 2: Results of quality control tests done on LH ODF.

Formulation code	% Drug content	Weight variation (g)	Thickness (mm)	Tensile strength (kg/mm^2)	Folding endurance	*In vitro*disintegration time (s)	Surface pH
F1	89.18±0.01	0.342±0.002	0.112±0.01	0.570±0.001	150.3±0.58	61.33±0.58	6.52±0.01
F2	89.18±0.02	0.254±0.001	0.116±0.01	0.566±0.004	170.0±1.00	92.33±1.53	6.43±0.01
F3	89.51±0.01	0.319±0.001	0.120±0.01	0.513±0.004	164.0±0.00	61.00±1.00	6.81±0.01
F4	90.50±0.01	0.351±0.001	0.116±0.01	0.492±0.010	172.3±0.38	64.66±0.58	6.41±0.01
F5	90.17±0.01	0.332±0.001	0.116±0.01	0.523±0.010	162.3±0.50	51.66±0.58	6.79±0.01
F6	89.44±0.01	0.380±0.001	0.113±0.01	0.525±0.004	173.0±1.00	68.33±0.58	6.70±0.02
F7	90.17±0.02	0.329±0.001	0.116±0.01	0.583±0.005	184.0±0.58	47.66±0.58	6.53±0.04
F7A	90.17±0.01	0.368±0.007	0.121±0.01	0.582±0.005	184.0±0.52	36.66±2.08	6.52±0.03
F7B	90.16±0.02	0.366±0.009	0.122±0.01	0.581±0.005	184.0±0.52	41.33±1.15	6.53±0.03

(All the values were calculated as mean±SD; n=3)

The *in vitro* drug release study gave an idea regarding the amount of the drug that is available for absorption into the systemic circulation. The release profile of the drug predicts the *in vivo* behavior of the drug in circulation.[37] The drug release study was carried out using a phosphate buffer pH 6.8 and 0.1N HCl using USP type I apparatus (basket). The cumulative percentage drug released fromeach formulation /stimecurvew asplottedat different time intervals.

All formulations exhibited a similar pattern of drug release with a maximum of 55% in phosphate buffer pH 6.8 and 85% in 0.1 N HCl. The formulation F7 was found to havea faster release (30% and 40 % within 15 min in phosphate buffer pH 6.8 and 0.1N HCl, respectively) as compared to other formulations as seen in %CDR verses time plots in phosphate buffer pH 6.8 (fig.5A) and 0.1N HCl (fig.5B). Percentage drug release in recently reported studies on LH films also reported 42.21% of pure drug release.[36]

Table 3: Release kinetics of the formulations in phosphate buffer pH 6.8.

Formulation	Zero-order		First-order		Higuchi		Peppas	
	R^2	K* min^{-1}	R^2	K* min^{-1}	R^2	K* min^{-1}	R^2	N
F1	0.771	0.295	0.822	0.004	0.915	4.51	0.905	0.746
F2	0.792	0.307	0.840	0.004	0.927	4.65	0.913	0.771
F3	0.749	0.285	0.797	0.004	0.907	4.39	0.875	0.684
F4	0.706	0.293	0.738	0.004	0.870	4.56	0.899	0.729
F5	0.738	0.278	0.787	0.0041	0.90	4.29	0.865	0.661
F6	0.672	0.296	0.685	0.004	0.845	4.64	0.891	0.727
F7	0.614	0.293	0.763	0.004	0.883	4.32	0.854	0.650

(*units for K =min^{-1})

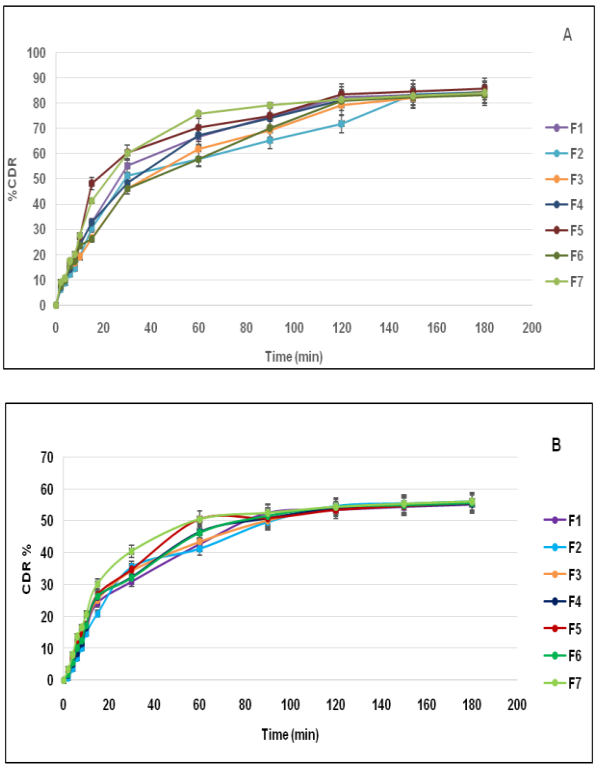

Fig. 5: Percent drug release curve for F1-F7 ODF formulations in [A] phosphate buffer pH 6.8 and [B] 0.1N HCl(mean±SD; n=3).

Regression coefficient values tabulated in table 3 and table 4 were found to be higher for first-order than for zero order. From these results, it is evident that all the formulations follow first-order drug release kinetics. Since the regression coefficient of the Higuchi plot was found to be close to 1 according to the tabulated data, it also reveals that all the formulations exhibit a diffusion drug release mechanism. In the case of Korsemeyer Peppas plot 'n' values higher than 0.5 indicates non–Fickian drug release kinetics.

Table 4: Release kinetics of the formulations in 0.1N HCl.

Formulation	Zero-order		First-order		Higuchi		Peppas	
	R^2	K*	R^2	K*	R^2	K*	R^2	n
F1	0.806	0.447	0.900	-0.009	0.938	6.751	0.885	0.710
F2	0.805	0.439	0.9533	-0.009	0.963	6.510	0.904	0.715
F3	0.869	0.450	0.954	-0.009	0.972	6.661	0.895	0.698
F4	0.828	0.447	0.918	-0.009	0.953	6.719	0.885	0.705
F5	0.751	0.430	0.873	-0.009	0.902	6.605	0.843	0.691
F6	0.868	0.444	0.9437	-0.009	0.972	6.580	0.886	0.694
F7	0.736	0.426	0.824	-0.009	0.896	6.576	0.838	0.681

(*units for K =min^{-1})

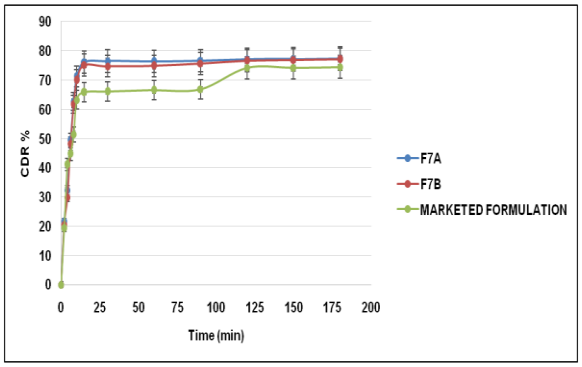

Fig. 6: Comparison of formulated ODF F7A and F7B with the marketed formulation.

Based on the analysis and comparison of all the evaluative tests of all the seven formulations, F7 (film base: HPMC E-15, E-3, E-5) was selected as an optimized formulation as it showed rapid release, optimum *in vitro* disintegration time with excellent physicochemical and mechanical properties.

Formulations were initially prepared without the incorporation of the superdisintegrants, which showed higher disintegration time and a longer period of release of the active agent, whereas after optimization, when the super disintegrants were added showed faster disintegration and rapid release. Various concentrations of super disintegrants were used and studied on a trial basis and the amount of disintegrants to be added was selected to achieve a faster release. Optimized formulation F7 (film base: HPMC E-3+HPMC E-5+HPMC E-15) was incorporated with SSG and crospovidone in the same amount and the release was observed. Results showed that SSG is more effective than crospovidone when both were compared.

The Dissolution studies carried out on the optimized formulation after incorporation of superdisintegrant 8% w/w when compared with the marketed (20 mg) tablet of LH exhibited 79 % of total release as compared to the 74 % of total release from the marketed formulation (fig. 6).

From the data obtained from physicochemical evaluation and *in vitro* dissolution studies it was found that formulation F7 gave the best results among all others and hence was considered as the optimized formulations.

Stability studies

No significant deviation was found in the results of stability samples from the previous results of the formulation. This indicates that the formulation is fairly stable at stated conditions and storage period.

CONCLUSION

The prepared ODFs of LH i.e., F1, F2, F3, F4, F5, F6, F7, F7A, and F7B (LH with either HPMC E-15 alone or in combination with HPMC E-3, HPMC E-5, or HPMC K4M) were in accordance and complyingwith the standard range of film-specific parameters. The formulation F7A (film of LH with the combination of HPMC E-3, HPMC E-5, and HPMC E-15 along with the SSG as a superdisintegrants) is a better fast-dissolving film of LH. The active ingredient was rapidly released *in vitro* as compared to the other formulations. Thus, the optimized formulation can be considered for intraoral drug delivery of LH for the faster onset of action and better patient compliance in the treatment of schizophrenia as compared to the other available formulations in the market.

Conflict of interests

Declared None.

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