Original Research Article

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

ABSTRACT

In a challenge to prepare stable Oro-dispersible tablet (ODT) of Desloratadine, using of dry resin were incorporated in a fast-disintegrating matrix to prepare an optimized ODT that achieving 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 dry stabilizer and the selected variables in optimization phase have strong influence on blend flowability, disintegration time and wetting time of the ODTs. Furthermore, by comparing the optimized formula with marketed one, the optimized formula showed a significant lower disintegration, lower wetting time with almost similar dissolution profile.

Keywords: Oral Disintegrating Tablets, Desloratadine, Quality by Design, Risk Assessment, FMEA.

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 ~~due to~~because no water is needed for ODT. When ODT comes in contact with saliva it ~~should~~ disintegrates instantly (within 30 sec) releasing the drug into oral cavity which becomes available for pre-gastric absorption. Accordingly, it bypasses the first pass effect, which may be good for drugs having~~e~~ 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]

~~The ODT~~Due to the rapid disintegration and release of the active substance in ODT, there is need to have ~~which contact the taste buds making the need for~~ 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 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 determine 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] ~~then~~ A control Strategy should be Identified to control the sources of variability from the raw materials and the manufacturing process, c~~C~~ontinually monitor and improve the manufacturing process to assure consistent product quality as displayed in supplementary file (Figure S1).

1.3 Desloratadine

Desloratadine (DSL) is a Tricyclic secondary amine (Figure.1) antihistaminic compound with bitter taste, which is active metabolite of loratadine. It is approximately 10 to 20 times more potent at H1-receptor binding than loratadine in-vitro and 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. ~~Very~~ Highly soluble in ethanol and in propylene glycol, ~~,~~ soluble in dichloromethane and ~~,~~ slightly soluble in water. DSL is classified, according to Biopharmaceutical Classification System (BCS) as a Class I drug.[6] Not hygroscopic[7], susceptible to degradation at a high temperature.[8] Due to its composition as 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 tablet.

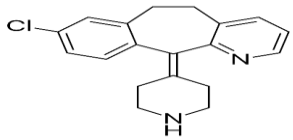


Figure 1. Chemical structures of DSL.

From the table below, summarizingy for some of available brands of DSL brands 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, how to get an optimized stable ODT within the framework of Quality by Design.

2. METHODOLOGY

2.1 Materials

Desloratadine was from (Glenmark), Crospovidone was from was from (BASF), Sodium Croscarmellose was from (JRS), Microcrystalline Cellulose was from (JRS), Mannitol (Pearlitol 100 SD) was from (ROQUETTE), Sodium Stearyl Fumarate was from (JRS), Tutti Frutti was from (FIRMENICH), Aspartame was from (VITASWEET),and Amberlite IRP 64 was from (COLORCON).

Comment [Y1]: Indicate the country

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 ratio of 1:2 (Midpoint of resin range 1:3), 4 % Crospovidone, 2 %Tutti Frutti, 3% Aspartame, Mannitol: Avicel 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 and the results were as follow under results and discussion.

2.2.2 Optimization phase:

In the optimization phase and in order to reach an optimized formula, we will trytried 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 in formula as follow:

Comment [Y2]: Where is the formula?

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 and application QbD by unit operation, continues with risk assessment on each unit operation and 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 are 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, 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 (Figure 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 QIO. 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)

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 diffferent 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 1: Risk analysis of Desloratadine ODT using FMEA

Comment [Y3]: Title should be at the top of each table

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 2: Initial 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		

Table 3: updated risk analysis data

2.2.2.9 PARETO Rule:

The Pareto principle states that for many outcomes roughly 80% of consequences come from 20% of the causes, so it indicates the cumulative impact. Pareto Charts (Figure 2&3) are useful to find the defects to prioritize in order to observe the greatest overall improvement. Based on the previous risk analysis data the effect of (Filler type and ratio), (Disintegrant type and ratio), (Sweetener agent) and (stabilizer) represent about 80 % of 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 / Filler (Type and ratio) will be studied in the next development optimization stage.

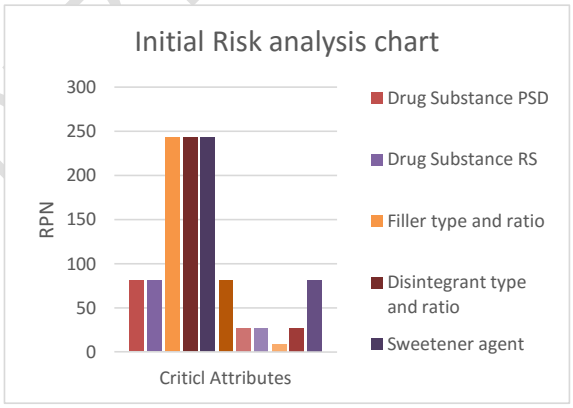


Figure 2. PARETO Chart for initial risk analysis.

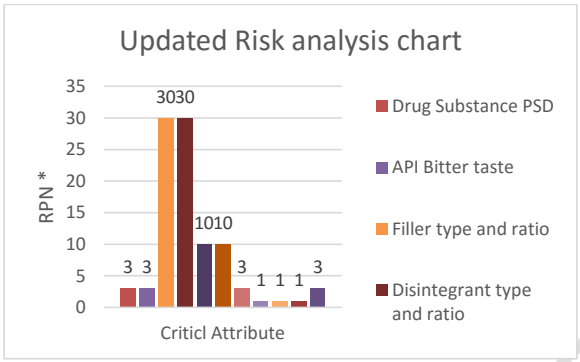


Figure 3. PARETO Chart for updated risk analysis.

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 (Avicel 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).

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	

Table 4. Variables in user defined mixture design.

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 ~~have been~~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 direct compression method. The first step in preparation ~~is~~ was Geometric mixing of API and Amberlite (Addition with equal weight). Then adding Disintegrant, Sweetener and flavor, mixing for 3 min and sifting the premix using 0.5 mm sieve. Then rinse the sieve with half of fillers into double cone mixer, add active premix and the other half of filler then mix for 15 min. The weight of sodium stearyl fumarate (Previously sieved using 0.5 mm sieve) was mixed with the powder in the small double cone for 3 min. Finally, the powder was compressed into tablets using (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 / 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 weighted directly in T zero DSC aluminum pan. The sample was heated to 300ºC at a rate of 20ºC/min under ~~an~~ dry nitrogen atmosphere ~~of dry nitrogen~~.

Micromeritics study:

Trials of Desloratadine ODT in (Table S2) and (Table 4) were subjected to micromeritics study. Bulk (BD) and tapped densities~~y~~ (TD) were measured, from which Hausner ratio (HR) and Compressibility index (CI) of the powder formulation w~~e~~are 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 ~~can be~~was determined by pouring known weight(M) of powder into a graduated cylinder and ~~measure~~ its bulk volume was measured (Vb). ~~it~~ 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~~to~~ 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.

2.2.2.11 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 pharmacopoeia. 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.

Comment [Y4]: reference

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 develop blue color on the upper surface of the tablet is noted as the wetting time (Figure 4).

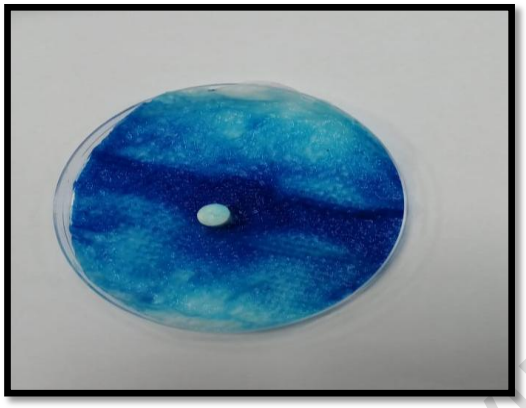


Figure 4. Wetting time test.

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.

In vitro drug release study:

In vitro dissolution studies of the optimized formula were performed according to USP monograph with type-II dissolution apparatus employing a paddle stirrer at 50 rpm using 0.1 N hydrochloric acid (degassed); 900 ml at 37±0.5ºC as 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, 15 min). The samples were analyzed for drug content by measuring the absorbance at 258 nm and drug concentration was calculated as per USP.

Comment [Y5]: year?

3. RESULTS AND DISCUSSION

3.1 Screening phase results

The Thermal behavior of physical mixtures of Desloratadine and selected excipients is illustrated in (Figure 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 ~~below~~ underin ~~(~~Table S14 and S15~~.)~~

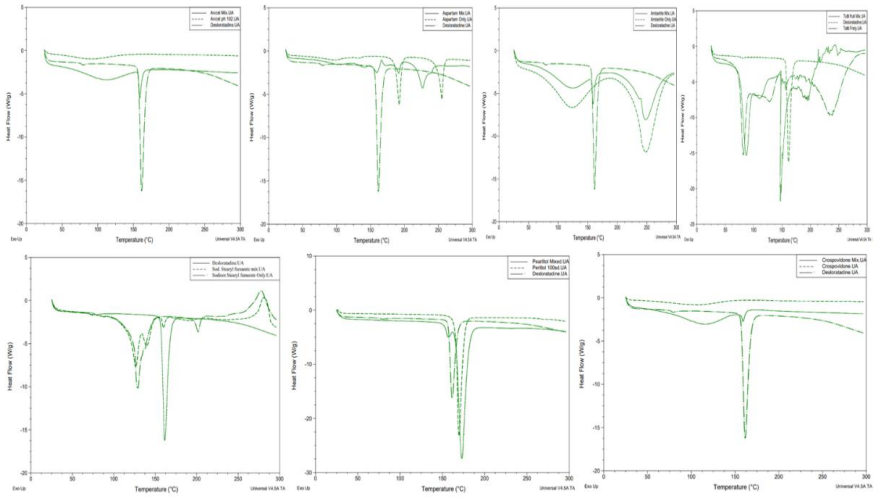


Figure 5. DSC Thermal behavior of physical mixtures

3.2 Optimization Phase results:

Pre-Formulation results:

All formulations were prepared according to the mentioned composition in (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.

Run No	Responses						
	Weight AV±SD	Hardness AV (Kp) ±SD	Friability %	Hausner ratio	Carr's index	Disintegration (Sec.)	Wetting time (se
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

Table 5. Pre-Formulation and IPC data**:**

Comment [Y6]: Why is there no standard deviation here? Was it done once?

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 were 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 were ranging from 12-40 second as shown below in (Figure 6). And according to USP pharmacopeia it should not exceed 30 sec. accordingly, an optimization (Verification) trial was performed to achieve the minimum disintegration time.

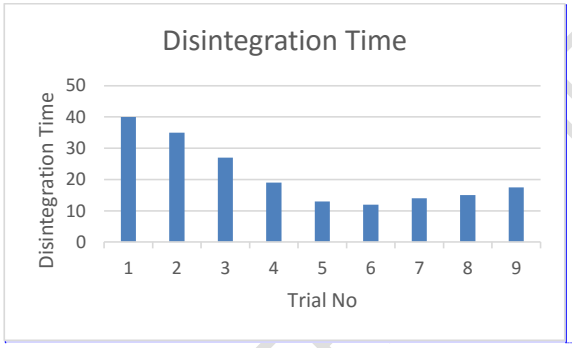


Figure 6. Disintegration time

Comment [Y7]: You dont need this graph siince the result has been presented in Table 5

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 effect on disintegration time, wetting time and Flowability behavior in terms of Hausner ratio.

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:

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

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

Hausner ratio (Y3) $=1.15 - 0.0058\ A - 0.0202\ B$ (3)

While A = X1 = Crospovidone and B =X2= Avicel PH 102

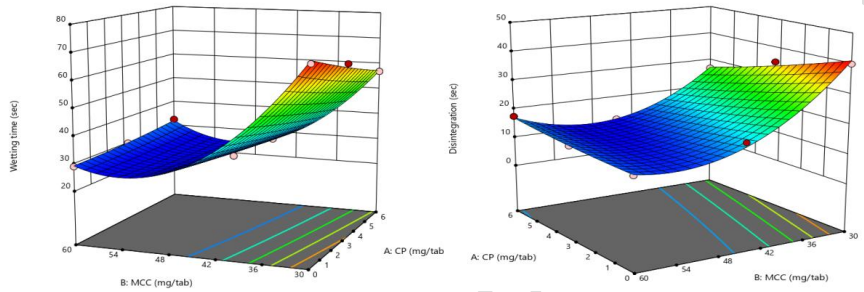
Equations (1-3) reflect the quantitative effect of the formulation factors, i.e., Crosspovidone amount in super disintegrants mixture (X1) and Avicel PH 102 in fillers combination (X2), and their interactions on the responses (Disintegration time “Y1”, Wetting time “Y2” and Hausner ratio “Y3”).

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

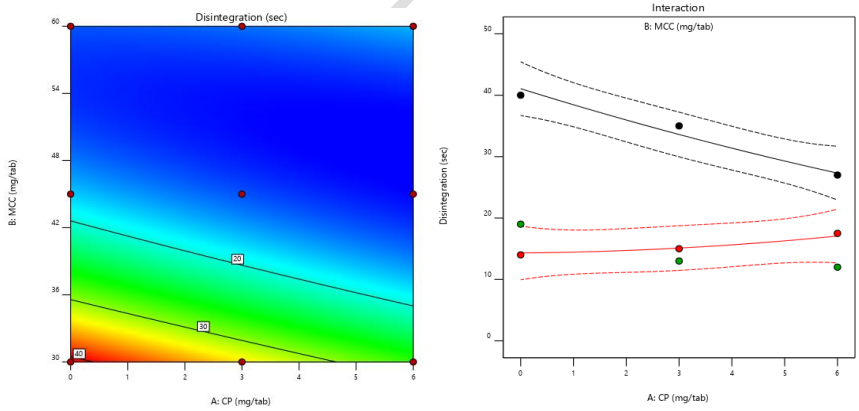
synergistic effect. A, B, AB and B2 have P-values less than 0.05, indicating that they are significantly affected on the disintegration time and Wetting time.

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 (Figures 7-9).



Figures 7. 3D surface graph models of wetting and disintegration time responses**.**



Figures 8. Two-dimensional response surface and contours graph of disintegration time**.**

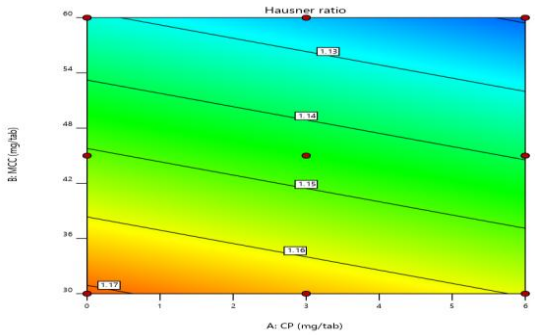


Figure 9. contours graph of Hausner ratio.

From the results analysis we find that the disintegration time decreased with increase the Crospovidone level while Sodium Croscarmellose has lower effect. Also, variation in Avicel amount has effect in decreasing disintegration time around 45 mg and this effect decreased up to 60 mg per tablet. From the data analysis, an optimized formula with minimum disintegration was identified.

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 (Avicel 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 (Table 7 and 8) and (Figure S3 and Figure S4).

Optimized Formula	
Materials	**Composition (mg/tab)**
API	5
CP	6
MCC 102	49.639
Pearlitol 100 SD	70.361
Amberlite IRP64	10
Aspartame	4.5
Tutti-Frutti	3
SSF	1.5
Total tablet weight	150 mg

Table 6. Optimized Formula Composition.

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 7. 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)

Table 8. Dissolution results of Optimized Formula VS Brand sample**.**

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

4. CONCLUSION

The Stability study showed that the suggested formula was stable under accelerated conditions by using resin (Amberlite IRP64®) as dry stabilizer in direct compression. Both Disintegrant and Filler (either type or amount) were identified as critical factors that may affect the formula along with both stabilizer and sweetener based upon Risk assessment Quality Bay design.

Desloratadine ODTs formulations were successfully prepared using direct compression method, the composition of tablet could be optimized using Numerical 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 tablets hardness and friability. In addition, the results of the optimization study showed that Desloratadine ODT containing Microcrystalline Cellulose (Avicel 102= 49.639 mg/ODT) can be formulated successfully using Crospovidone (6 mg/ODT) and furthermore, by comparing the optimized formula with marketed formula it showed significant lower disintegration time with almost similar dissolution.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS DISCLAIMER:

AUTHORS HAVE DECLARED THAT NO COMPETING INTERESTS EXIST. 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 BECAUSE WE DO NOT INTEND TO USE THESE PRODUCTS AS AN AVENUE FOR ANY LITIGATION BUT FOR THE ADVANCEMENT OF KNOWLEDGE. ALSO, THE

RESEARCH WAS NOT FUNDED BY THE PRODUCING COMPANY RATHER IT WAS FUNDED BY PERSONAL EFFORTS OF THE AUTHORS.

REFERENCES

1. Gujarati, N., *Oral Disintegrating Tablets: Background and Review on Recent Advancements.* Advance Pharmaceutical Journal, 2017. **2**(2): p. 1-24.
2. Patil, P., V. More, and N. Tour, *Recent trends in orodispersible tablets–An overview of formulation technology and future prospects.* International Journal of Pharma Sciences and Research, 2015. **6**(7): p. 1056-1066.
3. Chordiya, M.A., H.H. Gangurde, and V.N. Sancheti, *Quality by design: A Roadmap for quality pharmaceutical products.* Journal of Reports in Pharmaceutical Sciences, 2019. **8**(2): p. 289.
4. Gholve, S.B., et al., *Pelagia Research Library Analytical method development and validation by QbD approach–A review.* Der Pharm Sin, 2015. **6**(8): p. 18-24.
5. Geha, R.S. and E.O. Meltzer, *Desloratadine: a new, nonsedating, oral antihistamine.* Journal of Allergy and Clinical Immunology, 2001. **107**(4): p. 751-762.
6. Falcão, B.R., et al., *Development and validation of a dissolution method for desloratadine coated tablets.* Pharmaceutical and Biosciences Journal, 2017: p. 12-17.
7. Shi, Z., *Solid-State Characterization And Engineering Of Two Antihistamine Drugs-Loratadine And Desloratadine*. 2019.
8. Kumar, N., et al., *A validated stability-indicating RP-UPLC method for simultaneous determination of desloratadine and sodium benzoate in oral liquid pharmaceutical formulations.* Scientia pharmaceutica, 2012. **80**(1): p. 153-166.
9. Kodipyaka, P.R.M.B.D.N.S.M.S.G., *Stabilized desloratadine composition*. 2004, Dr Reddys Laboratories Ltd Dr Reddys Laboratories Inc.
10. Kodipyaka, P.R.M.B.D.N.S.M.S.G., *Stabilized desloratadine composition*. Dr Reddys Laboratories Ltd Dr Reddys Laboratories Inc.
11. Dehghani, H., A. Taheri, and A. Homayouni, *Design, optimization and evaluation of orally disintegrating tablet of meloxicam using its menthol based solid dispersions.* Current Drug Delivery, 2017. **14**(5): p. 709-717.
12. EMA, *CHMP assessment report, Desloratadine Teva*

EMA, Editor. 2011.

13. Chrysler Corporation, F.M.C.G.M.C., *Potential failure mode and effects analysis (FMEA) : reference manual*. 1995, [Detroit, Mich.]: Chrysler Corp. : Ford Motor Co. : General Motors Corp.

APPENDIX