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ASSESSMENT OF OPTIMIZED ODT FORMULATION WITH CONVENTIONAL MARKETED TABLET OF BILASTINE

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Abstract:

Bilastine is a novel new second generation antihistamine that is highly selective for the H_1 histamine receptor, and have no affinity for muscarinic, serotonergic, dopaminergic and noradrenergic receptors. After oral administration, the distribution of bilastine in the brain is limited. Avoids sedative effects of first-generation antihistamines because of its limited CNS penetration. Bilastine is approved for the symptomatic treatment of allergic rhinitis (AR) and chronic urticaria (CU). Its effectiveness is similar to cetirizine, fexofenadine and desloratadine. Bilastine can be classified into the same chemical group as many of the new antihistamines in the market, even it is neither a structural derivative, nor a metabolite or enantiomer of any of them, but a primitive molecule designed to meet all the requirements of the second-generation antihistamine. The absolute bioavailability of Bilastine is 61% and is not significantly metabolized in human. As Bilastine is found to be the substrate of efflux transporter P-glycoprotein, it is not being metabolized in the body. P-glycoprotein is found in the apical (luminal) membrane of the entire intestine from duodenum to rectum, with a high expression in the enterocytes of the small intestine. It reduces the oral availability of drugs that are its substrates. As an efflux transporter it limits the bioavailability of orally administered drugs by pumping them back into the lumen. This promotes drug elimination into the bile and urine. The main aim of this study is to develop and characterize orodispersible tablets of Bilastine which disintegrates in the oral cavity in a matter of second without the need of water. Bioavailability of the drug is enhanced due to its absorption from the mouth (Pregastric absorption) and also due to ready availability of the dosage form in the form of nearly solution or suspension at the site of action leading to quick onset of pharmacological action thereby reducing its interaction with P-glycoprotein.

Key words: Bilastine , antihistamine ,H_1 histamine receptor.

Introduction:

Bilastine being BCS class II drug with low solubility the absorption of the drug is dissolution rate limited. Here in case of Orodispersible tablet the use of superdisintegrants improves the solubility of the Bilastine which in turn improves the dissolution and drug absorption.

Orodispersible tablet is a relatively new novel dosage form in which the dosage form quickly disintegrates or disperses in the oral cavity in the absence of water. In the latter case, the drug bioavailability of the rapidly dispersing formulation may even be higher than the bioavailability observed in the standard conventional dosage form.

The optimized ODT formulation F8 was compared with the marketed conventional tablet of Bilastine manufactured by Sun Pharmaceuticals Industries Limited in the name of Bilasure 20mg.

Table 1: Comparison study of Conventional marketed tablet and Optimized ODT formulation F8

EVALUATION PARAMETERS	CONVENTIONAL MARKETED TABLET (BILASURE 20mg)	OPTIMIZED ODT FORMULATION (F8)
Hardness	10.33 kg/cm² ± 0.577	3.1kg/cm² ± 0
Wetting time	01:48 Minutes ± 0.075	12.26 seconds ± 0.208
Water absorption ratio	29.76 % ± 0.378	99.76 % ± 0.251
***Invitro* Disintegration time**	8.56 Minutes ± 0.602	7.55 seconds ± 0.406
***Invitro* Dispersion time**	15.23 Minutes ± 0.873	13.39 seconds ± 0.452
Drug content	98.5 % ± 0.274	96.73 % ± 0.271
%Drug release	68.33 % ± 0.678 (60 Minutes)	95.48 % ± 0.804 (30 Minutes)

The data is presented in an average of mean ± SD, n=3

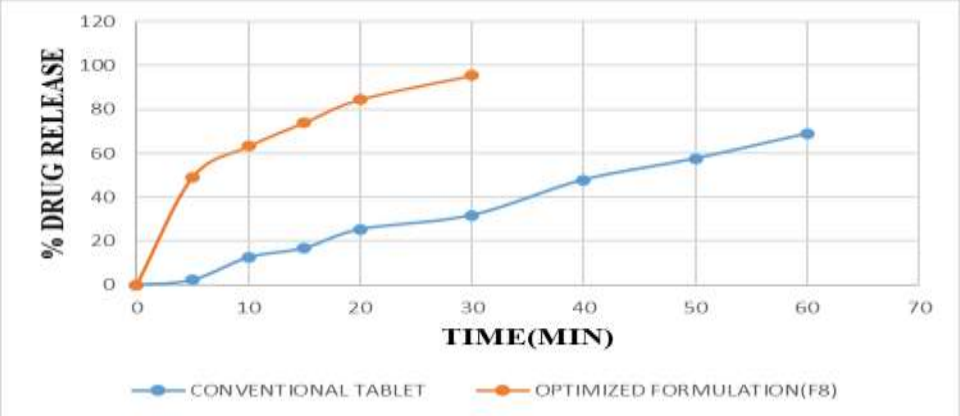

Figure 1: Graph representing % drug release comparison between Bilastine marketed conventional tablet & Optimized ODT formulation(F8)

STABILITY STUDY

The optimized formulation F8 was subjected to intermediate and accelerated short term stability studies at 30ºC ± 2ºC & RH 65 ± 5 % and 40ºC ± 2ºC & 75 ± 5 % for 3 months as per ICH guidelines and analysed for Physical appearance and physicochemical evaluation parameters like Hardness, Friability, Wetting time, Water absorption ratio, *Invitro* Disintegration time, *Invitro* Dispersion time, Drug content and % drug release.

Table 2: Stability Study of Optimised formulation F8 under Intermediate Condition (30ºC ± 2ºC & RH 65 ± 5 %)

EVALUATION PARAMETER	INITIAL	AFTER 3 MONTHS
Physical appearance	White, Smooth	No Changes
Weight variation (mg)	194.02 ± 1.156	193.98 ± 1.09
Friability (%)	0.191 ± 0.01	0.194 ± 0.04
Hardness (kg/cm²)	3.1 ± 0	3 ± 0.03
Wetting time (sec)	12.26 ± 0.208	12.30 ± 0.201

Water absorption ratio (%)	99.76 ± 0.25	98.30 ± 0.21
***Invitro* Disintegration time (sec)**	7.55 ± 0.406	8.07 ± 0.404
***Invitro* dispersion time (sec)**	13.39 ± 0.45	14.06 ± 0.45
Drug Content (%)	96.73 ± 0.27	96.45 ± 0.25

The data is presented in an average of mean ± SD, n=3

Table 3: % Drug Release of formulation F8 during stability study under Intermediate Condition (30ºC ± 2ºC & RH 65 ± 5 %)

TIME(MIN)	% DRUG RELEASE	
	INITIAL	**AFTER 3 MONTHS**
0	0	0
5	49.92 ± 1.29	47.83 ± 0.99
10	61.32 ± 0.86	59.22 ± 0.83
15	71.15 ± 0.77	68.07 ± 0.73
20	83.84 ± 0.41	80.26 ± 0.40
30	95.48 ± 0.80	94.01 ± 0.72

The data is presented in an average of mean ± SD, n=3

Table 4: Stability Study of Optimised formulation F8 under Accelerated Condition (40ºC ± 2ºC & RH 75 ± 5 %)

EVALUATION PARAMETER	**INITIAL**	**AFTER 3 MONTHS**
Physical Appearance	White, Smooth	No Changes
Weight variation (mg)	194.02 ± 1.156	193.92 ± 1.131
Friability (%)	0.191 ± 0.01	0.195 ± 0.09
Hardness (kg/cm²)	3.1 ± 0	2.8 ± 0.02
Wetting time (sec)	12.26 ± 0.208	12.33 ± 0.201
Water absorption ratio (%)	99.76 ± 0.25	99.68 ± 0.26
***Invitro* Disintegration time (sec)**	7.55 ± 0.406	8.05 ± 0.400
***Invitro* dispersion time (sec)**	13.39 ± 0.45	14.10 ± 0.43
Drug Content (%)	96.73 ± 0.27	96.01 ± 0.24

The data is presented in an average of mean ± SD, n=3

Table 5: % Drug Release of formulation F8 during stability study under Accelerated Condition (40ºC ± 2ºC & RH 75 ± 5 %)

TIME(MIN)	% DRUG RELEASE	
	INITIAL	**AFTER 3 MONTHS**
0	0	0
5	49.92 ± 1.29	47.55 ± 0.18
10	61.32 ± 0.86	59.92 ± 0.72

15	71.15 ± 0.77	68.15 ± 0.93
20	83.84 ± 0.41	82.27 ± 0.21
30	95.48 ± 0.80	94.35 ± 0.56

The data is presented in an average of mean ± SD, n=3

The objective of the present study was to formulate and evaluate orodispersible tablet for an antihistamine drug Bilastine. In this study, Bilastine orodispersible tablets prepared with Crospovidone, Sodium starch glycolate, Dehydrated banana powder were found to be ideal to increase the dissolution rate thereby improving the bioavailability of Bilastine.

The conclusion drawn from the present investigation is given below:

- The Bilastine was analysed for spectral (UV & FTIR) properties. Bilastine showed maximum absorption at wavelength 278 nm in 0.1N HCl. The value of regression coefficient of standard curve was found to be 0.9996 which showed linear relationship between concentration and absorbance. The results of FTIR showed that there was no interaction between the drug Bilastine, superdisintegrants and other excipients.
- Nine formulations were prepared by direct compression method using varying concentration and combination of both synthetic and natural superdisintegrants namely Crospovidone, Sodium starch glycolate & Dehydrated banana powder and the formulations are designated as F1 – F9. F1& F2 contains Crospovidone (3% & 4%), F3 & F4 contains Sodium starch glycolate (3% & 4%), F5 & F6 contains Dehydrated banana powder (3% & 4%), F7 contains Crospovidone (2%) and sodium starch glycolate (2%), F8 contains Crospovidone (2%) and Dehydrated banana powder (2%), F9 contains Sodium starch glycolate (2%) and Dehydrated banana powder (2%) respectively. The other excipients used were Mannitol and Microcrystalline cellulose as diluents, Magnesium stearate and talc as glidants and lubricants.
- When the superdisintegrants are used in higher concentration (within the permitted limits) as well as when used in combination, the wetting and disintegration was quick which in turn improves dissolution profile. Disintegration is much affected by hardness. Lower the hardness, the time taken for disintegration will be less & vice versa.
- The tablets were evaluated for parameters like thickness, hardness, friability, wetting time, water absorption ratio, *Invitro* disintegration time, *Invitro* dispersion time, % drug content and *Invitro* drug release studies.
- From the results of the drug content determination, it was inferred that there was uniform distribution of drug in the tablet and the deviations were within the acceptable limits (86.95 ± 0.543 to 96.73 ± 0.271%).
- Even though all the formulations showed good results, Formulation F8 was identified as best and ideal formulation based on wetting time, *Invitro* disintegration time, *Invitro* dispersion time and *Invitro* % drug release.
- The optimized formulation F8 containing combination of Crospovidone (2%) & Dehydrated banana powder (2%) showed maximum drug release of 95.48 ± 0.804 % at the end of 30 minutes.
- The model with highest regression coefficient (R^2) was chosen as the best fit model for that particular formulation. All the formulations F1-F9 showed good linearity and best fitting into first order (Rate of

drug release is concentration dependent). Based on n values of Korsmeyer Peppas model the release mechanism was found to be Super case II transport (relaxation / erosion).

- Stability study of the optimized formulation F8 showed no significant changes in the physical appearance, physicochemical properties and Invitro drug release of the tablet.
- The optimized formulation showed better release at the end of 30 minutes when compared to the marketed conventional product of Bilastine (Bilasure 20mg).
- As compared to conventional tablets, ODT is better as it gives quick action, higher bioavailability. ODT offers more compliance for patients who cannot swallow, such as the elderly, stroke victims, bedridden patients and patient who refuse to swallow such as paediatric, geriatric & psychiatric patients.
- Thus, the results of the above study clearly indicated that Bilastine may be formulated as Orodispersible tablets using superdisintegrants like Crospovidone, sodium starch glycolate and Dehydrated banana powder by direct compression method which have increased the bioavailability of Bilastine and improved the patient compliance in case of paediatric, geriatric and bedridden patients. The study also revealed the effectiveness of natural superdisintegrants like dehydrated banana powder which has given comparatively good results as of synthetic superdisintegrants.

Conventional dosage forms are pioneer of drug delivery systems. The most widely used and accepted route is oral administration. Oral dosage forms are widely used due to their ease of self-administration and low cost when compared with other dosage forms. It is however associated with some drawbacks such as dysphagia (difficulty in swallowing), low bioavailability and delayed onset of action. In order to overcome these issues researchers have developed orodispersible tablets an innovative and unique drug delivery system which is quickly gaining a lot of attention in the research field.

Bilastine is a novel new second generation antihistamine that is highly selective for the H_1 histamine receptor and have no affinity for muscarinic, serotonergic, dopaminergic and noradrenergic receptors. After oral administration, the distribution of Bilastine in the brain is limited. Hence unwanted side effects are avoided. Bilastine is approved for the symptomatic treatment of allergic rhinitis (AR) and chronic urticaria (CU).

It shows biological half-life of 14.5 hrs and bioavailability of 61%, it is having low solubility, so by super disintegrants the solubility is improved there by drug release. The main aim of this study is to develop and characterize orodispersible tablets of Bilastine which disintegrate in the oral cavity in a matter of second without need of water when placed upon tongue, so that it improves the patient acceptance and compliance for those having difficulty in swallowing. Bioavailability of the drug is enhanced due to absorption from mouth (Pregastric absorption) and also due to ready availability of the dosage form in the form of nearly solution or suspension at the site of action leading to quick onset of pharmacological action.

Nine formulations were prepared by direct compression method using varying concentration and combination of both synthetic and natural superdisintegrants namely Crospovidone, Sodium starch glycolate & Dehydrated banana powder and the formulations are designated as F1 – F9. F1& F2 contains Crospovidone (3% & 4%), F3 & F4 contains Sodium starch glycolate (3% & 4%), F5 & F6 contains Dehydrated banana powder (3% & 4%), F7 contains Crospovidone (2%) and sodium starch glycolate (2%), F8 contains Crospovidone (2%) and

Dehydrated banana powder (2%), F9 contains Sodium starch glycolate (2%) and Dehydrated banana powder (2%) respectively. The other excipients used were Mannitol and Microcrystalline cellulose as diluents, Magnesium stearate and talc as glidants and lubricants.

The identification characteristics of drug like melting point, solubility and UV analysis of Bilastine were performed. The absorption maxima of Bilastine in 0.1N HCl was found to be 278nm. The FTIR spectra revealed that, excipients used were compatible with the drug.

The prepared orodispersible tablets were evaluated for different precompression and postcompression parameters. The precompression parameters of all the formulations (F1-F9) were observed and the results were within the limits showing excellent & good flow properties.

The formulated tablets showed compliance for various physiochemical parameters viz. Weight variation, hardness, friability, wetting time, water absorption ratio, *Invitro* disintegration time, *Invitro* dispersion time, drug content and Invitro % drug release.

The drug content of all the formulations (F1-F9) were within acceptable range which ensured uniformity of the dose in the formulations.

Based on drug release, disintegration time and wetting studies, although all formulations (F1-F9) gave good results, it can be concluded that the formulation (F8) containing combination of Crospovidone (2%) and Dehydrated banana powder (2%) was identified as ideal and better formulation, because the water absorption ratio of the optimized formulation F8 was found to be 99.76 ± 0.251% with shorter wetting time of 12.26 ± 0.208 seconds and *Invitro* disintegration time of 7.55 ± 0.406 seconds. *Invitro* % drug release of the optimized formulation (F8) was found to be 95.48 ± 0.804 % at the end of 30 minutes, which was higher than the other formulations.

The kinetic drug release studies based on Korsmeyer peppas “n value” revealed that all the formulation that is F1-F9 followed Super case II transport mechanism for drug release.

Comparison of optimized formulation(F8) with conventional marketed product is done and the optimized formulation showed better release within 30minutes as compared to the marketed product. The drawbacks of the conventional dosage forms of Bilastine can be minimized by Bilastine Orodispersible tablets. The optimized formulation F8 was subjected to stability study for 3 months as per ICH guidelines. After 3 months there was no significant changes in the physical appearance, physicochemical parameters and *in-vitro* drug release, confirming the stability of the formulation F8.

Overall, it is understood that the superdisintegrants used had significant influence on the disintegration time which in turn have increased the drug release profile of the dosage form. Hence Bilastine can be formulated as orodispersible tablets where the bioavailability of the drug can be improved.

FURTHER AVENUES FOR EXPLORATION:

- Apart from dehydrated banana powder other natural superdisintegrants can be used and the disintegration and drug release profile can be compared.
- Long term stability studies can be carried out.
- The optimized formulation F8 should be evaluated periodically for reproducible results, so that it can be subjected to *invivo* studies.
- *Invivo* studies can be performed for better prediction. *Invivo Invitro* correlation can be done, since the *invivo* conditions have been mimicked.

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