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DEVELOPMENT AND CHARACTERIZATION OF THE ORODISPERSIBLE TABLET OF NATEGLINIDE USING FACTORIAL DESIGN FOR THE TREATMENT OF DIABETES

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ABSTRACT

Objective: The objective of the current research work was to prepare a taste-masked Orodispersible tablet of Nateglinide which improve patient compliance. **Method:** Taste Masked ion exchange resins were selected based on the preliminary studies and the process parameters of the Solvent evaporation method were also finalized by the same. 3^2 full factorial design was used for optimization. A mole of Kyron T-114 and % of Aspartame was taken as independent variables X1 & X2 respectively. % Drug release at 15 minutes, wetting time, Disintegration time, Water absorption ratio and Ability of taste masking were taken as dependent variables. Short term accelerated stability studies were performed for tablets prepared using optimized Orodispersible Tablet. **Results and Discussion:** Optimized batch composition had 1 Mole (49 mg) of Kyron T-114, 60 mg of Nateglinide and 3.31%(9.9 mg) Aspartame was prepared based on the values of the dependent variable of the design batches. All the evaluation parameters of the optimized batch met the acceptance criteria. The taste was improved as compared to pure Nateglinide. % *In-vitro* Drug release was found to be 94.40% at 15 minutes, *In-vitro* Disintegration Time 29 second and Taste masking as per taste panel gives the very slightly bitter for Optimized Orodispersible tablet. Stability data were also in the range of acceptance. **Conclusion:** A Taste masked Orodispersible tablet was developed successfully by the Solvent evaporation method.

This method proved as a successful method for the development of Masking the bitter Taste of Nateglinide by using the ion exchange resin.

Keywords: Nateglinide; Orodispersible Tablet; Solvent Evaporation Method; 3^2 Full factorial Design; Diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia, glycosuria, hyperlipidemia, negative nitrogen balance and sometimes ketonaemia.

Two major types of diabetes mellitus are **Type I** Insulin-dependent diabetes mellitus (IDDM), juvenile-onset diabetes mellitus: There is β-cell destruction in pancreatic islets: the majority of cases are autoimmune (type 1A) antibodies that destroy β-cells are detectable in blood, but some are idiopathic (type l B) no β-cell antibody is found. In all type 1 cases circulating insulin levels are low or very low and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition. **Type II** Noninsulin-dependent diabetes mellitus (NIDDM)/maturity-onset diabetes mellitus: There is no loss or moderate reduction in β-cell mass: insulin in circulation is low, normal or even high, no anti-β-cell antibody is demonstrable; has a high degree of a genetic predisposition; generally, has a late-onset (past middle age) **[1]**.

It is estimated that 50% of the population have the problem of swallowing tablets, especially the pediatrics and geriatric population **[2-4]**. One of the popular approaches in the taste masking of bitter drugs is based on Ion Exchange resin (IER). Ion Exchange Resin are solid and suitably insoluble high molecular weight poly-electrolytes that can exchange their mobile ions of equal charge with the surrounding medium **[5-10]**.

The oral route is the most preferred and patient-convenient means of drug administration. Most of the drugs are being taken in the form of tablets and capsules by almost all patients, including adult, pediatrics and geriatric patients **[11, 12]**.

MATERIAL AND METHOD

Materials

Nateglinide was obtained from Glenmark pharmaceuticals. Kyron T-114 and Kyron T-314 were obtained from Corel pharma, Ahmedabad. Aspartame-LR, Neotame-LR D-mannitol-LR was obtained from S D fine chemicals, Mumbai. Magnesium stearate-LR was obtained from ASES Chemical Works. Talc-LR was obtained from Vikas Pharma, Mumbai. Citric acid was obtained from Finar limited.

Method

Preparation of Taste Masked Drug-Resin Complex (DRC):

Accurately weighed quantity of resin was dispersed in a beaker containing 10 mL of

deionized water and allowed to swell for 1 hour. Accurately weighed quantity of Nateglinide and aspartame was mixed with Methanol. This solution was added slowly into the solution of resin and stirred for 5 hours. After 5 hours, the drug resin complex was separated from the dispersion by filtration and washed with deionized water. The complex was dried and evaluated for taste **[13, 14]**.

Preparation of Orodispersible Tablet:

Tablets were prepared using prepared optimized drug-resin complex and other excipients like diluent, disintegrant, sweetener, glidant and lubricant by direct compression method **[13, 14]**.

Full Factorial Design

A 3^2full factorial design was used to quantify the significant independent variables revealed from preliminary studies. In this design 2 factors were evaluated, each at 3 levels and experimental trials was performed at all 9 possible combinations generated by Design Expert 10.0.5. In full factorial design X1 and X2 are coded values and were shown in **Table 1**.

Table 1: 3^2 Full Factorial Design

Sr. No	Coded Value X1	Coded value X2	Decoded Value	
			X1= Mole of Resin	X2= % Sweetener
1	-1	-1	1	3%
2	0	0	2	5%
3	1	1	3	7%
Dependent Variables				
Y1 = % drug release at 15 minute				
Y2 = Wetting time				
Y3 = Disintegration time				
Y4 = Water absorption ratio				
Y5 = Ability of taste masking				

Table 2: The formula for Factorial Batches

Ingredients	Batch Code								
	A 1	A 2	A 3	A 4	A 5	A 6	A 7	A 8	A 9
Nateglinide	60	60	60	60	60	60	60	60	60
KyronT-114	49	98	147	49	98	147	49	98	147
KyronT-314	20	20	20	20	20	20	20	20	20
Aspartame	9	9	9	15	15	15	21	21	21
Mannitol	153	104	55	147	98	49	141	92	43
Lemon Oil	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	6	6	6	6	6	6	6	6	6
Total wt.(mg)	300	300	300	300	300	300	300	300	300

Formula of factorial Batches were shown in **Table 2**.

Evaluations parameters of tablets

The compressed tablets were evaluated for various parameters such as thickness, hardness, diameter and friability were represented in **Table 3 [15, 16]**.

Wetting time & Water Absorption Ratio:

The tablet was put on twice folded filter paper (5×5 cm) placed in the middle of a petri dish having an 8 cm diameter containing 10 mL of 0.05% Phenol-Red dye aqueous solution. The time necessary for the complete wetting of the outer surface of the tablet was determined by visual inspection. The measurements (n=3) were performed at room temperature. The wetted tablet was weighed and the water absorption ratio, WAR, was determined using the following equation **[17, 18]**.

WAR=Tablet Weight after Wetting- Tablet Weight before Wetting/Tablet weight before wetting*

Disintegration Time

The disintegration time of tablets was measured by placing 6 tablets in a disintegration test apparatus as per Indian pharmacopoeia 2014. After carefully placing the tablet in the apparatus the time required for the tablet to completely disintegrate into fine particles was noted and carried out in two replicates for minimization of error.

***In-Vitro* drug release**

In-Vitro drug release was carried out using USP type II Dissolution apparatus (paddle) at 37±0.5 °C, 50 rpm and 900mL Simulated salivary fluid (pH 6.8) as dissolution medium. Aliquots of 5 mL were withdrawn at specified intervals of time. A fresh medium was added to keep the volume constant. The withdrawn aliquots were filtered through 0.45 µm Whatman filter paper and the sample was analyzed using a UV spectrophotometer at 205 nm. The cumulative percentage drug release was calculated. **[19, 20]**

Stability Study

Stability testing is performed to ensure that drug products retain their fitness for use until the end of their expiration dates. An accelerated stability study was carried out for the final formulation (n=3) at 40ºC±2 ºC and 75±5% RH. Samples were withdrawn after two weeks and analyzed for visual appearance, disintegration time, drug release and drug content **[21]**.

RESULT

Pre- Compression Parameters of Tablet

Results indicate that the powder blend possesses passable to very poor and compressibility properties were observed as shown in **Table 3**.

Post Compression Parameters of Tablet

Thickness, Hardness, Diameter, Friability and average weight within a range were observed as shown in **Table 4**.

Wetting time was found to be in the range of 22 to 120 seconds. Disintegration time was found to be in the range of 25 to 185 seconds. The water absorption ratio was found to be in the range of 0.96 to 1.55 were observed as shown in **Table 5**.

***In-vitro* Dissolution study of Orodispersible Tablets (A1-A9):**

Percentage Drug Release of orodispersible tablets were shown in **Figure 1**. Based on observation A released study was performed up to the time of 20 min.

Result of Taste Masking was shown in **Figure 2**. The ability of taste masking was found to be in the range of 1 to 5.

The ability of taste masking was found to be in the range of 1 to 5 were observed as shown in **Table 6**.

Statistical Analysis

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis. The % Drug Release, Wetting Time, Disintegration Time, Water Absorption Ratio and Ability of Taste Masking was selected as dependent variables. The polynomial equations relating the responses, The % Drug Release, Wetting Time, Disintegration Time, Water Absorption Ratio and Ability of Taste Masking to the transformed factor are described below in **Figure 3**.

The relationship between the independent variables & dependent variables was not significant & model fitting the data was mean only as shown in **Figure 3**.

Optimization of Data Analysis

Observed responses of Nine formulations were fitted to various models using Design Expert 10.0.5.

Stability Study

Tablet kept at 40ºC±2 ºC and at 75±5% RH was assessed after 30 days for visual appearance, disintegration time and drug content and *in-vitro* drug release which showed there was no significant change in tablet characteristics and tablets were stable during thattime span.

Table 3: Pre-compression Evaluation Parameters of Powder Blend

Design Batch	Bulk Density	Tapped Density	Hausner's Ratio	Carr's Index (%)	The angle of Repose (Θ)
A1	0.32 ± 0.003	0.47 ±0.003	1.47 ± 0.003	31.91 ± 0.23	31.38 ± 0.28
A2	0.30± 0.004	0.45± 0.004	1.51 ± 0.006	33.33 ± 0.45	28.36 ± 0.52
A3	0.31± 0.002	0.43± 0.002	1.38 ± 0.004	27.90 ± 0.20	28.36 ± 0.17
A4	0.28± 0.002	0.43± 0.003	1.53 ± 0.005	34.88 ± 0.27	27.47 ± 0.32
A5	0.30± 0.004	0.44± 0.003	1.47 ± 0.002	31.81 ± 0.33	27.92 ± 0.36
A6	0.31± 0.004	0.44± 0.004	1.42 ± 0.001	29.54 ± 0.15	27.47 ± 0.20
A7	0.24± 0.004	0.35± 0.003	1.46 ± 0.003	31.42 ± 0.26	27.02 ± 0.29
A8	0.26± 0.003	0.35± 0.004	1.35 ± 0.007	27.77 ± 0.18	28.36 ± 0.26
A9	0.37± 0.003	0.47± 0.005	1.27 ± 0.004	21.27 ± 0.41	29.24 ± 0.36

Table 4: Characterization of Prepared Tablets

Design Batch	Thickness Tablet (mm)	Hardness kg/cm^2	Diameter (mm)	Friability (%)	Average Weight (mg)
A1	3.03 ± 0.15	04 ± 0.89	9.83 ± 0.96	0.49 ± 0.01	302 ± 2
A2	3.15 ± 0.20	4.2 ± 0.57	9.80 ± 0.98	0.78 ± 0.00	304 ± 1
A3	3.42 ± 0.21	4.3 ± 0.62	9.85 ± 0.89	0.89 ± 0.00	297 ± 5
A4	3.1 ± 0.26	3.8 ± 0.67	9.81 ± 0.78	0.19 ± 0.00	299 ± 4
A5	3.32 ± 0.12	4.2 ± 0.58	9.83 ± 0.76	0.24 ± 0.00	305 ± 1
A6	3.33 ± 0.15	3.9 ± 0.64	9.81 ± 0.84	0.54 ± 0.00	301 ± 2
A7	2.88 ± 0.18	4.6 ± 0.95	9.85 ± 0.86	0.36 ± 0.00	285 ± 6
A8	2.86 ± 0.11	4.3 ± 0.78	9.80 ± 0.97	0.72 ± 0.00	283 ± 4
A9	3.25 ± 0.14	3.4 ± 0.54	9.86 ± 0.99	0.49 ± 0.00	304 ± 1

Table 5: Wetting Time (Second), *In- vitro* Disintegration Time (Second) and Water Absorption ratio (%) of Designed Batch

Design Batch	Wetting time (sec)	*In-vitro* Disintegration Time (sec)	Water absorption ratio (%)
A1	39 ± 0.42	25 ± 0.26	126 ± 0.65
A2	70 ± 0.61	40 ± 0.04	106 ± 0.72
A3	120 ± 0.33	135 ± 0.56	116 ± 0.98
A4	60 ± 0.64	72 ± 0.53	160 ± 0.86
A5	90 ± 0.47	125 ± 0.46	96 ± 0.45
A6	100 ± 0.55	120 ± 0.72	103 ± 0.79
A7	80 ± 0.35	75 ± 0.39	136 ± 0.76
A8	120 ± 0.79	185 ± 0.45	126 ± 0.87
A9	22 ± 0.86	28 ± 0.26	155 ± 0.94

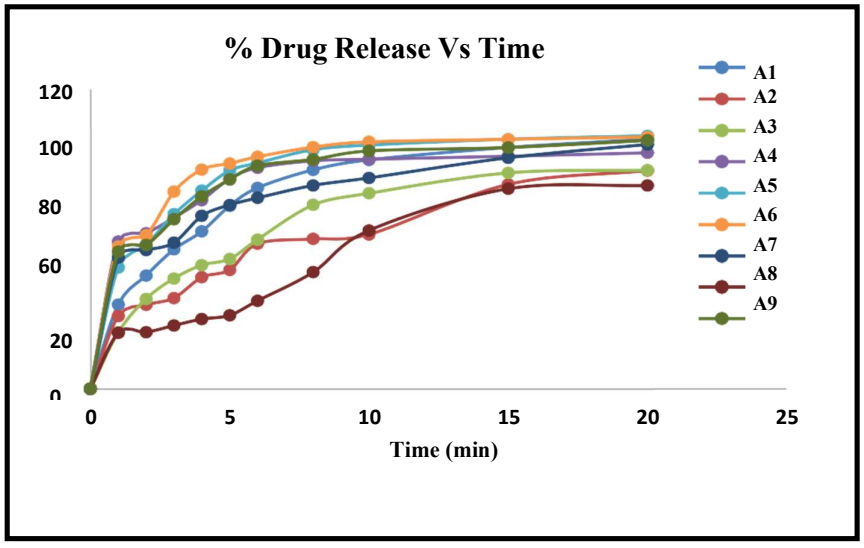
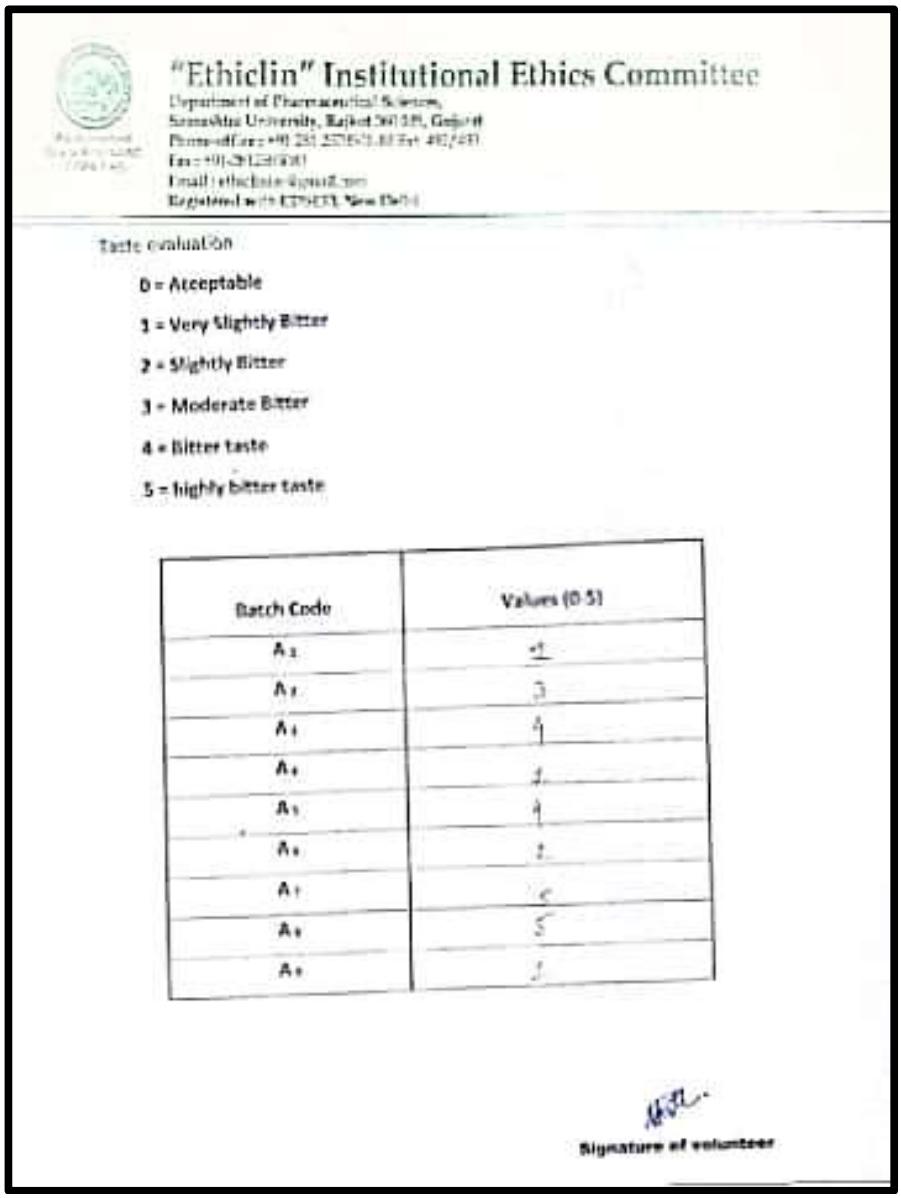


Figure 1: Percentage Drug Release of Orodispersible Nateglinide Tablet



"Ethiclin" Institutional Ethics Committee

Taste evaluation

0 = Acceptable

1 = Very Slightly Bitter

2 = Slightly Bitter

3 = Moderate Bitter

4 = Bitter taste

5 = highly bitter taste

Batch Code	Values (0-5)
A1	1
A2	3
A3	4
A4	1
A5	4
A6	2
A7	5
A8	5
A9	1

Signature of volunteer

Figure 2: Result of Taste Masking study by Ethics Committee

Table 6: Ability of Taste Masking

Batch No.	Ability of taste masking
A1	1
A2	3
A3	4
A4	1
A5	4
A6	2
A7	5
A8	5
A9	1

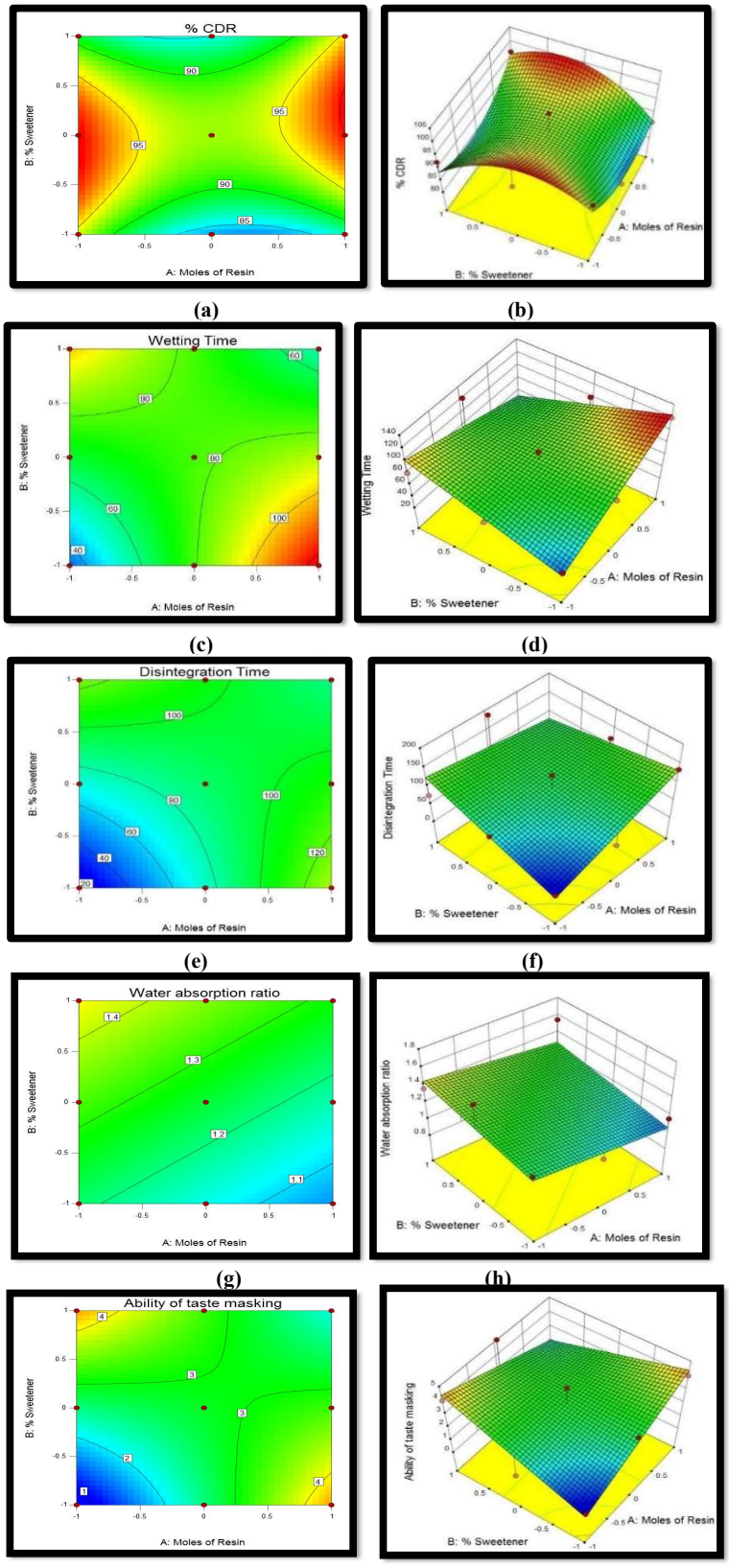


Figure 3: Nateglinide Tablet Contour plot for % CDR at 15 min. (a) Response surface plot for % CDR at 15 min. (b) Contour plot for Wetting Time(sec) (c) Response surface plot for Wetting Time(sec) (d) Contour plot for Disintegration Time(sec) (e) Response surface plot for Disintegration Time(sec) (f) Contour plot for Water absorption ratio (g) Response surface plot for Water absorption ratio (h) Contour plot for Ability of Taste Masking (i) Response surface plot for Ability of Taste Masking (j)

DISCUSSION

The prepared powder blend for all nine formulations was evaluated for Bulk density which ranged from 0.24 to 0.37, Tapped density ranged from 0.35 to 0.47, Carr's index ranged from 21.27 to 34.88, Hausner's ratio ranged from 1.27 to 1.53 and Angle of Repose ranged from 27º.02' to 31º.38'. All these results indicate that the powder blend possesses passable to very poor and compressibility properties. The prepared ODTs for all nine formulations were evaluated for the thickness of the tablet which range from 2.86 to 3.82 mm, Hardness of all batches prepared by direct compression was found to be 3.4 to 4.6 kg/cm^2. Diameter of Tablet was found to be in range from 9.80 to 9.86 mm and % friability was less than 1% for all the batch, indicating that the friability is within the prescribed limits. The results of friability indicate that the tablets possess good mechanical strength. As shown in Table no.1, two independent variables namely X1 (Resin ratio) & X2 (% Sweetener). Y1 (% drug release at 15 minutes), Y2 (wetting time), Y3 (Disintegration time), Y4 (Water absorption ratio), Y5 (Ability of taste masking), were selected as dependent variables.

Based on preliminary batches results, the low, medium and high values of independent variables were selected and the batches from A1 to A9 were formulated. The prepared ODTs for all nine formulations, where Disintegration time was found to be in the range of 25 to 185 seconds. Wetting time was found to be in the range of 22 to 120 seconds. The water absorption ratio was found to be in the range of 0.96 to 1.55. The ability of taste masking was found to be in the range of 1 to 5. The data transformation simplifies the calculations for model development. The data generated by the experimental design was utilized for drawing contour plots, to obtain an optimized region within the factorial space, and thereby produce an optimized formulation. It was seen that Regression models were developed for all response variables from multiple regression analysis andall parameters mostly followed linear models. Linear models best fitted to study the response, that was, % drug release at 15 minutes, wetting time (sec), Disintegration time (sec), Water absorption ratio and Ability of taste masking. Tablets were stable during stability period.

CONCLUSION

An Orodispersible tablet was prepared successfully with the Solvent evaporation method in the present investigation. 3^2 full factorial design was selected to study the effect of Mole of Kyron T-114 and % of Aspartame as independent variables on responses such as % Drug release at 15

minutes, Wetting time, Disintegration time, Water absorption ratio and Ability of taste masking. Optimization was carried out by design expert software version 10.0.5. which showed an optimized batch having 1 Mole (49 mg) of Kyron T-114 and 3.31%(9.9 mg) Aspartame as design components. The relationship between the independent variables & dependent variables was not significant & the model fitting the data was mean only. From the results obtained, it can be concluded that the complex of Nateglinide with Kyron T-114 Mask bitter taste of Nateglinide. In prospect Spray drying method for complex formation may show better tastemasking & % drug release as compared to prepared Orodispersible tablet by the solvent evaporation method.

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