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Development and optimization of orodispersible films for the treatment of mouth ulcer

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Abstract

Orodispersible dosage forms are new methods for drug delivery system. Orodispersible dosage forms are the most advanced form of oral solid dosage form Because of their more flexibility and convenience. It enhances the efficacy of APIs by dissolving in the oral cavity within a minute without the need for water. The aim of the study was to develop an orodispersible film (ODF) as an alternative dosage forms as compared to tablets, syrups, or suppositories. This is mainly focused on the treatment of mouth ulcers, especially for the peadiatric and geriatric patients. The Solvent Casting method was used to prepare orodispersible films of dexlansoprazole by incorporating polymers such as HPMC, Lycoat RS780, Croscarmelallose as disintegrates, and PEG 400 as plasticizers. The orodispersible films of dexlansoprazole were evaluated to weight variation, Drug content, surface pH, Disintegration time, Swelling Index, Folding Endurance, Film Thickness and In-vitro drug release. The drug release tests were carried out for 8 hours at 37°C1°C in phosphate buffer (pH 6.8). The optimised formulation was carried out with the help of a design expert in the Quadratic model 13.0.5.0 version. The optimised formulation of orodispersible films was subjected to an accelerated stability study and found to be stable at 40°C/75% RH for 3 month according to ICH guidelines. The results, results of the orodispersible films of dexlansopraole, evaluation of all physicochemical parameters will reveal good results. The orodispersible films of dexlansoprazole for the drug release study at 8h, % cumulative drug release of 83.90 to 96.80%. The optimised formulation for design was found to be DL15, which showed 86.90% drug release at 8h and DL15 was found to be stable when stored at 40ºC/75% RH for 3 month according to ICH guidelines with no significant changes on further stability study.

KEY-WORDS

Orodispersible films, Dexlansoprazole, HPMC & Lycoat RS 780, Mouth ulcer

Introduction:

The oral route is the most preferable way of drug administration for systemic effects because of its ease of administration, non-invasiveness, adaptability, patient compliance, and acceptability. In generally, geriatric,

peadiatric, nauseous, bedridden, and noncompliance patients have difficulty swallowing the oral dosage form; it is estimated that 50% of the population is affected by this problem, which leads to a higher risk of noncompliance and ineffective therapy[1]. Orodispersible films are gaining popularity for oral administration. Whereas breath fresheners and over-the-counter products are already widely available in the United States, the primary prescription of drug films was recently introduced in the EU and US markets. The official term named by the European Medicines Agency is orodispersible film (ODF)[2].

Oral delivery is currently the standard method in the pharmaceutical industry since it is safest, most convenient, and cost effective method of drug delivery with the better patient compliance. The Fast dissolving drug delivery system was introduced in the 1970s[3]. Orodispersible films have been identified as new beneficial dosage forms for specific patient populations. Orodispersible films (ODFs) are defined as "single- or multi-layer sheets of suitable material, to be placed in the mouth where they disperse rapidly"[4].

Dexlansoprazole (DSP) is proton pump inhibitor, used in treating gastroesophageal reflex disease (GERD) and ulcer colitis. DSP acts by decrease the acid level in stomach. DSP is acid liable drug which can be destroyed in acidic pH of the stomach. Gastroesophageal reflux disease (GERD) is long term symptom of mucosal damage caused by stomach acid enter from the stomach into the oesophagus. The most common symptoms are heart burn and regurgitation. Medications such as proton pump inhibitors, H2 receptor blockers and antacids are used in the treatment of GERD[5].

Dexlansoprazole works as a proton pump inhibitor, inhibiting stomach acid output by specifically inhibiting (H+, K+)-ATPase in the gastric parietal cell. Dexlansoprazole prevents the final step of acid produced by acting specifically on the proton pump. The U.S. Food and Drug Administration approved Dexlansoprazole under the brand name DELTONE in 2010. According to ICH guidelines, the developed method was approved and validated[6].

MATERIALS AND METHODS

Material

Dexlansoprazole was obtained as a free sample from Murli Krishna Pharm LTD in Maharastra, India. HPMC was obtained from the Karnataka College of Pharmacy in Bangalore. Lycoat RS 780 was obtained from shilpa medicare PVT, Tumakur, Croscarmelallose, and PEG 400 were received from Karnataka college of pharmacy in Bangalore. All the chemicals used were analytical grade.

Methods

Preparation of orodispersible films

Films were prepared by solvent casting method. The aqueous solution was prepared by dissolving the selected polymers in distilled water and allowed to stir on a magnetic stirrer with 1000 rpm for 20 minutes and was kept aside for 2 hr to remove all the air bubbles (solution I). In another beaker, the drug and other ingredient dissolve in water (solution II) and Both the solutions in solution 1 and solution 2 are mixed with continuous stirring to

form a homogenous mixture on a magnetic stirrer with 1000rpm for 2 hr and kept aside for 2 hr to remove all the air bubbles. All the remaining excipients were added to the above solution and allowed to dry at room temperature 40-50ºC for 24 hrs. After drying, these films were removed from the Petridish and cut into definite shapes and sizes. For further evaluation of films are packed with aluminium foil paper and kept in desiccators.

Formulation of orodispersible films of Dexlansoprazole

Table 1 : Composition of orodispersible films of Dexlansoprazol

F0RMULATION CODE	API (mg)	HPMC (mg)	LYCOAT RS 780 (mg)	CROS CARMELL ALOSE (mg)	PEG 400 (mg)	CITRIC ACID (mg)	SUCROSE (mg)	MENTHOL (mg)
DL1	30	37.5	45	6	5	5	3	1.5
DL2	30	37.5	30	6	5	5	3	1.5
DL3	30	37.5	45	6	12.5	5	3	1.5
DL4	30	45	45	6	8.7	5	3	1.5
DL5	30	45	37.5	6	5	5	3	1.5
DL6	30	37.5	37.5	6	8.7	5	3	1.5
DL7	30	45	30	6	8.7	5	3	1.5
DL8	30	37.5	37.5	6	8.7	5	3	1.5
DL9	30	30	37.5	6	12.5	5	3	1.5
DL10	30	30	45	6	8.7	5	3	1.5
DL11	30	37.5	30	6	12.5	5	3	1.5
DL12	30	30	30	6	8.7	5	3	1.5
DL13	30	30	37.5	6	5	5	3	1.5
DL14	30	45	37.5	6	12.5	5	3	1.5

EVALUATION

Weight variation

The formulated films were taking from each formulation, and average weight variations were noted. The weight of each film was determined using a digital weighing balance. The weight standard deviation (SD) was calculated from the mean value[7].

Thickness Test

The thickness of each film was measured using a micrometre screw gauge in various positions on the film. the average thickness and the standard deviation was determined[8].

Folding endurance

Folding endurance is determined by repeatedly folding the film at the same place until the film breaks. The folding endurance value is calculated as the number of times the film can be folded without breaking[9].

Surface pH

The film was allowed to swell for 2 hours on the surface of an agar plate. Agar plate was produced by dissolving

2% (w/v) agar in warm isotonic phosphate buffer (pH 6.8) with stirring, then pouring the solution into a petridish and allowing it to gel at room temperature. A pH paper was placed on the surface of the swollen film to determine the pH[10].

Swelling Index

Film swelling studies was conducted by using simulated salivary fluid. Each film sample is weighed and placed in a pre-weighed stainless steel wire mesh. The mesh containing film sample is submerged into a 15mL medium in a plastic container. Increase in the weight of the film was determined at pre-set time interval until a constant weight was observed[11].

The degree of swelling was calculated using parameters

$$\mathbf{SI} = \frac{wt - wo}{wo}$$

Where, SI = swelling index,

wt = weight of the film at time "t", and

wo = weight of the film at t = 0

Disintegration Time

The test was performed using disintegration test apparatus. Disintegration time provides an indication of the disintegration characteristics and dissolution characteristics of the film. The required size of film (2×2 cm2) is placed in a stainless steel wire mesh containing 25 ml of pH 6.8 simulated salivary fluids. Time taken by the film to break and dissolve is measured as disintegration time[12].

Drug Content

The Drug content determination of the film was carried out by dissolving the film in ($2 \times 2cm^2$) 100 ml of volumetric flask containg pH 6.8 phosphate buffer solution and kept aside for 24 hour. The Absorbance and drug concentration was analysed by using UV spectrophotometer at 285nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded[13].

In vitro drug diffusion studies:

In vitro drug release was performed using Franz diffusion cell with receptor compartment capacity of 150 mL. The dialysis membrane was inserted between donor and receptor compartment of diffusion cell. The film was kept on the dialysis membrane and was covered by the aluminium foil. The receptor compartment of diffusion cell contained pH 6.8 phosphate buffer. The whole setup was fixed on hot plate magnetic stirrer and solution in receptor compartment was stirred continuously using the magnetic beads and temperature was maintained at 37º C±1ºC. The samples were taken at different time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12min) and each time was replaced with required volume of fresh dissolution solution. The collected samples were analysed at 285 nm by using UV spectrometer[14].

Experimental design and Optimisation:

The runs or formulations, that are designed based on the Response surface method, are evaluated for the response. The tool used here is Design Expert trial version with Box-Behnken model. Variables used here are HPMC, Lycoat RS 780, and PEG 400 and responses are Folding endurance, Disintegration time, and drug release. The responses values are subjected to Quadratic model to find out the relationship between the variables used the response values obtained[15].

Accelerated Stability study

The stability studies were conducted according to ICH guidelines to investigate the effect of temperature, relative humidity on drug in formulation. Final optimized formulation was subjected to aggravated conditions of temperature and relative humidity by wrapping it in aluminium foil and packaging it in glass container. The films were kept in desicattor chamber, at 40 ± 20 °C temperature and 75 ± 5% RH for 3 months[16].

Results

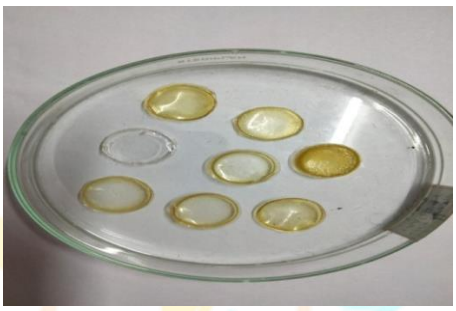

Figure 1: prepared orodispersible films of Dexlansoprazole

Evaluation studies of Orodispersible films:

Formulation Code	Drug Content %	Swelling Index %	Surface pH	Folding Endurance	Disintegration Time (Sec)	Film Thickness (mm)
DL1	96.69±0.15	87.02±0.69	4.48±0.09	124±7.14	37.1±1.52	0.25±0.03
DL2	95.10±0.13	85.12±2.50	4.43±0.12	114±5.88	31.5±0.12	0.23±0.05
DL3	96.73±0.16	91.17±1.17	4.54±0.10	139±6.23	38.6±0.23	0.28±0.07
DL4	98.53±0.18	86.04±3.51	4.84±0.21	165±8.12	44.2±0.18	0.33±0.06
DL5	94.49±0.17	89.06±0.81	4.79±0.15	154±9.87	41.6±1.05	0.31±0.08
DL6	95.76±0.10	93.15±4.91	4.57±0.13	126±4.56	34.3±3.09	0.26±0.02
DL7	97.28±0.19	87.08±7.53	4.76±0.16	149±6.45	42.1±0.17	0.29±0.05
DL8	96.82±0.10	95.01±5.35	4.58±0.26	125±5.29	34.2±2.12	0.22±0.09
DL9	95.24±0.12	90.05±0.95	4.38±0.23	82±5.87	28.1±0.10	0.30±0.12
DL10	95.92±0.20	94.10±1.88	4.45±0.14	97±7.55	29.6±4.06	0.27±0.15
DL11	96.17±0.22	84.09±7.18	4.48±0.19	120±8.8	34.7±0.38	0.24±0.01
DL12	93.82±0.19	88.13±3.83	4.33±0.20	75±9.45	25.2±1.15	0.32±0.04
DL13	94.82±0.21	92.09±6.72	4.37±0.09	81±8.25	26.5±5.11	0.29±0.10
DL14	98.73±0.24	95.03±8.23	4.87±0.25	161±6.28	43.5±6.15	0.35±0.14

Table 2: Evaluation studies for orodispersible films of Dexlansoprazole

In Vitro drug release Studies of Orodispersile Films of Dexlansoprazole :

Table 3: Comparative data of percentage in-vitro drug release for DL1-DL14 formulation

Time (min)	DL1	DL2	DL3	DL4	DL5	DL6	DL7	DL8	DL9	DL10	DL11	DL12	DL13	DL14
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	19.42	17.61	22.36	28.79	24.16	21.23	20.55	19.87	16.71	18.97	18.52	15.47	16.60	22.36
2	30.49	29.47	33.54	37.71	33.65	32.63	29.92	31.73	25.18	27.89	30.49	25.41	26.99	35.45
3	43.96	42.56	48.31	48.73	49.15	47.75	45.64	45.78	41.72	41.02	44.52	39.06	38.64	51.53
4	52.65	54.47	55.73	57.41	58.11	55.03	54.19	55.17	53.07	54.61	52.93	48.59	49.99	63.57
5	63.85	65.67	66.51	67.63	67.91	64.83	68.05	64.13	65.39	65.53	66.23	59.23	58.25	74.35
6	71.24	70.75	72.10	72.84	73.58	71.73	73.45	73.21	72.22	72.35	71.24	68.29	66.70	81.32
7	78.98	78.49	79.23	84.63	84.88	82.67	84.88	82.05	79.23	80.58	78.98	75.05	76.53	89.42
8	86.48	84.88	88.08	95.81	91.27	87.59	90.41	87.71	83.90	85.50	86.23	81.20	82.92	96.80

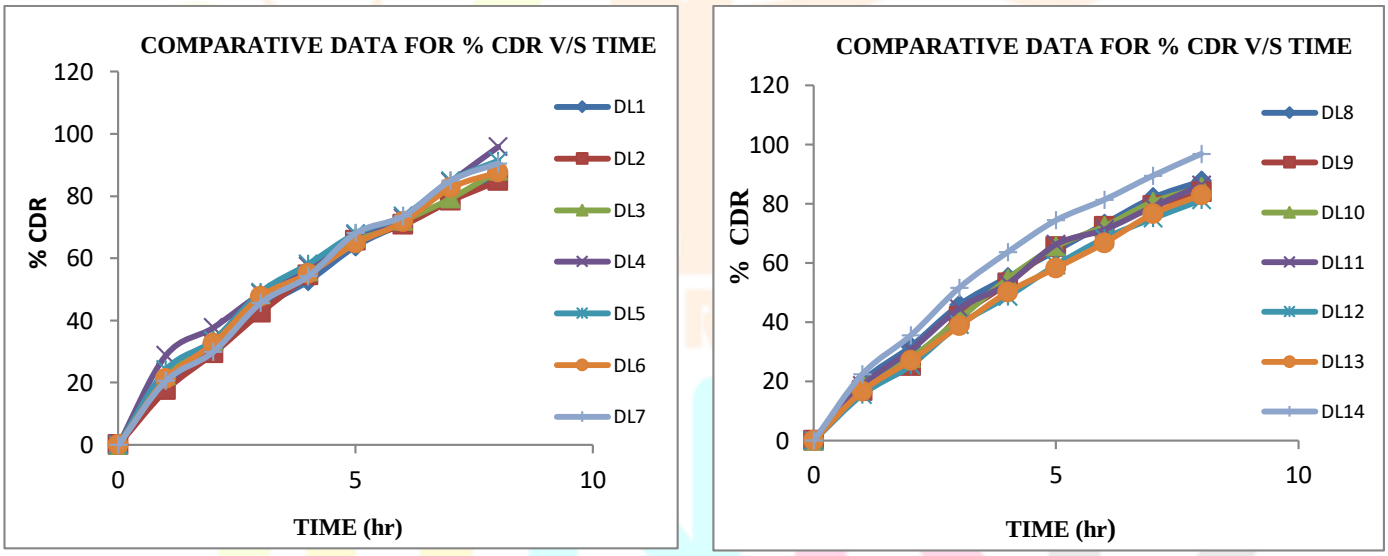

Figure 2: Comparison of in-vitro drug release for DL1-DL14 formulation

Optimization

Table 4: Summary of ANOVA and regression analysis for measured responses

Responses	Model	R^2	Adjusted R^2	SD	CV	SS	Df	MS	F-value	p-value	Model Significance
R1	Linear	0.986	0.983	3.90	3.19	11470.75	3	3823.58	251.37	<0.0001	Significant
R2	Linear	0.978	0.971	0.751	2.60	254.47	3	84.82	150.03	<0.0001	Significant
R3	Linear	0.907	0.880	1.57	1.79	241.51	3	80.50	32.79	<0.0001	Significant

R1: Folding endurance, R2: Disintegration time, and R3: Drug release. ANOVA: Analysis of variance, R^2: Coefficient of regression, SD: Standard deviation, CV: Coefficient of variation, SS: Sum of squares, df: Degree of freedom, MS: Mean sum of squares.

Response 1. Folding endurance

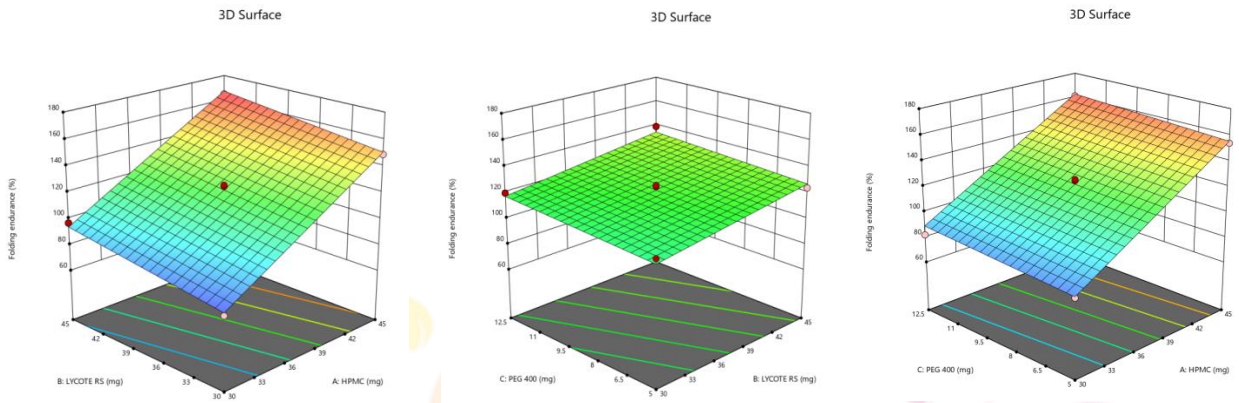

Figure 3: Three dimensional (3D) response surface diagrams represent the effect of folding endurance. (A) The influence of folding endurance on HPMC and Lycoat RS 780. (B) The influence of folding endurance on Lycoat RS 780 and PEG 400. (C) The influence of folding endurance on HPMC and PEG 400.

Response 2. Disintegration time

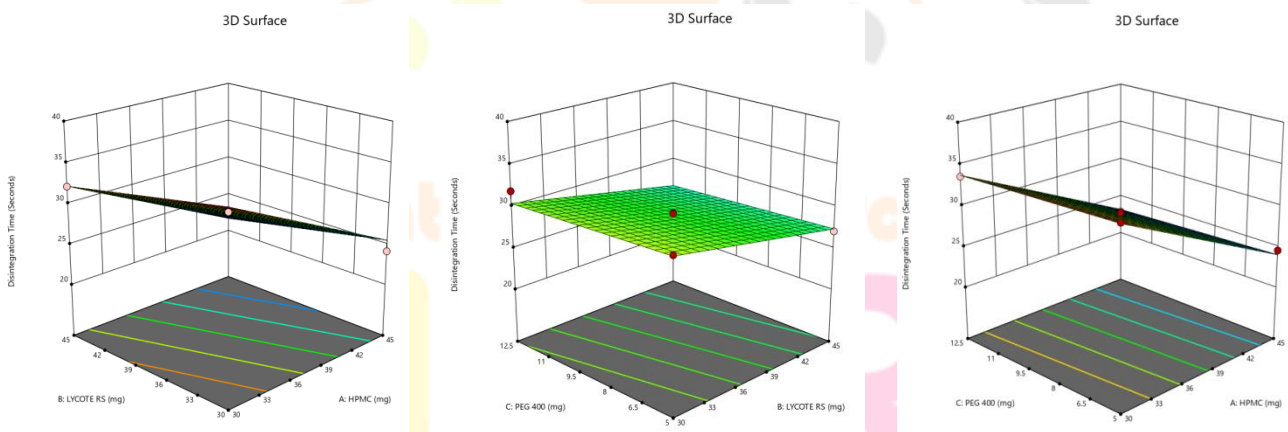

Figure 4: Three dimensional (3D) response surface diagrams represent the effect of disintegration time. (A) The influence of disintegration time on HPMC and Lycoat RS 780. (B) The influence of disintegration time on Lycoat RS 780 and PEG 400. (C) The influence of disintegration time on HPMC and PEG 400.

Response 3. Drug release

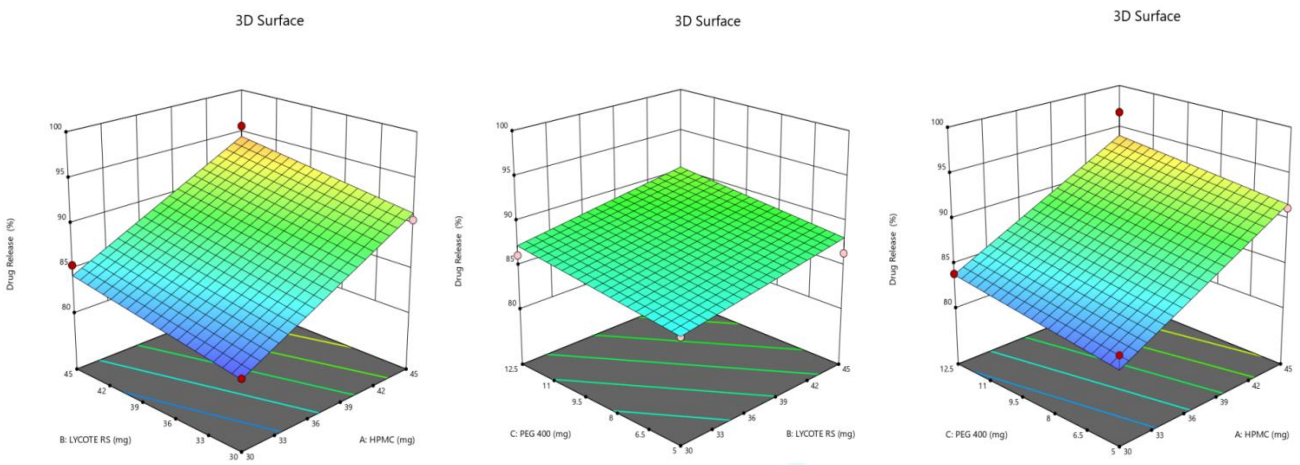

Figure 5: Three dimensional (3D) response surface diagrams represent the effect of Drug release. (A) The influence of Drug release on HPMC and Lycoat RS 780. (B) The influence of Drug release on Lycoat RS 780 and PEG 400. (C) The influence of Drug release on HPMC and PEG 400.

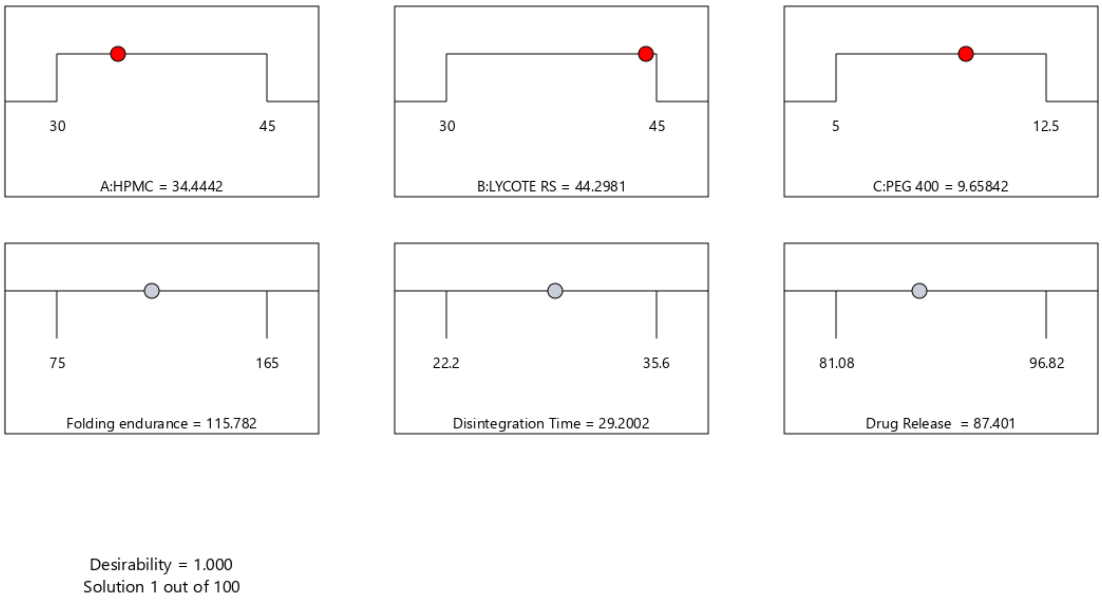

Figure 6: Numerical Optimized ramp profile graph of orodispersible films of Dexlansoprazole

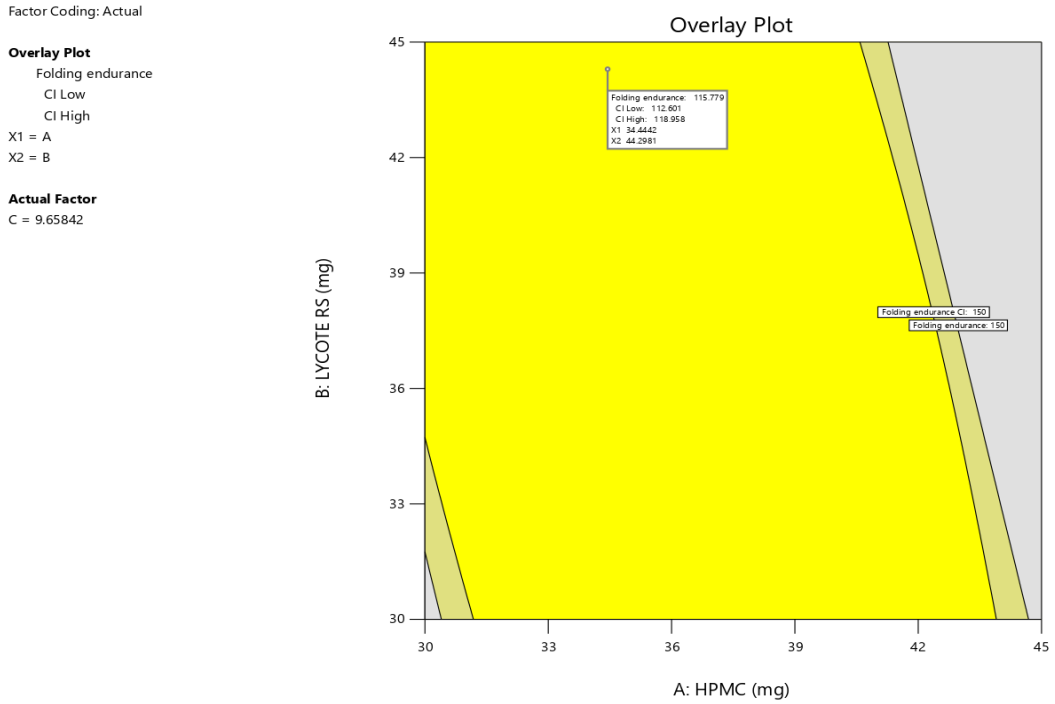

Figure 7: Graphical optimised overlay plot for the formulation of Orodispesible films of Dexlansoprazole

Optimised formulations

Table 5: Optimised formulations of ODF, predicted and experimental results DL15

Optimized Formulation	HPMC	Lycoat Rs 780	PEG 400	Folding Endurance	Disintegration Time	Drug Release
Predicted	34.64	40.11	10.70	112.88	30.06	86.90
Experimental	34.64	40.11	10.70	112.45	30.16	86.65

Accelerated stability studies

Table 6: Accelerated stability studies of Orodispersible films of Dexlansoprazole (DL15)

Time (hr)	Folding Endurance	Disintegration Time	Drug Release (%)
Initial	112.45	30.16	86.90
1 Month	112.75	30.09	86.65
2 Month	112.75	30.08	86.45
3 Month	112.75	30.08	86.45

DISCUSSION

Film Thickness:

Thickness of the film developed formulation DL1 to DL14 varied from 0.23 to 0.35 mm and was found to be uniform. The thickness of the films increased with increase in HPMC and Lycoat RS 780 concentration. The SD values were less than 1 for all formulations, an indication of more uniform of all orodispersible films as showed (Table No.2).

Folding Endurance:

Folding Endurance of the developed formulation DL1 to DL14 varied from 75 to165 as showed (Table No.2). It shows that all formulation had a good plasticity. The Folding Endurance of the film increases with increase in the HPMC and Lycoat RS 780 concentration Proportion.

Surface pH:

The surface pH was found to be in the range of 4.33 to 4.87 which is close to salivary pH, which indicates that films may have less potential to irritate the oral mucosa, there by they are comfortable. The results are given in Table 2.

Drug content :

Good uniformity of drug content was observed in all orodispersible films. The drug content is ranged from all formulation is 93.82% to 98.73% as showed Table No.2, Hence it was concluded that drug was uniformly distributed in all the formulations. As per USP requirements, drug content was found to be within the limits i.e. 85-115%.

Swelling index:

The Swelling index of the developed formulation DL1 to DL14 varied from 84.09% to 95.03%. The formulation DL14 is showed high % Swelling index i.e.95.03% and the formulation DL11 is showed less % Swelling index i.e.84.09% (Table No.2).

Disintegration time

Disintegration time of the developed formulations DL1 to DL14 varied from 25 - 44sec as showed (Table No.2). All the formulations were found to disintegrate within 60 sec. Disintegration time of the film increases with increase for the effect of polymer such as HPMC and Lycoat RS 780 Proportion.

In vitro Drug Diffusion studies

The in-vitro Drug Diffusion studies of orodispersible films of Dexlansoprazole from the prepared orodispersible films formulation was studied in pH 6.8 phosphate buffer for 8min. The DL14 formulation is showed high percentage of drug release i.e 96.80% and DL12 formulation is showed less percentage of drug release i.e 81.20%. As the ratio of polymer increased and release of drug will be decreased proportionally. The release rate from prepared formulation containing low polymer concentration was remarkably faster. In-vitro drug release of all formulations showed graphical represented in Figure No.18&19.

Optimization

Response 1. Folding endurance:

Summary of ANOVA:

ANOVA table represents shown Sum of Squares represents 11470.75 Degrees of Freedom(DF) was found by 3. Mean Square value of 382358, F Value was found 251.

37 and p-value was found to be <0.0001 states folding endurance is significantresponse with respect to factors of A-HPMC, B-LYCOAT RS 780 and C-PEG 400 as a variable.

3D surface profile:

3D surface graph shows the effect on folding endurance was observed when increase in the concentration of HPMC 37.5 mg to 45 mg in the formulation, Folding endurance was observed with 75-165 odd value which shows significant effect of HPMC on Folding endurance in presence of Lycoat RS 780.

When increase in the concentration of Lycoat RS 780 30 mg to 45 mg in the formulation, Folding endurance was observed with 75-165 odd value which shows significant effect of HPMC on Folding endurance in presence of PEG 400.

When increase in the concentration of PEG 400 5-12.5 mg in the formulation, Foldingendurance was observed with 75-165 odd value which shows significant effect of HPMC on Folding endurance in presence of HPMC.

Response 2: Disintegration time

Summary of ANOVA:

ANOVA table represents shown Sum of Squares represents 254.47, Degrees of Freedom(DF) was found by 3. Mean Square value of 84.82, F Value was found and p-value was found to be <0.0001 states Disintegration time is significant response with respect to factors of A-HPMC, B-LYCOAT RS 780 and C-PEG 400 as a variable.

3D surface profile:

3D surface graph shows the effect on folding endurance was observed when increase in the concentration of HPMC 37.5 mg to 45 mg in the formulation, Disintegration time was observed with 25-44sec which shows significant effect of HPMC on Disintegration time in presence of Lycoat RS 780.

When increase in the concentration of Lycoat RS 780 30 mg to 45 mg in the formulation, Disintegration time was observed with 25-44sec which shows significant effect of HPMC on Folding endurance in

presence of PEG 400.

When increase in the concentration of PEG 400 5-12.5 mg in the formulation, Disintegration time was observed with 25-44sec which shows significant effect of HPMC on Disintegration time in presence of HPMC.

Response 3: Drug Release

Summary of ANOVA:

ANOVA table represents shown Sum of Squares represents 241.51, Degrees of Freedom(DF) was found by 3. Mean Square value of 80.50, F Value was found 32.79 and p-value was found to be <0.0001 states Drug release is significant response with respect to factors of A-HPMC, B-LYCOAT RS 780 and C-PEG 400 as a variable.

3D surface profile:

3D surface graph shows the effect on folding endurance was observed when increase in the concentration of HPMC 37.5 mg to 45 mg in the formulation, Drug release was observed with 81.92-96.20 which shows significant effect of HPMC on Drug release was in presence of Lycoat RS 780.

When increase in the concentration of Lycoat RS 780 30 mg to 45 mg in the sformulation, Drug release was observed with 81.92-96.20 which shows significant effect of HPMC on Drug release in presence of PEG 400.

When increase in the concentration of PEG 400 5-12.5 mg in the formulation, Drug release was observed with 81.92-96.20 which shows significant effect of HPMC on Drug release in presence of HPMC.

Accelerated stability studies

The optimized formulation DL15 was evaluated for the stability studies which were storage for 3 months temperature at 40±2ºC and 75±5% relative humidity. From the evaluation, it was found that there are no significant changes in physical appearance, folding endurance, and disintegration time and percentage drug release.

Conclusion

In present research work, the developed orodispersible films of dexlansoprazole was prepared by solvent casting method using concentration of HPMC and Lycoat RS 780 as film forming polymer, crascarmellalose as disintegrates and PEG 400 as plasticizers. The prepared film were evaluated to weight variation, surface pH, folding endurance, film thickness, disintegration time , swelling index , drug content and in vitro drug release.

The optimized formulation DL15 was done by selecting the box behnken design model and response surface method. The physicochemical properties of optimised formulation DL15 were evaluated to folding endurance, disintegration time and drug release. The optimized formulation DL15 of orodispersible films were subjected to accelerated stability study and to be found at 40°C/75% RH for 1month according to ICH guidelines. Finally, It can be concluded that developed orodispersible films of Dexlansoprazole, which is mainly focused on treatment of mouth ulcer, especially for the peadiatric and geriatric population.

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