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Evaluation and Characterization of Stabilized Drug, Formulated as Oro Dispersible Tablet Using Advanced Method

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

In a challenge to prepare a stable Oro-dispersible tablet (ODT) of Desloratadine, using dry resin was incorporated into a fast-disintegrating matrix to prepare an optimized ODT that achieved the desired criteria of stabilization and patient acceptance. In this study, the critical process parameters (CPPs) and critical material attributes (CMAs) were determined via risk assessment methods within the framework of Quality by Design (QbD). The results showed that resin (Amberlite IRP64®) can be used as a dry stabilizer and the selected variables in the optimization phase have a strong influence on the blend flowability, disintegration time, and wetting time of the ODTs. Furthermore, by comparing the optimized formula with the marketed one, the optimized formula showed a significantly lower disintegration, lower wetting time, and an almost similar dissolution profile.

Keywords: Oral disintegrating tablets; desloratadine; quality by design; risk assessment; FMEA.

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1. INTRODUCTION

1.1 Oro-dispersible Tablet

Oral dosage forms are the most common and preferred in drug formulations for its ease of administration, accurate dosing, self-medication, patient compliance and even for its economic manufacturing. From all oral dosage forms, ODT is the most preferred one in case of elderly patient who can't swallow or chew or in case of emergency, as in cases like strokes because no water is needed for ODT. When ODT comes in contact with saliva, it disintegrates instantly (within 30 seconds) releasing the drug into the oral cavity, which becomes available for pre-gastric absorption. Accordingly, it bypasses the first pass effect, which may be good for drugs having significant hepatic metabolism, and finally gives the same effect with reduced therapeutic dose and decreasing the adverse effects. The choice of a suitable type and an optimal amount of disintegrants is paramount for ensuring a high disintegration rate.

The addition of other formulation components such as water-soluble excipients or effervescent agents can further enhance dissolution or disintegration properties [1].

Due to the rapid disintegration and release of the active substance in ODT, there is a need to have a pleasant taste as this is a key aspect for patient palatability. Thus, the taste-masking of bitter active substances is a critical obstacle to overcome for the successful development of ODT formulations [2].

1.2 Quality by Design

Quality by design (QbD) is defined as a systematic approach for development that begins with a predefined aim and emphasizes product, process understanding and process control, based on sound science and quality risk management. QbD identifies characteristics that are critical to quality, translates them into the attributes that the drug product should possess, and establish how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics. The main concept of QbD is that all final product-critical quality attributes are affected by raw materials and process parameters. Hence, if we identify the cause-and-effect relationship between the various inputs and responses by carefully designed experiments, we can control the quality of the product by simply controlling the inputs like raw material specifications or process parameters, etc. As a result, the final product will always conform to the quality specifications [3].

The QbD approach begins with a predefined Quality Target Product Profile (QTPP), identification of an initial list of Critical Quality Attributes (CQAs), Critical material attributes (CMAs) and Critical Process Parameters (CPPs) using Quality risk assessment (QRA) tools, such as Failure Mode Effects Analysis (FMEA) and Risk ranking. According to determined factors (CPP and CMA) and responses (CQAs) we can proceed in Design of Experiments (DoE) which determines the relationship among factors that influence outputs of a process. DoE results can help identify optimal conditions, the critical factors that most influence CQAs. Based on the acceptable range of CQAs, the design space of CPPs can be determined [4]. A control strategy should be identified to control the sources of variability from the raw materials and the manufacturing process, continually monitor and improve the manufacturing process to assure consistent product quality as displayed in supplementary file (Fig. S1).

1.3 Desloratadine

Desloratadine (DSL) is a tricyclic secondary amine (Fig. 1) antihistaminic compound with a bitter taste, which is an active metabolite of loratadine. It is approximately 10 to 20 times more potent at H1-receptor binding than loratadine in vitro and has 2.5 to 4 times more antihistaminic potency in animals. DSL was also shown to have a significantly longer elimination half-life than loratadine [5]. DSL is a white to light pink-colored powder. According to the manufacturer, it is highly soluble in ethanol and propylene glycol, soluble in dichloromethane, and slightly soluble in water. Biopharmaceutical Classification System (BCS), DSL is classified as a Class I drug [6]. Not hygroscopic [7], prone to degradation at high temperatures [8]. Due to its composition as a secondary amine, DSL is susceptible to Millard reaction in the presence of common excipients such as lactose to form N-formyl desloratadine, which is the major degradation product. Over time, the lactose and DSL react to form a colored product, and there is a high degree of DSL degradation. The intensity of the color is typically dependent on the amount of DSL present, the conditions of storage, such as humidity and temperature, as well as the

length of storage time [9]. To overcome both issues, bitter taste and incompatibility, DSL is prepared as coated granules or lyophilized stabilized tablets.

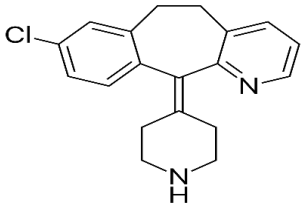

Fig. 1. Chemical structures of DSL

From the table below, summarizing some available brands of DSL in the market (Table S1), it is obvious that it can be prepared as Film coated tablet or as ODT either by Lyophilization, API coating, Complex formation with API or Patented technique as Orasolv.

Therefore, the objective of our study was to investigate the stability problems of Desloratadine ODT and the effect of Polacrilex Resin as dry stabilizer, to get an optimized stable ODT within the framework of Quality by Design.

2. METHODOLOGY

2.1 Materials

Desloratadine was from (Glenmark-India), Crospovidone (BASF-Germany), Sodium Croscarmellose (JRS-Germany), Microcrystalline Cellulose (Vivapur 102) (JRS-Germany), Mannitol (Pearlitol 100 SD) (ROQUETTE-France), Sodium Stearyl Fumarate (JRS-Spain), Tutti Frutti (FIRMENICH- Switzerland), Aspartame (VITASWEET-China) and Amberlite IRP 64 (COLORCON-France).

2.2 Methods

In our study we will include two phases, Screening phase (to study the effect of resin as dry stabilizer) and Optimization phase (to get an optimized formula in comparison to marketed product).

2.2.1 Screening phase

As screening trials, an incompatibility studies using Differential Scanning Calorimetry were done to ensure Desloratadine compatibility with the selected excipients. And to investigate the stabilizing effect of Polacrilex Resin (Amberlite IRP64®) Two formulae were suggested (Table S2) one contain 10 mg Resin and second one without resin, and the weight difference was compensated in fillers. As reported, DSL can be loaded to resin in ratio from 1:3 to API forming Drug-Resin complex [10]. The screening formula includes API: Resin in a ratio of 1:2 (Midpoint of resin range 1:3), 4% Crospovidone, 2%Tutti Frutti, 3% Aspartame, Mannitol: Microcrystalline Cellulose in 2:1 ratio [11] and 1% Sodium Stearyl fumarate. Tutti Frutti/Aspartame was selected based on palatability study, in which (Acesulfame/pepper mint) were also tried (Table S3). The trials were prepared under controlled humidity, packed into Alu/Alu blisters and charged into accelerated stability study carried out at 40±2ºC in stability chamber having 75 ± 5% RH. Samples were withdrawn after one and three months and evaluated for change in Related substances (RS), assay, hardness, disintegration time and for physical changes.

2.2.2 Optimization phase

In the optimization phase and in order to reach an optimized formula, we tried to identify the critical factors that may affect the formula based upon Risk assessment Quality by Design.

So, the purpose of this phase is to identify which material attributes (CMAs) and process parameters (CPPs) affect the drug product's Critical Quality Attributes (CQAs) to understand and predict sources of variability in the manufacturing process so that an appropriate control strategy can be implemented to ensure that the CQAs are within the desired requirements using QbD risk assessment, which can be implemented as follows.

2.2.2.1 Creating Knowledge Space

First step of Quality by Design (QbD) framework starts with definition of Quality Target Product Profile (QTPP) and determining of patient requirement then to define CQAs which ensure the desired product quality, application of QbD by unit operation, continues with risk assessment on each unit operation, conduct designed experiments and finally reaching an optimized formula.

2.2.2.2 Quality Target Product Profile (QTPP)

The QTPP is derived from the desired labelling information that describes indications,

contraindications, dosage form, dose frequency and pharmacokinetics (QTPP for Desloratadine ODT is given in (Table S4).

2.2.2.3 Identify CQAs

CQAs are derived from QTPP and includes all physical, chemical, biological and microbial tests that ensure the desired product quality (Table S5) summarizes the quality attributes of ODT and indicates which attributes were classified as drug product CQAs).

2.2.2.4 Identification of possible Critical Material Attributes (CMAs)

The CMAs includes both APIs and excipients. Accordingly, the below assessment (Table S6 to Table S9) will discuss raw materials attributes and whether any have high, medium or low risk on CQAs with justification [12].

2.2.2.5 Identification of possible Critical Process Parameters (CPPs)

To identify all possible CPPs we should outline preparation steps, critical parameters and their effect on CQAs. Starting with Manufacturing Process Mapping and risk assessment will discuss CPPs' impact on CQAs (Table S10:S11) with justification.

2.2.2.6 Manufacturing process mapping

The purpose of Manufacturing process mapping is to help us in identifying all CPPs that may impact Critical Quality Attributes (CQAs) considering the order of preparation steps. Manufacturing steps, input and output material attributes and also all process parameters for all steps are displayed in supplementary file (Fig. S2).

2.2.2.7 Risk assessment

A risk-based approach needs to be applied throughout the development process of the drug product to assure that, in addition to meeting the expectations of patients and clinicians, the drug product is capable of meeting appropriate quality standards in routine manufacture at commercial scale. Where appropriate, structured methodologies such as Failure Modes and Effects Analysis (FMEA) and statistical Design of Experiment (DOE) are to be used to identify risks and improve overall product understanding so that an appropriate control strategy and risk management can be applied in line with current regulatory expectations outlined within ICH Q8, Q9 and Q10. Experimental work has to be focused on areas of higher risk to provide the appropriate control strategy. There are many tools that can be used for risk assessment and management. One of them is Failure Mode Effects Analysis (FMEA).

2.2.2.8 Failure Mode Effects Analysis (FMEA)

FMEA phases can be classified into three major categories as highlighted in the (Table S12).

Some definition used in Failure Mode Effects Analysis (FMEA) [13]:

Failure Mode: The manner in which a component, subsystem, or system could potentially fail to meet the design intent.

Occurrence (O) - how likely is the cause to occur and result in the failure mode?

Severity (S) - how serious are the end effects?

Detection (D) - how likely is the failure to be detected before it reaches the customer.

According to FMEA each component has its own Risk Priority Number (RPN), that could be calculated as per (Table S13) and its RPN may be updated if its risk could be managed.

Risk Analysis of Desloratadine ODT using FMEA tool are shown below in (Table 1 : 3).

2.2.2.9 PARETO Rule

The Pareto principle states that for many outcomes, roughly 80% of the consequences come from 20% of the causes, so it indicates the cumulative impact. Figs. 2 and 3 are useful for finding the defects to prioritize in order to observe the greatest overall improvement. Based on the previous risk analysis data, the effects of (filler type and ratio), (disintegrant type and ratio), (sweetener agent) and (stabilizer) represent about 80 percent of the total Risk Priority Number (RPN). According to preliminary results, the effect of both stabilizer and sweetener can be controlled by using 10 mg/tablet of Amberlite IRP 64 and 3% Aspartame with 2% Tutti Frutti, respectively. So, only disintegrant and filler types (and ratios) will be studied in the next development optimization stage.

Table 1. Risk analysis of Desloratadine ODT using FMEA

FMEA Analysis																
Project: Desloratadine ODT 5 mg				Owner: Mo'men Safari Saber									Date: 8/2020			
Items of CMA/CPP	Initial Risk Assessment									Updated Risk Assessment						
	Potential Failure Mode (CQAs)	Effect(s) of Failure	Potential Cause(s)	Current Controls	S	O	D	RPN	RPN %	Recommended Action	Action taken	S	O	D	RPN*	RPN* %
Drug Substance PSD	Content Uniformity	Poor CU will affect safety and efficacy	Un equal distribution	PSD analysis	9	9	1	81	7	Using of micronized API	D90 NMT 50 micron.	3	3	1	9	3
API Bitter taste	Palatability	Low patient compliance	Wrong amount of sweetener Non-Taste masked API	Palatability test	9	3	3	81	7	Trying different sweeteners	Using aspartame based on Palatability test	3	1	3	9	3
Drug Substance RS	Impurities, Assay	Failed RS results, ↓assay results	API degradation	RS analysis	9	9	1	81	7	Strict limit of starting RS limit	Total impurities NMT 0.5 %	3	3	1	9	3
Filler type and ratio	Flowability, CU, Hardness, Disintegration, Dissolution and taste	Bad flowability and compressibility - Poor CU	Un proper type /amount of fillers	Pre-formulation tests, CU Tests	9	9	3	243	20	Choosing appropriate fillers type and amount.	Using MCC/Mannitol mixture in different ratio	9	3	3	81	30
Disintegrant type and ratio	Disintegration/ Dissolution	Disintegration time > 30 sec.	Un proper type /amount Less than optimum	Disintegration-Dissolution-Wetting time tests	9	9	3	243	20	Choosing appropriate disintegrant	Using SCC/CP mixture in different ratio	9	3	3	81	30
Sweetener agent	Palatability	Low patient compliance	Using wrong amount of taste masking ingredient	Palatability test in pre-formulation stage	9	3	9	243	20	Choosing appropriate sweetener	Use Aspartame with 3%	3	3	3	27	10
Stabilizer	Degradation Products	Failed RS results, Stability, ↓assay results	API degradation	Stability (RS, Assay) analysis	9	9	1	81	7	use appropriate stabilizer	use Amberlite IRP 64 in ration 2:1 to API	9	3	1	27	10
Geometric Mixing	Content Uniformity	Poor CU	Un equal distribution of API/un proper mixing order or mixer type	Blend uniformity-CU Test	9	3	1	27	2	Geometric Mixing of API with Filler	-Mixing order -API sifting (0.5 mm) - rinse sieve with filler	3	3	1	9	3
Sifting	Blend Uniformity, Disintegration	-Uniformity of dosage units may get affected - Disintegration time variation	Un equal distribution of (API-disintegrant)	Blend uniformity test-Disintegration time	9	3	1	27	2	Sifting the final unlubricated blend	Sifting the final unlubricated blend using 0.5 mm sieve	3	1	1	3	1
Final Blending	Blend Uniformity	Uniformity variation	Un equal distribution of API/ mixer type	Blend uniformity test	9	1	1	9	1	Use appropriate mixing (Mixer type -time)	mixing for 15 min. using double cone blender	3	1	1	3	1
Lubrication	Appearance	Sticking in tablets and unaccepted appearance	Un proper amount/Type of lubricant/ mixer type	Physical description Tests	1	3	9	27	2	Use appropriate lubricant (type-amount)	using sieved (0.5 mm) SSF - 1% mixing for 3 min using double cone blender	1	1	3	3	1
Compression	Appearance, Hardness, Weight Disintegration, Dissolution and taste	Capping, ↑ Disintegration/ Dissolution - Poor CU	↑Hardness-Weight variation	IPC tests(weight-hardness-friability-disintegration)	9	9	1	81	7	Control compression parameters with narrow limits	weight: 150 mg ±5% Hardness 4-7 kp, Disintegration NMT 30 sec Punch 7 mm rounded Friability less than 1%	3	3	1	9	3
Risk Priority Number (RPN) =								1224	100	Updated Risk Priority Number (RPN*) =					270	100.0

Table 2. Initial risk analysis data

Critical Attribute	S	O	D	RPN	RPN %	S	O	D	RPN*	RPN* %
Drug Substance PSD	9	9	1	81	7	3	3	1	9	3
API Bitter taste	9	3	3	81	7	3	1	3	9	3
Drug Substance RS	9	9	1	81	7	3	3	1	9	3
Filler type and ratio	9	9	3	243	20	9	3	3	81	30
Disintegrant type and ratio	9	9	3	243	20	9	3	3	81	30
Sweetener agent	9	3	9	243	20	3	3	3	27	10
Stabilizer	9	9	1	81	7	9	3	1	27	10
Geometric Mixing	9	3	1	27	2	3	3	1	9	3
Sifting	9	3	1	27	2	3	1	1	3	1
Final Blending	9	1	1	9	1	3	1	1	3	1
Lubrication	1	3	9	27	2	1	1	3	3	1
Compression	9	9	1	81	7	3	3	1	9	3
Risk Priority Number (RPN) =				1224	100				270	100.0

Table 3. Updated risk analysis data

Critical Attribute	RPN	RPN*	Cumulative %	
Filler type and ratio	243	81	80%	60%
Disintegrant type and ratio	243	81		
Sweetener agent	243	27		
Stabilizer	81	27		
API Bitter taste	81	9		
Drug Substance PSD	81	9		
Drug Substance RS	81	9		
Compression	81	9		
Geometric Mixing	27	9		
Lubrication	27	3		
Sifting	27	3		
Final Blending	9	3		
(RPN) =	1224	270		

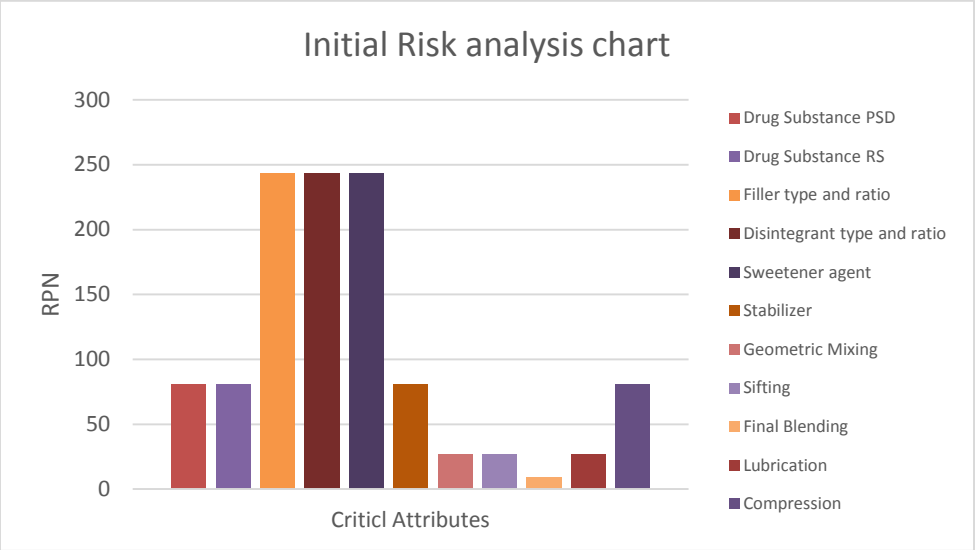

Fig. 2. PARETO Chart for initial risk analysis

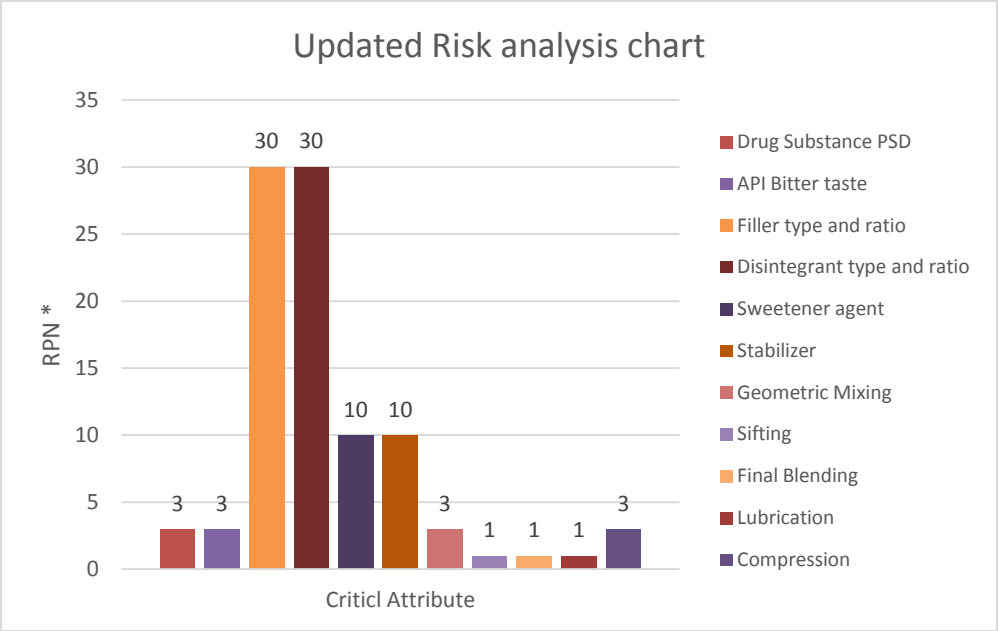

Fig. 3. PARETO Chart for updated risk analysis

2.2.2.10 Experimental design phase

Three levels factorial design used to study the effects of different variables on the characteristics of the produced ODT. The process was optimized to obtain the minimum disintegration time.

These variables are:

1- The type and concentration of super disintegrants (X1), mixture combination of Crospovidone (CP) or Sodium Croscarmellose (SCC) in three levels (0,3 or 6 mg and total equal to 6 mg).

2- The type and concentration of Fillers (X2), mixture combination of Microcrystalline cellulose (Vivapur 102®) in three levels (30,45 or 60 mg) and Spray dried Mannitol (Pearlitol SD 100®) in three levels (90,75 or 60 mg) respectively and total equal to 120 mg as shown in (Table 4).

Table 4. Variables in user defined mixture design

Run No	Composition (mg/tab)									Weight
	Active Pharmaceutical Ingredient	Disintegrant		Filler		Amberlite IRP64	Aspartame	Tutti-Frutti	Sodium Stearyl Fumarate	
		Crospovidone	Croscarmellose Sodium	Microcrystalline cellulose	Pearlitol 100 SD					
1	5	0	6	30	90	10	4.5	3	1.5	150 mg
2	5	3	3	30	90	10	4.5	3	1.5	
3	5	6	0	30	90	10	4.5	3	1.5	
4	5	0	6	45	75	10	4.5	3	1.5	
5	5	3	3	45	75	10	4.5	3	1.5	
6	5	6	0	45	75	10	4.5	3	1.5	
7	5	0	6	60	60	10	4.5	3	1.5	
8	5	3	3	60	60	10	4.5	3	1.5	
9	5	6	0	60	60	10	4.5	3	1.5	

The responses selected for evaluation and optimization were disintegration time (Y1), Wetting time (Y2) and Hausner ratio (Y3).

Hausner ratio and Carr's index for each formula were calculated to define the flowability behavior. All trials were compressed via direct compression method (DC), evaluated physically (For, Weight, Hardness, Disintegration time, wetting time and Friability). The results were analyzed using a statistical package (Design-Expert® Version 12).

Tablet manufacturing

ODTs were manufactured by the direct compression method. The first step in preparation was geometric mixing of API and Amberlite (an addition with equal weight). Then add disintegrant, sweetener, and flavor, mixing for 3 minutes and sifting the premix using a 0.5 mm sieve. Then rinse the sieve with half of the fillers into a double cone mixer, add the active premix and the other half of the fillers, and mix for 15 minutes. The weight of sodium stearyl fumarate (previously sieved using a 0.5 mm sieve) was mixed with the powder in the small double cone for 3 minutes. Finally, the powder was compressed into tablets using an ELIZA PRESS EP-200 L tablet compressing machine with 7 mm diameter rounded flat punches. The tablets were collected during compression for in-process control (IPC) check of weight and hardness and were stored in amber glass bottles with high density polyethylene (HDPE) caps for other testing.

2.2.2.11 Pre-Formulation studies

In a preliminary study, the selection of excipients was based on compatibility study using Differential Scanning Calorimetry (DSC) Analysis.

Differential Scanning Calorimetry (DSC) Analysis

DSC thermograms were obtained by using DSC 25 model of TA instruments. Thermal analysis was carried out for physical mixture of Desloratadine and excipients in a 1:1 weight/weight ratio. Sample of about 3 mg mixture were weighed directly in T zero DSC aluminum pan. The sample was heated to 300ºC at a rate of 20ºC/min under dry nitrogen atmosphere.

Micromeritics study

Trials of Desloratadine ODT in (Table S2) and (Table 4) were subjected to micromeritics study. Bulk (BD) and tapped densities (TD) were measured, from which Hausner ratio (HR) and Compressibility index (CI) of the powder formulation were determined.

Bulk Density

Bulk density (ρb) is defined as the weight of powder divided by its bulk volume and is expressed as g/cm3. It was determined by pouring known weight(M) of powder into a graduated cylinder and its bulk volume was measured (Vb). Bulk density was calculated using the following formula: ρb = M/Vb.

Tapped Density

Tapped density (ρt) can be defined as the weight of powder(M) divided by its tapped volume (Minimum volume after tapping =Vt). The measuring cylinder containing a known weight of powder (M) was tapped on a hard-wooden surface 10-15 times from a height of 2.5 cm (or till the powder volume becomes constant) or using tapped density apparatus. It was calculated using the following formula: ρt = M/Vt.

Hausner ratio

Hausner ratio represent interparticle friction, so could be used to predict ease of powder flow. It was calculated by the following formula: Hausner ratio = ρt/ρb (Tapped density /Bulk density). The Lower the ratio the better is flowability.

Carr's index

Carr's index or compressibility index of blend was determined using the following formula: Carr's index = [(ρt – ρb)/ ρt] ×100. The Lower Carr's index the better is flowability and compressibility.

2.2.2.12 post-compression evaluation studies

Weight variation

Ten tablets from each batch were individually weighed and the average weight and standard deviation were reported.

Hardness

Tablet hardness was determined using (Pharma test: PTB 311E, Germany) hardness tester for 10 tablets of each batch. The average hardness and standard deviation were reported.

Friability

20 tablets were weighed (W1) and placed into the Single drum automated friability tester (Pharma Test: PT F20E, Germany) that was rotated at 25 rpm for 4 min. The tablets then were reweighed after removal of fines (W2), and the friability was calculated by: $F = [(W1-W2)/W1] \times 100$.

In vitro disintegration time

The disintegration time of the tablets was determined as per USP pharmacopoeia (chapter 701). The test was carried out using tablet disintegration apparatus (Pharma Test: PTZ Auto1EZ, Germany). Distilled water at 37±0.2°C was used as a disintegrating medium. The time required to obtain complete disintegration of all the tablets was recorded.

Wetting time

The wetting time of the tablets is measure by using a simple procedure. Place a piece of tissue papers in a Petri dish containing Methylene blue 0.2% w/v solution (3 ml). A tablet is carefully placed on the surface of the tissue paper. The time required for developing a blue color on the upper surface of the tablet is noted as the wetting time (Fig. 4).

Assay and Related substances

Analysis of both assay and related substances were performed according to USP monograph using 4.6-mm × 25-cm; 5-µm column and the calculations were performed as per USP.

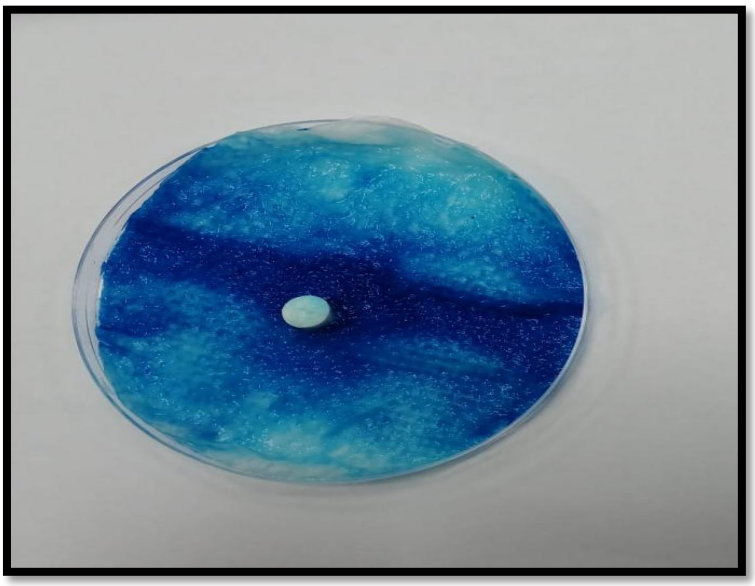

Fig. 4. Wetting time test

In vitro drug release study

In vitro dissolution studies of the optimized formula were performed according to the USP Revision Bulletin (2018) with type-II dissolution apparatus employing a paddle stirrer at 50 rpm using 0.1 N hydrochloric acid (degassed) and 900 ml at 37±0.5°C as the dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals (3, 6, 10, and 15 minutes). The samples were analyzed for drug content by measuring the absorbance at 258 nm, and drug concentration was calculated as per USP.

3. RESULTS AND DISCUSSION

3.1 Screening Phase Results

The Thermal behavior of physical mixtures of Desloratadine and selected excipients is illustrated in (Fig. 5) plus the Stability study of screening phase showed selected excipients are compatible with API and that the formula was stable under accelerated conditions by using resin (Amberlite IRP64®) as stabilizer in comparison with another formula without resin. Screening trials in process and stability results are shown in Tables S14 and S15.

3.2 Optimization Phase Results

Pre-Formulation results

All formulations were prepared according to the mentioned composition (Table 4). All results of (Hausner ratio, Carr's index, Weight, Hardness, Friability and wetting time) are summarized in (Table 5). Disintegration time, wetting time and flowability results for all formulations showed that the selected variables have strong influence on blend flowability, disintegration time and wetting time of the ODTs.

Discussion and Results Analysis

The prepared Desloratadine ODT formulations were evaluated for the different parameters to ensure compliance of the prepared tablets with pharmacopeia and patient needs (Table 5). The weight of each tablet showed variability of no more than 2.28%, which met the specification of the USP/BP limits. The average weight of the nine formulations was found to be in the range of 148.4 – 153.7 mg. Hardness, friability and wetting time of all tablet formulations ranged from 4.42 to 5.21 KP, 0.23 to 0.44% and 27 to 70 seconds, respectively.

The disintegration time results ranged from 12-40 seconds. And according to USP pharmacopeia it should not exceed 30 sec. accordingly, an optimization (Verification) trial was performed to achieve the minimum disintegration time.

The suggested analysis Model for both Disintegration and Wetting time is Quadratic Model, while the selected Model for Hausner ratio is Linear.

From the analysis of models, the variables have strong effects on disintegration time, wetting time and flowability behavior in terms of Hausner ratio.

Table 5. Pre-formulation and IPC data

Run No	Responses						
	Weight AV±SD	Hardness AV (Kp) ±SD	Friability %	Hausner ratio	Carr's index	Disintegration (Sec.)	Wetting time (sec.)
1	150.10±1.91	4.81±0.43	0.37	1.177	15.00	40±1.41	70±2.21
2	148.90±1.90	4.57±0.55	0.34	1.144	12.61	35±1.79	65±2.29
3	151.60±1.84	5.21±0.48	0.43	1.176	14.94	27±1.52	57±2.36
4	153.70±1.57	4.67±0.42	0.29	1.151	13.10	19±0.63	34±1.31
5	151.10±2.28	4.42±0.45	0.44	1.147	12.79	13±1.3	28±1.51
6	150.90±1.66	4.91±0.51	0.23	1.136	11.97	12±1.26	27±0.53
7	151.40±1.17	4.57±0.41	0.30	1.141	12.37	14±1.05	29±0.34
8	150.50±2.07	5.2±0.61	0.40	1.113	10.17	15±1.14	30±0.62
9	148.40±1.69	5.09±0.46	0.24	1.122	10.86	17.5±0.94	32.5±0.91

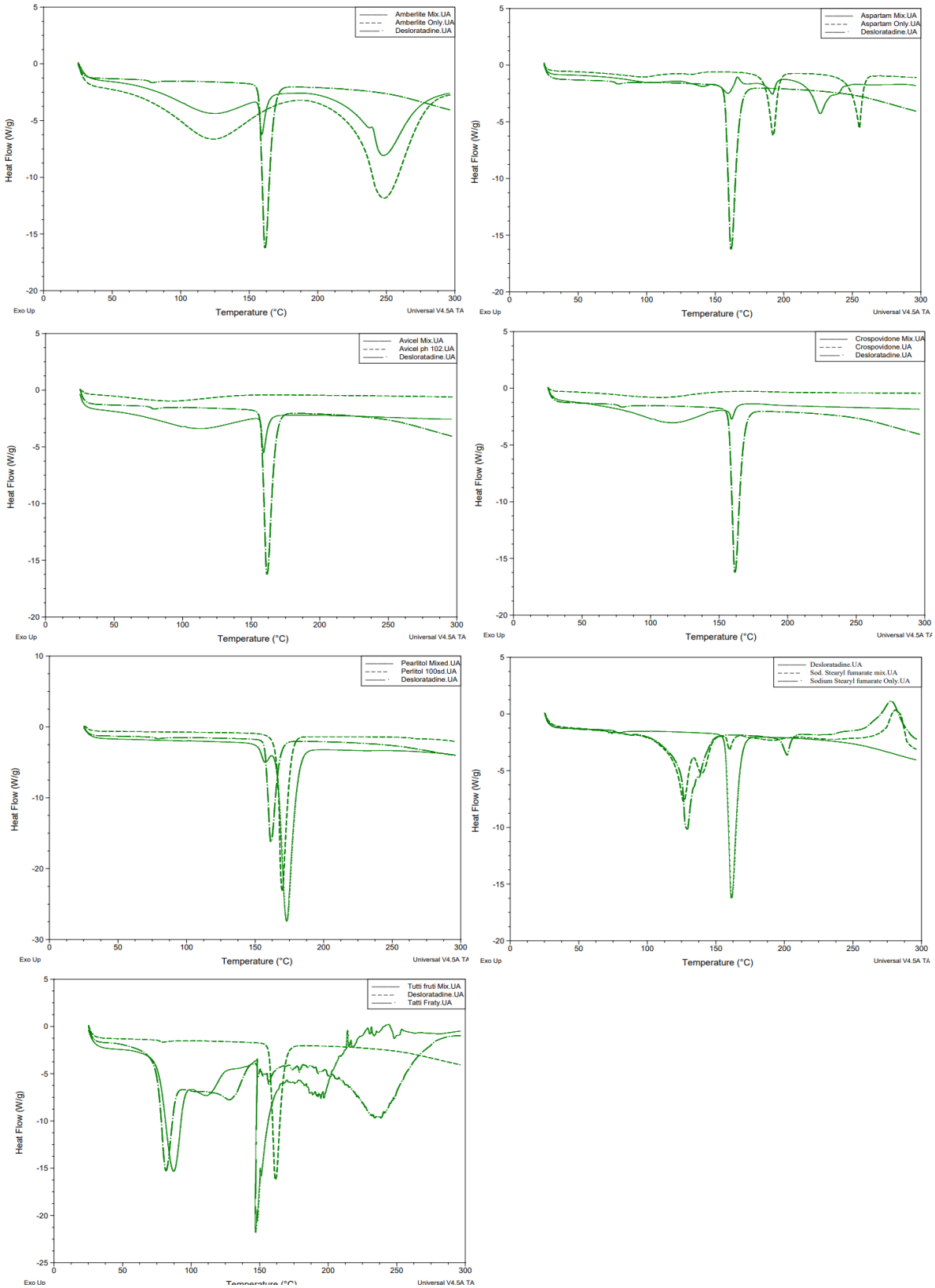

Fig. 5. DSC Thermal behavior of physical mixtures

The final equation in terms of coded can predict the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The resulting equations of analysis for each response variable were as follows:

$$\text{Disintegration time (Y1)} = 14.28 - 2.75\,A - 9.25\,B + 4.13\,AB + 0.5833\,A^2 + 10.08\,B^2 \quad (1)$$

$$\text{Wetting time (Y2)} = 29.28 - 2.75\,A - 16.75\,B + 4.12\,AB + 0.5833\,A^2 + 17.58\,B^2 \quad (2)$$

$$\text{Hausner ratio (Y3)} = 1.15 - 0.0058\,A - 0.0202\,B \quad (3)$$

While A = X1 = Crospovidone and B =X2= Microcrystalline Cellulose PH 102

Equations (1-3) reflect the quantitative effect of the formulation factors, i.e., Crospovidone amount in super disintegrants mixture (X1) and Microcrystalline Cellulose PH 102 in fillers combination (X2), and their interactions on the responses (Disintegration time "Y1", Wetting time "Y2" and Hausner ratio "Y3").

A positive sign represents a synergistic effect while a negative sign represents an antagonistic effect. From regression equations 1 and 2, both A and B has an antagonistic effect on (Disintegration time "Y1", Wetting time "Y2") while A2, B2 and AB have a synergistic effect. A, B, AB and B2 have P-values less than 0.05, indicating that they are significantly affected on the disintegration time and Wetting time.

From regression equation 3, A, B and AB have an antagonistic effect on (Hausner ratio "Y3") while A2 and B2 have a synergistic effect. B has P-values less than 0.05, indicating that it is significantly affected on the Hausner ratio.

3D surface, contours and two-dimensional response surface plots were determined graphically using the Design Expert software to understand the relationship between the studied factors and the obtained responses as per (Figs. 6-8).

The results analysis indicates that increasing the Crospovidone concentration decreases the disintegration time, whereas increasing the Sodium Croscarmellose concentration has a negligible effect. Additionally, varying the Microcrystalline Cellulose amount results in a decrease in disintegration time around 45 mg, and this effect is reduced to 60 mg per tablet. An optimized formula with the least amount of disintegration was identified through data analysis.

Model Verification and optimization

The optimized trial which was suggested by software to achieve minimum disintegration contains 6 mg X1 (Crospovidone) and 49.639 mg X2 (Microcrystalline Cellulose PH 102) with desirability equal to 0.845. The optimized formula was prepared as per (Table 6) and characterized for its disintegration time, wetting time. The predicted values obtained from optimization were compared to the observed ones and Market sample results as shown in (Tables 7 and 8) and (Fig. S3 and Fig. S4).

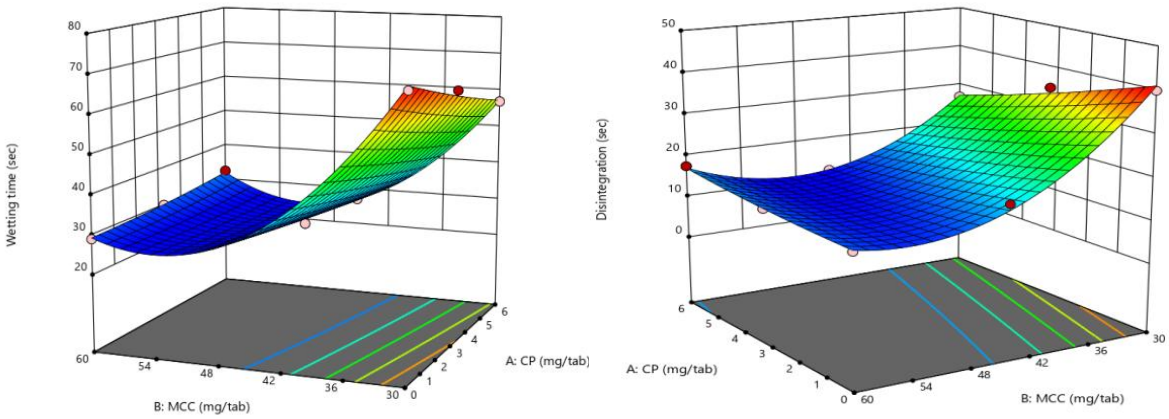

Fig. 6. 3D surface graph models of wetting and disintegration time responses

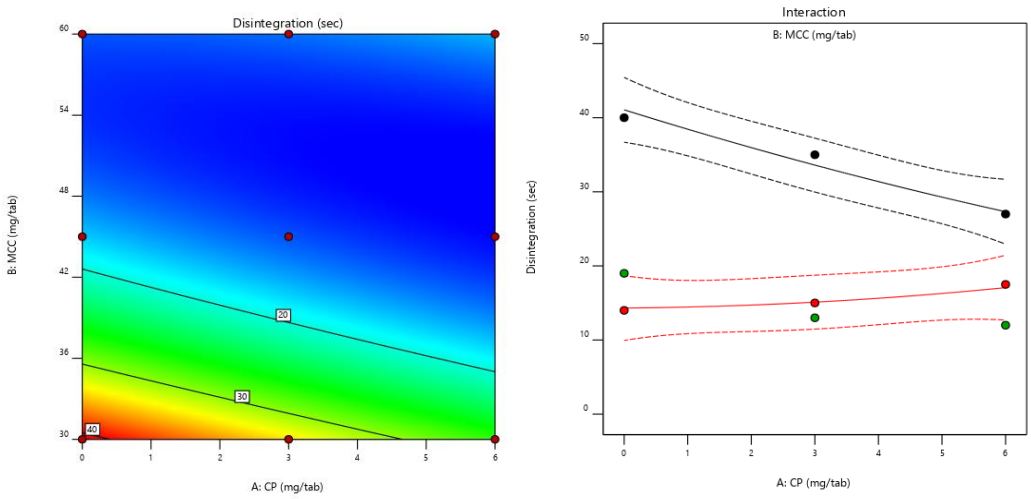

Fig. 7. Two-dimensional response surface and contours graph of disintegration time

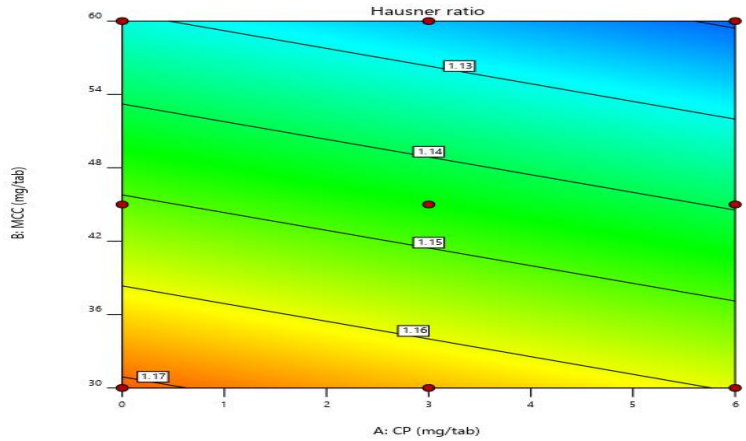

Fig. 8. Contours graph of Hausner ratio

Table 6. Optimized formula composition

Optimized Formula	
Materials	**Composition (mg/tab)**
API	5
Crospovidone	6
Microcrystalline Cellulos 102	49.639
Pearlitol 100 SD	70.361
Amberlite IRP64	10
Aspartame	4.5
Tutti-Frutti	3
Sodium Stearyl Fumarate	1.5
Total tablet weight	150 mg

Table 7. Results of Optimized Formula VS Brand sample

Parameters	**Optimized Formula**		**Brand sample**
	Predicted	**Observed**	
Wetting time	24.89 sec	25.1 sec.	31 sec.
Disintegration	11.49 sec.	11.2 sec.	12.30 sec

Table 8. Dissolution results of Optimized Formula VS Brand sample

Time point	Optimized Formula (Min-Max/ RSD)	Brand sample (Min-Max/ RSD)
3	87 (82-90/3.1)	85 (81-89/3.2)
6	96 (94-97/1.5)	96 (93-100/2.2)
10	96 (95-98/1.4)	97 (95-100/1.8)
15	98 (97-99/0.7)	97 (95-100/1.6)

From comparative results shown above in (Tables 7 and 8) it was clear that optimized formula give a significant lower disintegration and wetting time and almost a similar dissolution as per (Fig. S5).

4. CONCLUSION

The stability study showed that the suggested formula was stable under accelerated conditions by using resin (Amberlite IRP64®) as a dry stabilizer in direct compression. Based upon risk assessment quality bay design, both disintegrant and filler (either type or amount) were identified as critical factors that may affect the formula along with both stabilizer and sweetener.

Desloratadine ODT formulations were successfully prepared using the direct compression method. The composition of the tablet could be optimized using numeric optimization in factorial design to obtain rapid disintegration time (11.2 sec), wetting time (25.1 sec), and Hausner ratio (1.13) along with acceptable tablet hardness and friability. In addition, the results of the optimization study showed that Desloratadine ODT containing Microcrystalline Cellulose 102 (49.639 mg/ODT) can be formulated successfully using Crospovidone (6 mg/ODT) and, furthermore, by comparing the optimized formula with the marketed formula, it showed significant lower disintegration time with almost similar dissolution.

SUPPLEMENTARY DATA

Supplementary data is available in this link: https://journaljpri.com/index.php/JPRI/libraryFiles/downloadPublic/33

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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