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Original Article

# DEVELOPMENT OF ORODISPERSIBLE TABLETS OF LORATADINE CONTAINING AN AMORPHOUS SOLID DISPERSION OF THE DRUG IN SOLUPLUS® USING DESIGN OF EXPERIMENTS

**HEMA A. NAIR*, GAAYATHRI GADHIRAJU, GUNDETI SUNNY**

**Sri Venkateshwara College of Pharmacy, Madhapur, Hyderabad-500081, Telangana, India**
***Corresponding author: Hema A. Nair; Email: hemajit@rediffmail.com**

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**ABSTRACT**

**Objective:** The objective of the present work was to develop an orodispersible tablet of loratadine, an orally active, non-sedating anti-histaminic, belonging to BCS Class II. The drug was prepared as a solid dispersion using Soluplus® as carrier and formulated into an optimal tablet using Design of Experiments.

**Methods:** Solid dispersions of loratadine with varying ratios of Soluplus® were prepared by solvent evaporation and subjected to solubility study in simulated salivary fluid. Selected composition was characterized by differential scanning calorimetry and X-ray diffraction and formulated into an orodispersible tablet by direct compression after addition of suitable excipients. DOE based on a full factorial design was used to optimize the product using a trial version of JMP software, so as to obtain a tablet with low friability, rapid disintegration and maximal drug dissolution within 5 min. The optimized tablet was prepared and evaluated for several attributes, including *in vivo* disintegration and palatability.

**Results:** A solid dispersion prepared with a 1: 4 ratio of loratadine: Soluplus® was found to show a 130-fold increase in drug solubility in the simulated salivary fluid. X-ray diffraction revealed loratadine in amorphous form. The exercise using DOE for optimization of the orodispersible tablet formula served to balance the proportion of crospovidone as super disintegrant and PVP as dry binder and yielded a formulation with good mechanical strength, rapid *in vitro* disintegration (39 sec) and dissolution of 93.78% of the drug within 5 min. When evaluated *in vivo,* the tablets were found to disintegrate in about 60 secs and were reported to be palatable.

**Conclusion:** A patient-friendly dosage form containing a highly soluble form of loratadine was prepared and could be of potential benefit in offering quick relief from allergic conditions.

**Keywords:** Loratadine, Soluplus®, Amorphous solid dispersions, DOE, Orodispersible tablets


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## INTRODUCTION

Orally Disintegrating Tablets (ODTs) are today an established means of administering relatively low dose drugs. These dosage forms disintegrate rapidly when they are placed in the mouth and are expected to release the drug as soon as they come in contact with the saliva thus combining the advantages of the liquid and tablet formulations [1]. As these dosage forms disintegrate/dissolve fast they are suitable for patients who suffer from dysphagia and for pediatric and geriatric patients and their use results in a higher rate of patient compliance. The two key features that such a dosage form must possess is a rapid disintegration time of 30 seconds or less, and a tablet weight of 500 mg or less to qualify being labelled as an ODT [2].

The convenience offered by ODTs is reflected in the growth of the market for these products. The current ODT market size is reported to be nearly 20,000 million USD with a projected growth of more than 27,000 million USD at an annual CAGR of 8.5% [3]. Besides immediate release products, ODTs which disintegrate to sustained release fragments have also been developed [4].

Several technologies have been used for preparation of ODTs including direct compression with addition of superdisintegrants, sublimation, microwave-assisted treatments, etc. Formulation of ODTs presents several challenges including need for taste masking, poor mechanical strength and specialized packing requirements.

In case of administration of drugs as ODTs, a significant advantage may be gained if the drug dissolves in the mouth itself. In this case there is potential for absorption through oral mucosal tissues and other pregastric areas, which can offer additional benefit of bypassing first pass metabolism and providing rapid therapeutic action. This may be advantageous in case of drugs like loratadine. Loratadine is an orally active, second-generation, non-sedating anti-histaminic and is widely used in the management of symptoms of allergic rhinitis and several other allergic conditions including dermatologic ones [5]. Hence a dosage form that enables rapid dissolution and absorption is preferable. Loratadine being a BCS class II drug, reports of preparation into solid dispersions exist. Solid dispersions with enhanced solubility have been prepared using carriers such as PVP [6].

A relatively novel carrier, Soluplus®, has recently been explored for preparation of amorphous solid dispersions [7]. Soluplus® is a polymeric solubilizer with an amphiphilic chemical structure and because of its bifunctional character it is capable of solubilizing poorly soluble drugs in aqueous media. It has a glass transition temperature of approximately 70 °C and therefore it is being widely investigated as a matrix polymer for solid solutions prepared by melt extrusion [8]. It is soluble in water in any ratio and at high polymer concentration it forms colloidal Soluplus® micelles [9].

The objective of the present work therefore was to prepare an amorphous solid dispersion of loratadine using Soluplus®® as a carrier for bringing about rapid dissolution of the active and to formulate the same as an orodispersible tablet using design of experiments to optimize the product.

## MATERIALS AND METHODS

### Materials

Chemo India Formulations Pvt. Ltd. provided a gift sample of loratadine and Soluplus® (BASF) was obtained as a gift sample from IMCD India Pvt. Ltd. All other materials were purchased: microcrystalline cellulose (AVICEL PH 102) from Signet Excipients Pvt. Ltd, Mumbai, India, buffer salts, PVP K-30 and magnesium

stearate from SDFCL, Mumbai, India, sodium saccharine from NR-CHEM, India, mannitol from FINAR Chemicals Pvt. Ltd, India, methanol from avantor performance materials India limited, and ethanol from Changshu Yangyuan Chemicals, Suzhou, Jiangsu, China.

**Evaluation of Soluplus® as a suitable solid dispersion carrier by film casting**

To ascertain the utility of Soluplus® as a suitable solid dispersion carrier, the film casting method was used: for the experiment, 10 mg loratadine and 20 mg Soluplus® were dissolved in dichloromethane, the solution was poured into a levelled petri dish and the solvent was allowed to evaporate at room temperature. The resultant film was visually examined for presence of drug crystals.

**Preparation of solid dispersion by solvent evaporation**

Weighed amount of Soluplus® was transferred to a glass mortar, 3 ml of ethanol was added to it and mixed until dissolved. Proportionate amount of loratadine was added and dissolved and the mixture was triturated until the solvent evaporated. The resultant solid dispersions were sieved through mesh 60 and stored in a desiccator. Solid dispersions were prepared in the ratios of 1:1,1:2,1:3,1:4,1:5 of drug: polymer. Physical mixtures of loratadine and Soluplus® were also prepared in the same ratio by trituration in mortars.

**Characterization of solid dispersions**

**Saturation solubility studies**

Drug, solid dispersions and physical mixtures equivalent to 10 mg loratadine were taken in test tubes and 5 ml pH 6.75 Simulated Salivary Fluid (SSF) [10] was added to each tube. The test tubes were placed on rotary shaker under ambient conditions for 48 h. Next, the solutions were filtered and aliquots of 1 ml of each filtrate were diluted as required with SSF and analyzed by UV spectrophotometry at 247 nm. The entire experiment was carried out in duplicate and the value reported as mean of the two estimations. The solubility enhancement ratios were calculated as [11].

$$E: \frac{\text{Solubility of loratadine from the solid dispersion/physical mixture}}{\text{Solubility of pure drug}}$$

**Differential scanning calorimetry (DSC)**

Samples of loratadine, Soluplus® along with solid dispersion and physical mixtures of both in the ratio 1:4 (loratadine: Soluplus®) were weighed accurately into aluminum pans, crimped and heated from 30–300 °C at the rate of 10 °C/min under nitrogen purge on a Shimadzu (DSC-60) differential scanning calorimeter [12].

**Powder X-ray diffractometry (XRD)**

Loratadine, Soluplus® and the solid dispersion (1:4 ratio) were subjected to the XRD study. Samples were placed on a zero-background sample holder. CuK" 1 radiation was used as X-ray source. Soller slits (0.04 rad) were used for the incident and diffracted beam path. The results were recorded over a range of 0–40° ($2\theta$) using the Cu-target X-ray tube and Xe-filled detector on a Shimadzu maxima XRD-7000, X-ray diffractometer [12].

**Formulation of mouth dissolving tablets of loratadine**

The formulation of loratadine mouth dissolve tablets was based on a quality target product profile which was developed to identify the critical quality attributes. The identified attributes at target levels were built into the formulation and the product optimized using design of experiments (DOE) [13].

Based on a survey of literature, excipients were selected for the tablet as follows: microcrystalline cellulose (MCC) was used as diluent; mannitol was used as the diluent and for enhancement of mouth feel, saccharin was incorporated as the sweetener, crospovidone was included as super disintegrant and magnesium stearate was the lubricant. Early trials without the addition of a binder resulted in tablets which were excessively friable. Hence PVP was included as a dry binder.

Based on preliminary experiments, disintegration time, friability and drug dissolution were taken as critical attributes and served as dependent variables during optimization using DOE.

A full factorial design was used for the optimization process (table 1). For the design, two different independent variables were included, each at 3 levels. The levels were selected from a thorough literature survey.

**Table 1: Full factorial design: independent variables and their levels, dependent variables and their targets used for optimization**

| **Independent variables and coded levels** | | | |
|---|---|---|---|
| **Independent variable (mg/tablet)** | **Low (mg) (-1)** | **Medium (mg) (0)** | **High (mg) (+1)** |
| Amount of Crospovidone | 10 | 30 | 50 |
| Amount of PVP-K30 | 0 | 10 | 20 |
| **Dependent variables and targets** | | | |
| | % Friability | Disintegration time (sec) | % Loratadine dissolved at 5 min |
| **Target for optimization** | Minimize | Minimize | More than 90% |

Nine different formulations were prepared as per the randomized sequence suggested by JMP Trial version 16.1.0 statistical software comprising of solid dispersions of loratadine and Soluplus®, and other excipients in suitable quantities.

The formulations prepared are detailed in table 2. The quantity of the diluent, microcrystalline cellulose was varied so as to ensure a tablet weight of 300 mg in each case. All ingredients were sieved through 60 mesh prior to weighing. The ingredients for each formulation were weighed accurately and mixed in a zip-lock bag by tumbling for about 3 min. Magnesium stearate as lubricant was added and further blended for a minute. The lubricated blend was subjected to direct compression using circular, 10.5 mm diameter, flat-faced punches on a Remik tablet machine.

**Table 2: Formulations of loratadine mouth-dissolving tablets prepared as per the full factorial design**

| S. No. | Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Loratadine as solid dispersion* | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| 2. | MCC(Avicel) | 92 | 102 | 72 | 112 | 122 | 92 | 82 | 112 | 132 |
| 3. | Crospovidone | 50 | 30 | 50 | 10 | 10 | 30 | 50 | 30 | 10 |
| 4. | PVP K-30 | - | 10 | 20 | 20 | 10 | 20 | 10 | - | - |
| 5. | Sodium saccharin | 03 | 03 | 03 | 03 | 03 | 03 | 03 | 03 | 03 |
| 6. | Mannitol | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 7. | Magnesium stearate | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 |

*Loratadine 10 mg+Soluplus® 40 mg

Each formulation was prepared in triplicate and subjected to friability, disintegration and dissolution test along with other evaluation tests as described in the following sections, responses were measured and the mean response was considered for optimization.

Three quadratic models were generated from the results of the experiments to relate the independent variables with the responses. Contour plots were used to express the relationship between the responses and the independent variables. An optimal formulation based on the targets defined in table 1 was identified.

**Evaluation parameters**

**Angle of repose**

The flow property of each blend was evaluated prior to compression by measuring the angle of repose. Each blend was passed through a funnel fixed to a burette stand at a height of 4 cm. Angle of repose was calculated using the formula:

Angle of repose = $\tan^{-1}(h/r)$ where h is the height and r is the radius of the pile formed due to the powder flow.

**Hardness**

A Labindia hardness tester was used for the study. The hardness of 5 tablets of each formulation was noted and the average calculated.

**Friability**

The test was carried out as per the Indian Pharmacopeia, wherein 22 tablets of each formulation were subjected to the friability test using the Roche friabilator [14]. The tablets were carefully weighed and then subjected to 100 revolutions at 25 rpm. Tablets were dedusted and reweighed. The percentage friability was expressed as the loss of weight and was calculated by the formula:

$$\% \text{ Friability: } \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial Weight}} \times 100$$

**Wetting time and disintegration time**

A piece of filter paper was folded twice and placed in a small petri dish containing 15 ml of distilled water. The tablet was placed on the paper and the time taken for the water to reach the upper surface of the tablet was noted as the wetting time in seconds. Following this the tablets were allowed to disintegrate and the time for the tablet to completely disintegrate was measured in seconds and reported as the disintegration time [15].

***In vitro* dissolution study**

The *in vitro* dissolution study was carried out in the USP type II dissolution test apparatus with certain modifications [16]. A petri dish was placed in the dissolution basket and a 500 ml beaker containing the dissolution medium was placed on the petri plate in the basket. Water was taken in the basket for maintaining of the temperature of the medium within the inner beaker. SSF (200 ml) was used as the of dissolution medium maintained at 37±0.5 °C. One tablet was added to the medium and the paddle was stirred at 50 rpm. After exactly 5 min, a sufficient quantity of the dissolution medium was withdrawn and the sample was filtered through Whatman filter paper, suitably diluted and the dissolved drug was quantified using medium as blank at 247 nm.

**Optimization**

The prediction profiler in the JMP Trial version 16.1.0 software was used to arrive at an optimal product with the appropriate level of dry binder and super disintegrant to result in a formulation with minimum friability, minimum disintegration time and a drug dissolution of more than 90% within 5 min.

**Preparation and evaluation of the optimal formula**

Three batches of loratadine mouth disintegrating tablets were prepared using the optimized formulation as suggested by the software (table 3) and they were evaluated for the pre-compression parameters (i.e., angle of repose) and post-compression parameters (hardness, friability, wetting time and disintegration times and *in vitro* dissolution studies) as described earlier.

**Table 3: Optimized formula for loratadine mouth dissolve tablets**

| S. No. | Ingredients | Amount in mg |
|---|---|---|
| 1. | Loratadine as solid dispersion | 50 |
| 2. | Microcrystalline cellulose | 86 |
| 3. | Crospovidone | 50 |
| 4. | PVP K-30 | 06 |
| 5. | Sodium saccharin | 03 |
| 6. | Mannitol | 100 |
| 7. | Magnesium stearate | 05 |

In the case of the dependent variables used for optimization, the predicted value as reported by the software was compared with the actual value obtained and the % error rate was computed as [17, 18]:

$$\% \text{ Prediction Error} = \frac{|\text{Predicted value} - \text{Observed value}|}{\text{Observed value}} \times 100$$

**Evaluation of *in vivo* disintegration time and palatability**

Three volunteers were included in the study after signing an informed consent form. They were asked to rinse the mouth thoroughly and also have a sip of water prior to the test. They were instructed to place the tablet on the tongue and lightly press it between the tongue and upper palate. The time for the tablet to disintegrate, the mouth-feel, as well as the taste perception, were to be observed. The disintegrated mass was to be spitted out without ingesting and the mouth thoroughly rinsed.

**RESULTS AND DISCUSSION**

**Evaluation of Soluplus® as a suitable solid dispersion carrier for loratadine**

Film casting studies have been proposed as a means of obtaining a general insight on the solid-state solubility of a drug and polymer. A solid dispersion resulting in a clear film is indicative of the inhibition of precipitation and hence drug polymer miscibility, whereas phase separation can be identified by an opaque film [19]. In the present studies, a layer containing a 1:2 ratio of loratadine: Soluplus® resulted in a clear film formed on the casting surface, with no signs of presence of loratadine crystals. This outcome was considered as an indication that the drug was dispersed molecularly in the polymer and that the polymer was suitable for preparation of an amorphous solid dispersion of the drug.

**Preparation of solid dispersion by solvent evaporation**

The dispersions made via solvent evaporation were free-flowing powders irrespective of the proportion of Soluplus® and could be easily sieved through mesh 60. Also, it was feasible to prepare the solid dispersions using ethanol, which is a class 3 solvent and, therefore, relatively safe for use.

**Characterization of solid dispersions**

**Saturation solubility studies**

Loratadine is a weak base with pKa of about 6. It, therefore, shows pH-dependent solubility. A study on the solubility of loratadine at different pH values normally occurring in the physiological milieu of the gastrointestinal tract reports that the lowest value for solubility (0.004–0.006 mg/ml) was obtained in the highest pH media tested (6.5, 7.5) whereas the highest solubility (4.59 mg/ml) was obtained at the gastric pH of 1.2 [20].

In the present studies, solubility was estimated at pH 6.75 in simulated salivary fluid since dissolution in the oral milieu was the intended outcome. The saturation solubility was found to be 0.015 mg/ml in SSF, which was close to the reported solubility at this pH.

At all ratios tested, Soluplus® was found to increase the solubility of loratadine in SSF several fold (fig. 1). The solubility of the drug when tested as a physical mixture increased from 19 fold to 87 fold with respect to the solubility of loratadine, as the proportion of Soluplus®: drug on a weight-by-weight ratio was increased from 1

to 5. Soluplus® is an amphiphilic polymer with a Critical Micelle Concentration (CMC) of 7.6 mg/l [21]. Since the concentration of Soluplus® in all the solutions was above the CMC (the lowest concentration at the 1:1 ratio of carrier: drug being 10 mg/5 ml SSF), the increase in solubility of loratadine in the physical mixtures can be attributed to solubilization into Soluplus® micelles.

Nevertheless, the enhancement in solubility from the solid dispersions was even more remarkable and more so, at the higher ratios of drug: polymer. This increase in solubility over the physical mixtures could be attributed to the ability of Soluplus® to present the drug as an amorphous solid dispersion. Further, Soluplus® is also reported to provide and maintain super saturated condition of poorly soluble materials and this has been presented as a reason for increased bioavailability of a drug from solid dispersions in the polymer [22]. Since the 1: 4 ratio of drug: polymer resulted in the highest enhancement at the lower concentration of excipient, which was more than 130 times the native solubility of loratadine in SSF, this product was further characterized and then incorporated into the mouth-dissolving tablets.

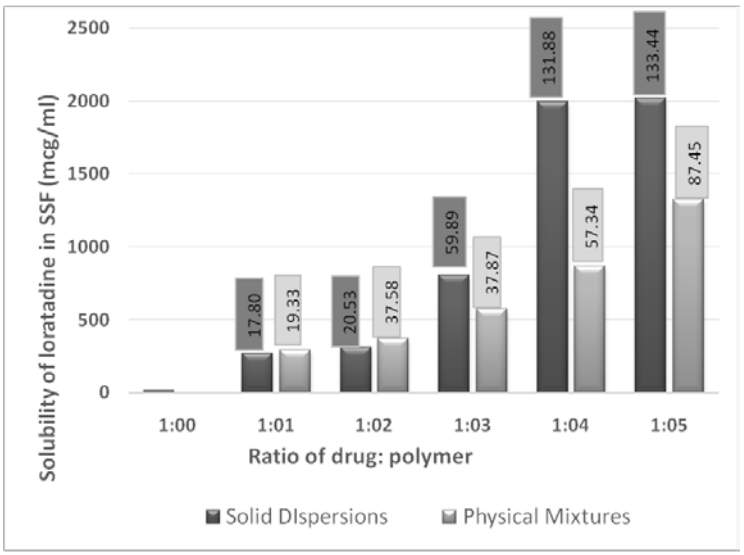


**Fig. 1: Graph indicating solubility of loratadine from solid dispersions and physical mixtures in SSF. The figure in the bars above indicate E (solubility enhancement ratio): the ratio of solubility of drug from test samples to that of native drug in SSF**

**Differential scanning calorimetry**

The DSC curve of loratadine showed a melting endotherm at 140.5 °C. The broad endothermal event in the thermogram for Soluplus® corresponds to its glass transition temperature at about 70 °C. The DSC scan for the physical mixture as well as the solid dispersion, however, fail to record the melting point of the drug. This could possibly be due to amorphization or dissolution of the drug into the rubbery state assumed by the carrier beyond its glass transition temperature. The endotherms are depicted in fig. 2.

**Powder X-ray diffractometry**

The X-ray diffractogram of loratadine showed sharp XRD peaks indicative of the crystalline nature of the drug. The peaks were, however obliterated in the diffractogram for the solid dispersion indicating that the drug was no longer present in the crystalline form (fig. 3). The results are thus indicative of formation of an amorphous solid dispersion of loratadine in Soluplus®.

**Design of experiment for optimization of the formulation**

The Quality by design (QbD) path for product development works towards designing and developing formulations and manufacturing processes to ensure predefined product quality. Hence, the quality aspects of the product need to be identified upfront and, based on these, a Quality Target Product Profile (QTPP) needs to be constructed. The target profile for the loratadine mouth-dissolve tablets was identified as described in table 4.

**Table 4: Quality target profile of loratadine orodispersible tablets**

| QTPP element | Target | Justification |
|---|---|---|
| Route of administration and dosage form | Oral, Tablet | Identical to commercially available common dosage form |
| Dosage design | Oral disintegrating tablets | To provide a dosage form offering greater convenience |
| Dosage strength | 10 mg | Pharmaceutical equivalence requirement: common marketed strength |
| Disintegration time | Less than one minute | Attribute for mouth-dissolving tablets |
| Dissolution time | Drug available in solution within 5 min | To overcome the solubility limitation of the drug since it is a BCS class-II drug and to allow for absorption in the mouth to provide prompt action. |
| Friability | Low | To prevent breakage during packaging, handling etc. |
| Appearance | Elegant | To ensure patient acceptability |
| Taste | Palatable with good mouth-feel | To ensure patient acceptability |

Based on the QTPP developed above and the results of preliminary studies, friability, disintegration time and the dissolution of the drug were taken as critical quality and performance attributes for optimization. Preliminary experiments with the formulation devoid of dry binder resulted in tablets which were very prone to chipping and breakage. However, increasing the hardness during compression was found to adversely impact the disintegration time. Hence, a full factorial design ($3^2$) was used to study the impact of varying two

factors in the tablet formulation: viz the level of disintegrant i.e. crospovidone added to each tablet and the level of dry binder i.e. PVP per tablet on the critical quality attributes as given in table 1.

The outcome of the evaluation tests carried out on the 9 batches of tablets prepared as per the DOE exercise are captured in table 5.

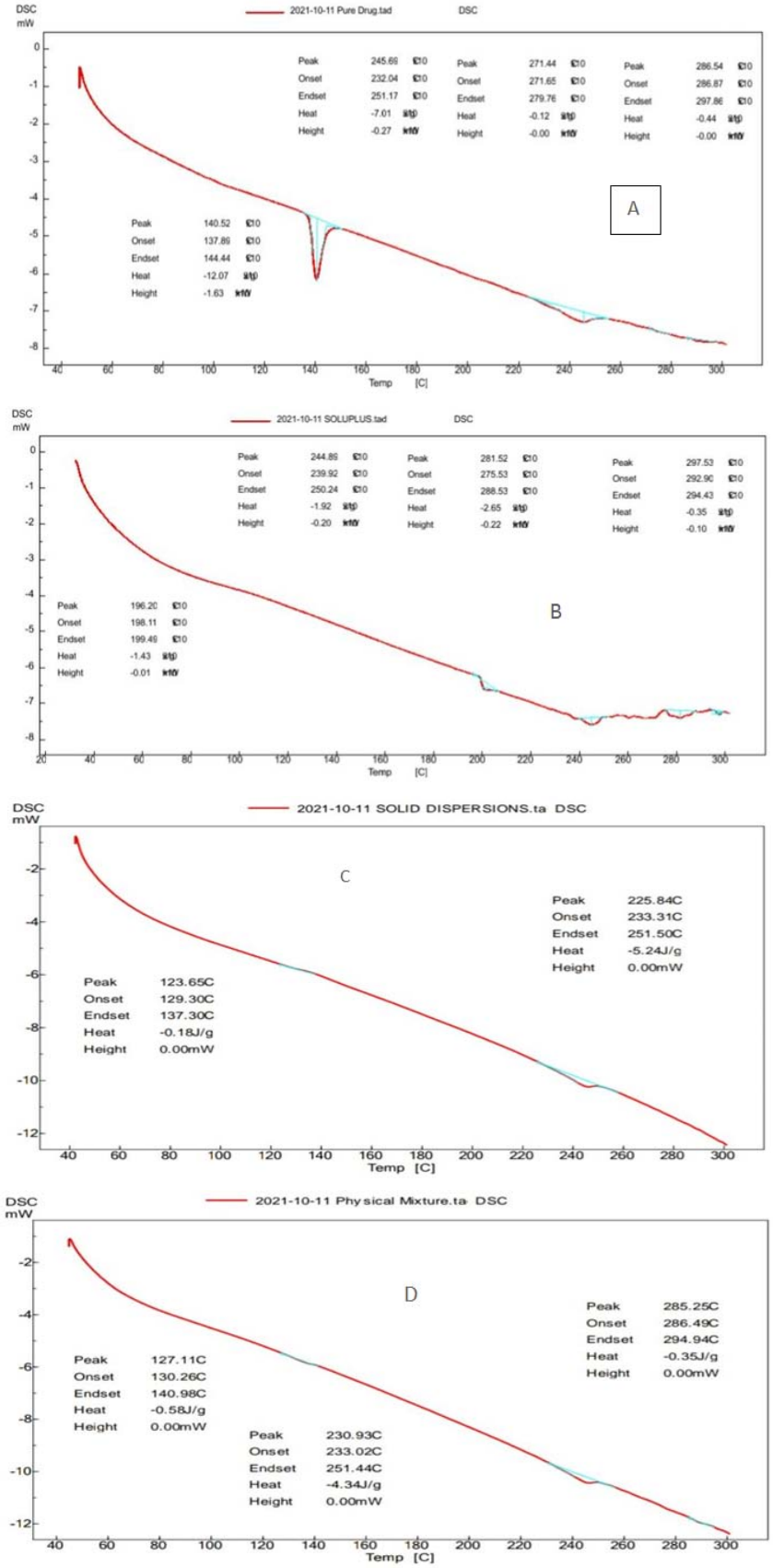


**Fig. 2: DSC thermograms of: A. Loratadine; B. Soluplus® C. Solid dispersion D. Physical mixture**

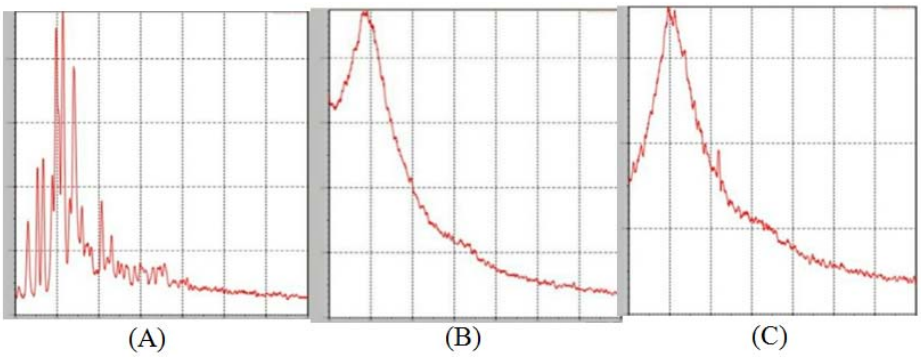


**Fig. 3: XRD peaks for (A)Loratadine (B) Soluplus® and (C) Loratadine: Soluplus® (1:4) solid dispersion**

**Table 5: Evaluation of the tablet blend and the compressed tablets prepared as per the full factorial design**

| Formula | Angle of repose° | Hardness (Kg/cm²) | Friability (% loss in weight) | Wetting time (s) | Disintegrating time (s) | % Loratadine dissolved in 5 min |
|---|---|---|---|---|---|---|
| F1 | 34.2±0.2 | 2.8±0.5 | 0.249±0.016 | 17±0.3 | 39±1.3 | 87.4±2.3 |
| F2 | 34.8±0.2 | 3.1±0.6 | 0.683±0.084 | 20±0.3 | 42±0.8 | 72.3±1.6 |
| F3 | 35.7±0.9 | 3.9±0.5 | 0.364±0.023 | 15±0.4 | 38 v 0.8 | 94.6±0.3 |
| F4 | 32.6±0.6 | 4.2±0.8 | 0.215±0.006 | 21±0.3 | 46±0.3 | 61.2±0.5 |
| F5 | 33.0±1.0 | 4.1±1.0 | 0.566±0.032 | 19±0.9 | 48±1.0 | 67.4±1.9 |
| F6 | 31.7±0.5 | 4.1±0.8 | 0.299±0.024 | 15±0.4 | 41±1.2 | 71.5±2.6 |
| F7 | 34.6±0.2 | 3.6±0.5 | 0.967±0.100 | 15±0.6 | 37±0.8 | 97.9±1.5 |
| F8 | 32.6±0.3 | 2.9±0.2 | 0.199±0.031 | 21±0.4 | 48±0.9 | 63.1±0.9 |
| F9 | 35.9±0.6 | 3.0±0.1 | 0.083±0.002 | 25±0.6 | 60±0.6 | 53.1±1.2 |

Each value is expressed as mean±standard deviation (n = 3)

All the blends were found to have angle of repose between 31.00 to 36.00 and therefore are found to have good flow. The tablets were found to show an average hardness between 2.8 to 4.0 and were found to be wetted within a few seconds when placed in a turgid environment.

The dissolution of the drug was rapid in all cases with at least 50% drug being soluble in 200 ml of the dissolution medium within 5 min. The smaller volume of the dissolution medium helped to overcome issues of sensitivity of the UV spectrophotometric analytical method used for quantification by limiting the extent of dilution of the drug in the dissolution medium and also served to increase the discriminatory nature of the test [23].

**Statistical treatment of data**

The data was statistically treated to generate quadratic models for expressing the relationship between the dependent variables and the independent variables by using JMP software Trial version 16.1.0. The utility of these models was ascertained by calculation of the regression coefficient between the observed and predicted value which were found to be close to unity in all cases, as seen from fig. 4.

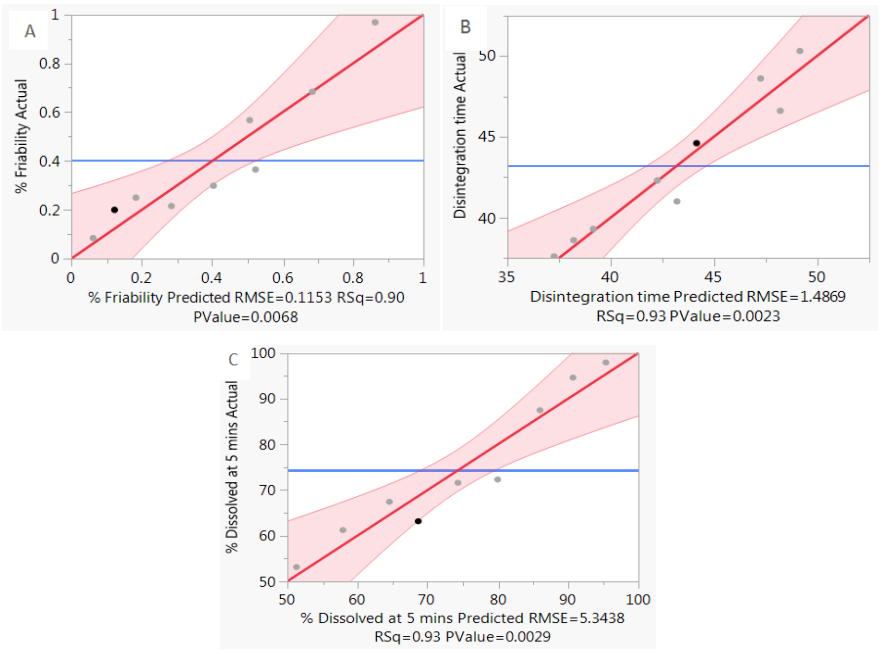


**Fig. 4: Observed and predicted values of (A) % Friability (B) Disintegration time and (C) % Loratadine dissolved at 5 min**

ANOVA was used to test the significance of the terms used for constructing the equation describing the relationship between the dependent variables and terms having p less than 0.05 were taken to be significant. Also, terms with positive coefficients have a positive correlation with the dependent variable whereas terms with negative coefficients have an inverse relationship with the dependent variable.

The final equations in term of the actual factors are presented below:

**% Friability** = 0.4031444+0.1194167 x level of cross povidone-0.280917 x level of PVP-0.058725 x level of crospovidone x level of PVP

**Disintegration time** = 43.211111-5 x level of crospovidone+0.95 x level of PVP–0.129 x level of crospovidone x level of PVP.

**Dissolution at 5 min** = 74.302222+16.371667 x level of crospovidone+5.648333 x level of PVP–0.9625 x level of crospovidone x level of PVP

The contour plots to further demonstrate these relationships are included in fig. 5.

**Optimization**

The composition of the suggested optimized formulation is derived from fig. 6 and is given in table 3.

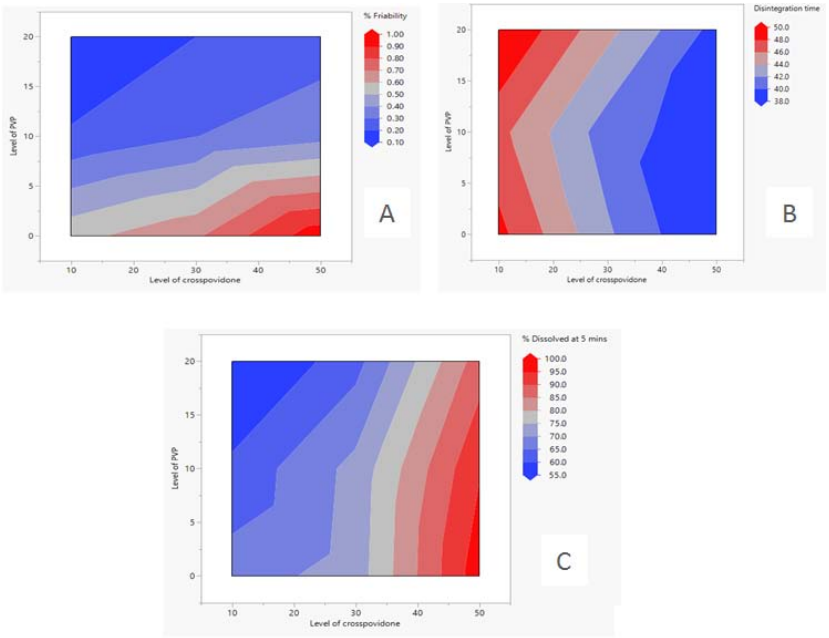


**Fig. 5: Contour plots showing the relation between the factors and each of the dependent variables: (A) % Friability, (B) Disintegration time and (C) % dissolved at 5 min**

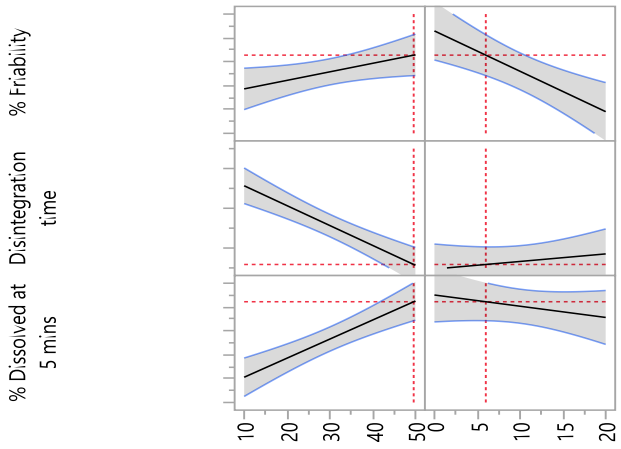


**Fig. 6: Level of crospovidone and PVP to be used is in final formulation as suggested by JMP software**

**Evaluation of optimized formula**

The optimized formula was evaluated for the pre-compression and post-compression parameters and the results are presented in table 6. The developed formulation was found to have all properties within the desirable range and the observed values were in good agreement with the predicted values with a low error prediction rate and good reproducibility.

**Table 6: Evaluation of blend and tablets prepared using the optimized formula**

| Property | Actual result±SD (n = 3) | Predicted result | % Prediction error |
|---|---|---|---|
| Angle of repose ( °) | 29.4±0.9 | | |
| % Friability | 0.623±0.041 | 0.655 | 5.1 |
| Disintegration time (sec) | 39.3±1.13 | 37.93 | 2.7 |
| % Loratadine dissolved in 5 min | 93.78±2.84 | 92.23 | 1.65 |
| Wetting time (sec) | 17±3.6 | - | - |
| Hardness (kg/cm$^2$) | 4.0±0.5 | - | - |

The tablets were found to be extremely palatable by all the volunteers with no bitterness. The volunteers also reported a pleasant moth feel. The *in vivo* disintegration time was found to be between 50–65 seconds as reported by all the volunteers, which is more than the time of 39 seconds, probably due to the limited moisture available on the tongue surface.

## CONCLUSION

Soluplus® was found to be a suitable excipient for the preparation of solid dispersions of loratadine. The dispersions were found to result in a phenomenal increase in the solubility of loratadine in aqueous medium. DOE was successfully employed to arrive at an optimal formula for loratadine tablets which yielded the fast disintegrating/mouth-dissolving tablet with good physical integrity and palatability. Studies on the stability of the amorphous dispersions and also on the final tablet are, however, necessary. Further, comparisons with the commercially available mouth dissolve tablets of loratadine (Claritin RediTabs®), including bioequivalence studies, are warranted.

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## AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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