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FORMULATION AND EVALUTION OF ORO-DISPERSIBLE TABLET OF AZELASTINE BY QBD

Himani Rawal* **and Sachin K. Jain**

Oriental College of Pharmacy and Research, Oriental University, Indore.

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***Corresponding Author**
Himani Rawal
Oriental College of Pharmacy and Research, Oriental University, Indore.

ABSTRACT

The main objective of this work is to formulate and evaluate oro-dispersible tablet of Azelastine by QBD. The preformulation parameters like solubility, partition coefficient etc give good results and same as that given in the literature. The oro-dispersible tablet of azelastine was prepared with 2^3 factorial design. The evaluation parameters were studied like pre-compression parameters and post compression parameters. The precompression parameters like angle of repose, hardness, bulk density, tapped density was studied with good results. The post compression parameters like hardness, friability etc. was studied with good results. There were eight formulation batches prepared out of which F-3 batch showed better results as compared to other batches. The in-vitro drug release of F-3 batch was found to be 98.2 %. All the parameters were successfully evaluated. **Materials and Methods:** Azelastine was purchased from the Schon Pharmaceuticals, Indore. A Shimadzu-1700 UV-Visible spectrophotometer with 1 cm matched silica cells were used for spectrophotometric analysis. **Results and Discussion:** The preformulation studies were successfully done. The Infrared spectrum of the drug showed major peaks at wave number characteristic of the Azelastine as compared to standard graph shown in Indian Pharmacopoeia. Solubility studies of drug in different solvent systems were performed. The oro-dispersible tablet of azelastine was prepared with 2^3 factorial design. There were eight formulation batches prepared out of which F-3 batch showed better results as compared to other batches. The in-vitro drug release of F-3 batch was found to be 98.2 %. All the parameters were successfully evaluated.

KEYWORDS: Azelastine, Oro-dispersible tablet, Quality by design.

1.0 INTRODUCTION

Allergies, also known as allergic diseases, are various conditions caused by hypersensitivity of the immune system to typically harmless substances in the environment. These diseases include hay fever, food allergies, atopic dermatitis, allergic asthma, and anaphylaxis. Symptoms may include red eyes, an itchy rash, sneezing, coughing, a runnynose, shortness of breath, or swelling. Note that food intolerances and food poisoning are separate conditions.

Common allergens include pollen and certain foods. Metals and other substances may also cause such problems. Food, insect stings, and medications are common causes of severe reactions. Their development is due to both genetic and environmental factors. The underlying mechanism involves immunoglobulin E antibodies (IgE), part of the body's immune system, binding to an allergen and then to a receptor on mast cells or basophils where it triggers the release of inflammatory chemicals such as histamine. Diagnosis is typically based on a person's medical history. Further testing of the skin or blood may be useful in certain cases. Positive tests, however, may not necessarily mean there is a significant allergy to the substance in question.

1.1. Quality by Design

Quality by design (QbD) is a concept first outlined by quality expert Joseph M. Juran in publications, most notably *Juran on Quality by Design*. Designing for quality andinnovation is one of the three universal processes of the Juran Trilogy, in which Juran describes what is required to achieve breakthroughs in new products, services, and processes. Juran believed that quality could be planned, and that most quality crises and problems relate to the way in which quality was planned.

1.2. An orally disintegrating tablet or **orally dissolving tablet** (**ODT**) is a drug dosage form available for a limited range of over-the-counter (OTC) and prescription medications. ODTs differ from traditional tablets in that they are designed to be dissolved on the tongue ratherthan swallowed whole. The ODT serves as an alternative dosage form for patients who experience dysphagia (difficulty in swallowing) or for where compliance is a known issue and therefore an easier dosage form to take ensures that medication is taken. Common among all age groups, dysphagia is observed in about 35% of the general population, as well as up to 60% of the elderly institutionalized population and 18-22% of all patients in long-term care facilities. ODTs may have a faster onset of effect than tablets or capsules, and have the

convenience of a tablet that can be taken without water. During the last decade, ODTs have become available in a variety of therapeutic markets, both OTC and by prescription.

1.2.1. Advantages of ODT

They are easy to consume and as such are convenient for such patients as "the elderly, stroke victims, bedridden patients, patients affected by kidney failure, and people who refuse to swallow, such as pediatric, geriatric, and psychiatric patients";

Increased bioavailability (rapid absorption) due to pregastric absorption;

Don't require water to consume and thus suitable for "patient compliant for disabled, bedridden patients, and for travelers and busy people who do not always have access to water";

Good mouth feel;

Improved safety due to low risk of choking or suffocation during oral administration.

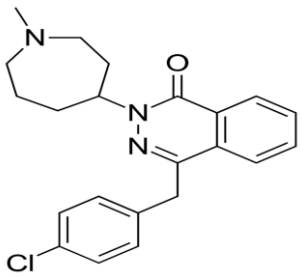

Fig.1: Chemical Structure of Azelastine.

2.0 MATERIALS AND METHODS

Materials: Azelastine was purchased from the Schon Pharmaceuticals, Indore.

A Shimadzu-1700 UV-Visible spectrophotometer with 1 cm matched silica cells were used for spectrophotometric analysis.

3.0. PREFORMULATION STUDIES

3.1. Melting Point of Drug- It is used to determine the drug's purity. In the range as defined, the melting point should be. Thiele tube Apparatus is used.

Procedure

Firstly, in the capillary tube a small quantity of powder whose melting point is to be determined is placed. The capillary tube was then placed in the melting point apparatus. The temperature at which the powder started to melt up to temperature at which complete melting was observed was noted.

3.2. Infrared Spectral Analysis of Drug

The information regarding the various groups present in a particular compound can be obtained from the IR spectrum of that particular drug. Infra red transmission spectra were obtained using infrared spectrophotometer. KBr pellets were used for obtaining the infrared spectrum. Small quantity of drug was used for IR analysis. The prepared pellets of KBr containing the drugs were then placed in the holder of IR spectrophotometer and IR spectrum was taken using a scanning range of 400-4000 cm-1. The obtained IR spectrum of Azelastine was interpreted for the presence of different group present in the drug.

3.3. Solubility Studies

Various solvents such as water, DMSO, ethanol and methanol were selected. Equilibrium solubility of drug in these solvents were determined. 5 ml of solvents were taken in volumetric flask and excessive quantity of drug was dissolved in them. These volumetric flask were then kept on a shaker for the period of 5 hours. The saturated solution resulting after this step were kept aside for 24 hours, then they were filtered with the aid of sintered glass filter and finally were analyzed using UV-Visible Spectrophotometer.

3.4. Calibration curve of Azelastine

Preparation of Regressed Calibration Curve

Stock solution of azelastine was prepared in methanol having concentration 100 µg/ml. Further dilutions were prepared from this stock solution having concentrations of 5µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml and 25 µg/ml. Then the absorbance of these diluted solutions was determined at λ_{max} i.e., 288 nm. With the obtained data graph was plotted between concentration and absorbance. It was observed that at the selected concentration range, graph obeyed Beer-Lambert's Law.

Table 1: Calibration curve of Azelastine in Methanol.

S. No.	Concentration (µg/ml)	Absorbance
l.	0	0
2.	5	0.121
3.	10	0.249
4.	15	0.345
5.	20	0.485
6.	25	0.6
7.	30	0.7

3.5 .Partition coefficient

The ratio of unionized drug distribution between the organic and aqueous phase at equilibrium is known as Partition Coefficient.

Procedure

50mg of drug was dissolved in 50ml of water which was transferred to a separating funnel and to it was added 50ml of octanol. Funnel was shaked for 30 min and stand for 5 min aqueous layer was separated and centrifuged for 1hour at 2000 rpm.1ml of this taken and diluted up to 10ml. The aqueous phase is assayed before (Σc) and after partitioning (C_W) [the aqueous concentration] by using UV-visible spectrophotometer and $K_{o/w}$ calculated by using formula.

$K_{o/w} = (\Sigma C - C_w)/ (C_w)$

Table 2: Partition coefficient of drug.

S. No.	Material	Observation	Specification
1.	Azelastine	2.2	2.2

4.0 Formulation And Optimization of OrodispersibleTablet Of Azelastine

4.1. Preparation of oro dispersible tablet

4.1.1. All the ingredients were passed through 60 # sieve separately, Magnesium stearate & Talc through 40 #. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed with 8 mm sizes flat round punch to get tablet using Rimek Compression Machine.

Table 3: Formulation composition of different formulations.

S.No	Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
1	Azelastine	10	10	10	10	10	10	10	10
2	Guar gum	5	5	4	8	4	8	4	5
3	Cross Carmellosesodium	6	6	7	7	6	6	7	5
4	Micro crystallinecellulose	65	65.5	65.5	65.5	70	70.5	70.5	65.5
5	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
6	Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	Peppermint	1	1	1	1	1	1	1	1
8	Sodium sachharin	2	2	2	2	2	2	2	2
9	Mannitol	8	8	8	8	8	8	8	8

4.2. Design of Experiment

Table 4: 2^3 Factorial design with upper limit and lower limit of all factors.

S.No	Three Factors	Two levels -1	+1
1.	Conc. of Guar gum	4	8
2.	Conc. of Cross Carmellose sodium	5.5	10.5
3.	Conc. of Micro crystalline cellulose	65.5	70.5

4.3. Statistical Optimization technique

The optimization phase was designed statistically using 2^3 factorial design (Design expert 9.0, state Ease, INC 2021, east Hennepin Ave. suite 480, Minneapolis MN 55413) in which three variables namely concentrations of Gum Guar, C.S.S and M.C.C. were kept at two levels. Main interactive influences were tested using statistical methods. Upper and lower limits of factorial design are shown in table no 5. Eight formulations ofoptimization phase were categorized in to four groups for ease of analysis and comparison as follows.

Group I: All variables at low level (Formulation F1).

Group II: Any one of three variables at high level (Formulations F2, F3 & F5). 3. Group III: Any two of three variables at high level (Formulations F4, F6, & F7). 4. Group IV: All three variables at high level (Formulation F8).

4.4. Evaluations of oro dispersible tablets

4.4.1. Pre- compression parameters

4.4.1.1.Carr's index- Carr Index of any solid is calculated for compressibility of a powder which is based on true density (ρT) and bulk density (ρB), CI=100[(ρT–ρB)/ρB]. A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

4.4.1.2. Angle of repose- Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles.

4.4.1.3. Hausner ratio- The powder content (W) is weighed, and the bulk density is calculated as W/V50 g/ml. Bulk density may be used as an indication of flow properties. The ratio of tapped density W/V50 to fluffy density (W/V0 g/ml) is known as the Hausner ratio.

4.4.2. Post compression studies

4.4.2.1. Weight variation- Twenty tablets are selected at random, individually weighed in a single pan electronic balance and the average weight is calculated. The uniformity of weight is determined according to I.P. specification. As per IP (2007) not more than two of individual weights should deviate from average weight by more than 5% and none deviate more than twice that percentage.

4.4.2.2. Thickness

The thickness and diameter of the tablets are carried out using digital vernier caliper. Threetablets are used from each batch and results were expressed in millimeter (mm)

4.4.2.3. Hardness test

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packing and shipping. Monsanto hardness tester is used to measure the hardness of tablet. Three tablets from each batch are used for hardness test and results are expressed in Kg/cm^2.

4.4.2.4. Friability

It is done in Roche friabiliator apparatus. Pre-weighed samples of 20 tablets are placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted andreweighed. The percentage friability is calculated by the following expression.

4.4.2.5. Wetting time -The wetting time of tablets indicates the inner structure of the tablets and the hydrophilicity of the excipients which should be in the range of sec. The wetting time of the various formulations was illustrated in the Table No.17. The values were found in therange of 29 – 41.6 sec and designate that all the superdisintegrants having goodhydrophilicity.

4.4.2.6. Modified disintegration test: The disintegration is prior step for the dissolution of a tablet and was performed by a method which is stated under the materials and methods. The modified disintegrationtime of the various formulations was depicted in the Table No.17 and the values are lies in range of 34 – 43.6 sec. Among all the formulations F3 has shown lower disintegration time which contains the 5%of sodium starch glycolate. From the results obtained it has shown that with the increasing concentration of superdisintegrant the disintegration time has been decreased.

4.4.2.7. Water absorption ratio: It is important criteria for understanding the capacity of disintegrants to swellin the presence of water. The water absorption ratio of the various formulations was depicted in the Table No.17. The results are lies in the range of 25.31 – 29.2. The formulations containing low concentration of superdisintegrants shows lower water absorption ratio compare to formulations containing higher concentration of superdisintegrants, which may be because of less swelling property.

4.4.2.8. In Vitro dispersion time: The In Vitro dispersion time is measured by the time taken to undergo uniform dispersion. The In Vitro dispersion time of the various formulations was shown in the Table No. The results are lies in the range of 62 – 77 sec. The results showed that the crospovidone is the best superdisintegrant which may be because of showing less swelling efficiency, high water uptake capacity and spongy nature which yields porous tablet that disperse in a matter of seconds. And the results also showed that as the concentration of superdisintegrant increases the In Vitro dispersion time decreases.

4.4.2.9. In Vitro drug release: In Vitro release of various formulations was studied and was shown in the Table No. The fast dissolution of all the formulations is might be due to quick disintegration of the tablets to fine particles and rapid absorption. Thus formulation F3 showed maximum drug release i.e., 99.5% at the end of 15 min which contains 5% of the crospovidone as superdisintegrant compared to other formulations containing croscarmellose sodium. It might be due to more gelling tendency and low water uptake of Croscarmellose sodium and more swellingtendency.

5.0 RESULTS AND DISCUSSIONS

5.1. Preformulation studies

5.1.1. Melting point determination – The melting point of drug was found to be.

Table 5: Melting point of drug.

Drug	Melting point	Observed Melting point
Azelastine	225-228°C	225°C

5.1.2. FTIR Spectrum of drug- FTIR Spectrum of drug sample was determined and the data was recorded in the fig.

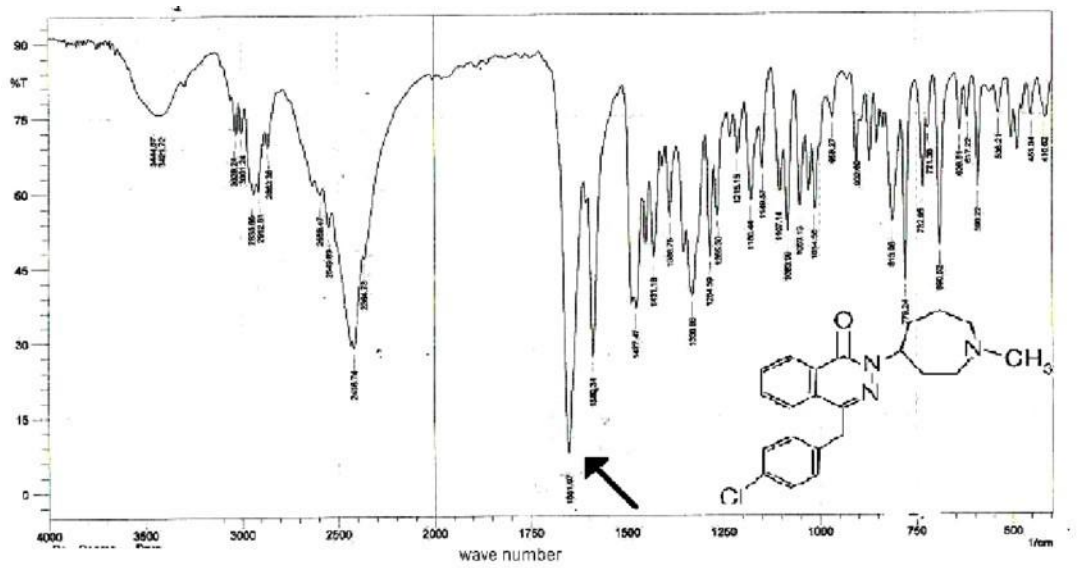

Fig.2: FTIR spectrum of Azelastine.

5.1.3. Calibration curve of Azelastine in Methanol- The calibration curve of azelastine in methanol was determined. The results were recorded in the fig.

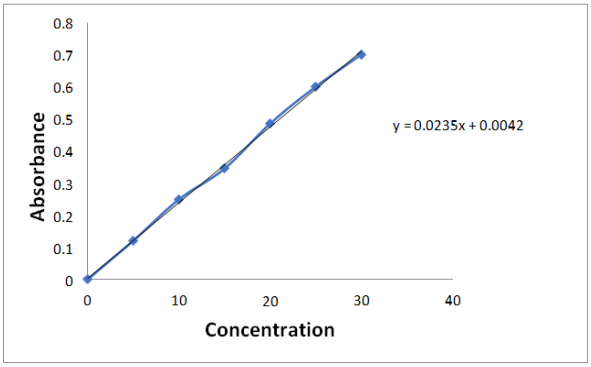

Fig.3: Calibration curve of Azelastine in Methanol.

5.1.4. Partition coefficient determination – The partition coefficient of drug was found to be.

Table 6: Partition coefficient of drug.

Drug	Parition coefficient	Observed Partition coefficient
Azelastine	2.2	2.23

5.2. Evaluations of oro dispersible tablet

5.2.1. Pre-compression parameters- The pre-compression parameters of the prepared tablets were shown in the table.

Table 7: Pre- compressional Evaluations parameter of powder blend.

Formulation code	Angle of repose	Bulk density	Tapped density	Compressibility index	Hausner ratio
F-1	19.29	0.90	1.04	12.43	1.12
F-2	22.29	0.95	1.06	11.51	1.10
F-3	18.22	0.93	1.11	15.12	1.12
F-4	12.65	0.98	1.06	7.80	0.83
F-5	18.93	0.91	1.11	15.12	1.12
F-6	19.86	0.96	1.04	12.68	1.13
F-7	15.03	0.92	1.02	13.78	1.15
F-8	22.29	0.90	1.12	12.89	1.13

5.2.2. Post-compression parameters- The post-compression parameters of the prepared tablets were shown in the table:8.

Table 8: Post- compressional Evaluations parameter of powder blend.

Formulation code	Hardness	Friability(%)	Weight variation (mg)	Thickness (mm)
F-1	2.5	0.39	97.21	3.2
F-2	3.1	0.44	100.30	3.0
F-3	2.6	0.35	100.50	3.2
F-4	3.0	0.38	101.45	3.1
F-5	2.6	0.43	102.10	3.3
F-6	2.5	0.44	100.20	3.1
F-7	2.8	0.34	101.10	3.0
F-8	3.2	0.36	98.88	3.2

Table 9: Evaluation parameters of prepared different formulations.

S. No	Formulation code	Wetting time (sec)	In-vitro disintegration time (sec)	Water absorption ratio	In-vitro dispersion time	Drug content
1	F-1	36	41	25	70	98.90
2	F-2	34	40	26	70	99.71
3	F-3	28	34	28	65	96.78
4	F-4	35	43	26	77	99.15
5	F-5	40	42	25	67	97.40
6	F-6	41	37	27	63	98.76
7	F-7	37	43	26	75	99.30
8	F-8	33	39	25	73	98.56

Table 10: In-vitro dissolution of all the formulation batches.

Time (inmins)	Formulation Code							
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
0	0	0	0	0	0	0	0	0
3	63.3	66.9	69.8	68.0	69.7	68.2	65.1	67.3
6	71.8	72.0	72.5	71.7	72.0	70.4	72.1	74.5
9	80.2	79.1	78.3	78.0	79.0	76.3	76.2	78.9
12	87.9	86.2	89.4	85.6	87.0	88.2	84.5	86.5
15	94.5	95.6	98.2	91.9	94.2	96.3	90.0	92.6

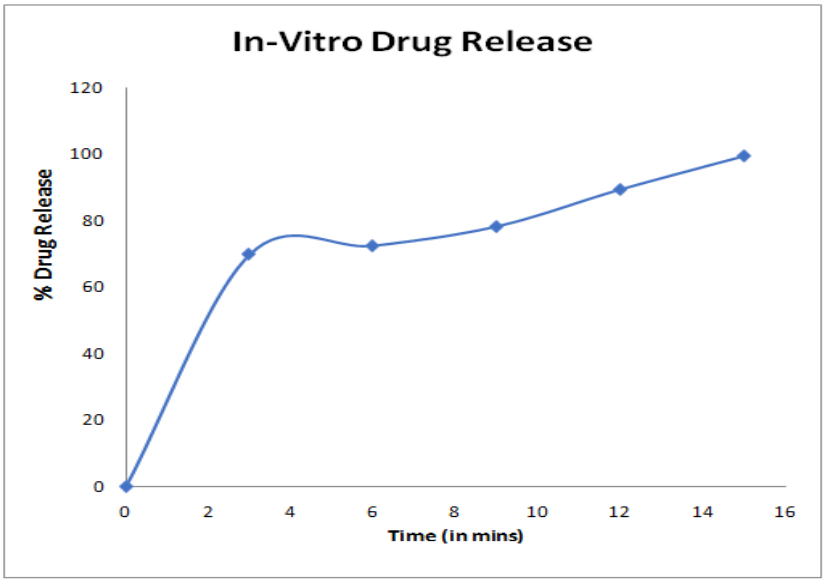

Fig.4: In-vitro Drug Release of the Azelastine formulation (F-8).

6.0. SUMMARY AND CONCLUSION

The aim of the present research work is to formulate and evaluate oro-dispersible tablet of azelastine by QBD Approach. The main objective of this research is to formulate and evaluate the oro-dispersible tablet of anti-allergic drug by QBD approach.

Azelastine, sold under the brand name Optivar among others, is a H_1 receptor-blocking medication primarily used as a nasal spray to treat allergic rhinitis (hay fever) and as eye drops for allergic conjunctivitis. Other uses may include asthma and skin rashes for which it is taken by mouth. Onset of effects is within minutes when used in the eyes and within an hour when used in the nose. Effects last for up to 12 hours.

The purpose of the study is to formulate and develop oro-dispersible tablet of azelastine byQBD approach. Treatment of allergy.

The melting point of pure drug was found to be 225 C. The solubility studies were successfully done with different solvents like Methanol, DMSO etc. The IR spectra of azelastine was recorded.

The calibration curve of azelastine was prepared with different dilutions in the range of 5-25 µg/ml with y= 0.0235 x + 0.0042 and $R^{2=}$ 0.9987.

The partition coefficient of pure drug was found to be 2.2.

The oro-dispersible tablet of azelastine was prepared with 2^3 factorial design. The formulation batches The evaluation parameters were studied like pre-compression parameters and post compression parameters. The precompression parameters like angle of repose, hardness, bulk density, tapped density was studied with good results. The post compression parameters like hardness, friability etc. was studied with good results.

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There were eight formulation batches prepared out of which F-3 batch showed better results as compared to other batches.

The in-vitro drug release of F-3 batch was found to be 98.2%. All the parameters were successfully evaluated.

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