

Long Term Stability Study of Miconazole Muco-Adhesive Tablets

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الخلاصة

الثبوتية هي معرفة مقدار استقرار المنتج الصيدلاني من حيث المواصفات الكيميائية والفيزيائية ضمن ظروف خزن محددة لهذا الغرض.

يتضمن هذا البحث دراسة التغيرات الكيميائية والفيزيائية لتركيبية مختبرية لحبوب ميكونازول اللاصقة في الاغشية المخاطية لغرض الاستفادة منها في الاستخدام الموقعي. تم اختيار ثلاث نماذج مختلفة ضمن دراسة الاستقرار المعجلة لمدة 180 يوما مع حرارة ورطوبة مختلفة. تم اجراء التحليل بموجب دستور الادوية الامريكي -27. تم تقدير المادة الفعالة بواسطة كروماتوغرافيا الاداء العالي والاذابة بواسطة تحاليل الطيف فوق بنفسجي.

تم استخدام المكونات التالية في تحضير الحبوب: 10 ملغم من ميكونازول اضافة الى كاربابول 934 صوديوم لوريل سلفيت، هيدروكسي ميثل سيليلوز واللاكتوز باستخدام الميثانول كمذيب عند المزج. لم يلاحظ اي تغير كيميائي او فيزيائي خلال الخزن ($p < 0.005$).

اظهرت النتائج كفاءة عالية للحبوب المصنعة من ناحية تقدير المادة الفعالة والاذابة ضمن المحددات الدستورية. كما اظهرت النتائج ان التركيبية صالحة لمدة ثلاث سنوات من تاريخ التحضير ويمكن استخدامها لغرض العلاج الموقعي. يمكن استخدام هذه التركيبية لغرض الانتاج بكميات كبير وبسهولة.

Abstract:

Stability is the ability of a drug substance or drug product to remain within established specifications to maintain its identity, strength, quality, and purity throughout the retest or expiration dating periods. Physical, chemical data are generated as a function of time and storage conditions. The purpose of this study is design to evaluate of the stability life of Miconazole muco-adhesive tablets in experiential formula.

Tablets used in the Stability study were prepared in three different batches with same preparing percentages. Long-term testing was cover a 180 days duration for three different batches at the time of study. Prepared tablets were storied under conditions of high relative humidity and temperatures that applies particularly to solid stability tests. The prepared samples were analyzed according USP 27 methods of analysis. Assays were performed by HPLC while the dissolution was performed by UV analysis.

The assays, dissolutions and disintegration values predicated stable formula under long term stability study conditions. These results had shown non-significant changes ($p>0.05$) for assay and disintegration over 3 years.

This formula provided successful distribution of Miconazole in muco-adhesive tablet for mass production. This formula could be achieved for oral disease with high efficiency.

Introduction:

In recent years significant interest has been shown in development of novel bio-adhesive dosage forms for mucosal delivery of drugs that attempt to overcome the required criteria^[1]. A bio-ad-hesive dosage form necessitates the use of mucoa-dhesive polymers to adhere to mucosa for significant period of time^[2]. High molecular weight polymers are generally used for bio-adhesion, hydrogen bonding due to hydrophilic groups such as $-\text{COOH}$ or $-\text{OH}$ plays an important role in bio-adhesion^[3].

Miconazole, an antifungal of the azole family that acts by the inhibiting ergosterol synthesis. This drug is marketed worldwide and is indicated for buccal or oesophageal candidiasis infections. It has well established tolerance and efficacy profiles^[4]. Miconazole has broad spectrum of activity against different species of candida show high or medium sensitivity with minimum inhibitory concentration (MIC) of between 1-10 $\mu\text{g/ml}$ for *C. albicans* and less than $\leq 1 \mu\text{g/ml}$ for *C. tropicalis* and *C. krusei*^[5,6]. A study in vitro indicating antimicrobial synergism of miconazole and benzoyl peroxide against *Staphylococcus* spp. and *Propionibacterium acnes*^[7].

Ramana et. al, develop bioad-ahesive drug delivery tablets containing metoprolol to ensure satisfactory drug release during dissolution and to avoid first pass metabolism and prolong duration of action in oral cavity by using mucoadhesive polymers like carbopol-934, hydroxymethylcellulose, n-hydroxyetyhylcellulose, and Na carboxymethylcellulose^[8].

Stability is defined as the capacity of a drug substance or a drug product to remain within specifications established to ensure its identity, strength, quality, and purity throughout the rest period or expiration dating period as appropriate^[9] according to the long duration of room temperature shelf lives

(age up to several years). Stability test are often performed under stressed conditions (e.g., elevated temperatures) to accelerate the degradation process^[10].

In rational design and evaluation of dosage form for drugs the stability of components considered as the major criterion in determining their stability^[11].

Several forms of instability can occur, either, there may be chemical degradation of the drug leading to substantial lowering of the quantity of therapeutic agent in the dosage form, or degradation of active drug, there may be chemical degradation of the drug so substantial lowering of the quantity of therapeutic agent in the dosage form.

The aim of this study is the evaluation the stability life of miconazole muco-adhesive tablets in experiential formula for dental application. Especially, no similar study was reported to the time of publishing this research concern with formulation or stability of Miconazole mucoadhesive tablets.

Materials and methods:

Twenty tablets were weighed individually and the average weight was determined. Percentage deviation was calculated and checked for weight variation. Thickness was measured using vernier calipers. Samples were prepared in three different batches. The ingredients of the prepared tablets were listed in table -1. The HPLC analysis method was obtained from the USP -27 for assays and dissolution analysis^[18]. The HPLC method was achieved by dissolving the powder of one tab in chloroform than injected into the HPLC system which equipped with 4.6 mm X 25 cm L7 column with low rate of 1.2 ml/ min. The Mobile phase was degassed mixture of n-Hexane, chloroform, methanol and ammonium hydroxide (60:30:10:1). Detection was recorded at 230 nm^[9, 12].

Results:

Table-1, represent the composition of tablets. Initial parameters for the prepared tablets are listed in table- 2. All collected data were in the accepted limits. Table-3, represents the assays of tablets at different storage temperatures and humidity in period of 180 days. Collected results predicted non significant changes of the Miconazole with time.

The evaluations of the physicochemical properties were listed in table-3. The collected data shows no changes in color, hardness, identification, related substances, or assay of the active ingredient. The changes of assays of the prepared tablets are listed in table-4.

Chemical compounds	Weight in mg.
Miconazole	10.00
Carbapol 934	185.00
Sodium lauryl sulphate	16.20
Hydroxypropylmethylcellulose	80.60
Lactose monohydrate	67.30
Sucrose	3.40
Magnesium stearate	2.50
mint flavour	0.01
Yellow colour/ Index No. 18965	0.01
Total weight	365.02

Table-1: The chemical composition of the muco-adhesive Miconazole 10 mg tablets

Test	Result
Shape	Circular biconvex
Color	Yellow
Related substance	-
Identification	+
Wt. variation	2.245
Disintegration	2.33 mins
Dissolution	88.22 %
% Assay	108.630

Table 2: Initial parameters of Muco-adhesive Miconazole tablets

Where: (+) Represents response of miconazole detection in the HPLC system
 (-) Represents no response of miconazole detection in the HPLC system

Conditions	Assay	Color	Related substance	Hardness Kg/mm²	Identification
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Table-3: Physicochemical properties of muco-adhesive Miconazole tablets

Conditions	30 Days	60 Days	90 Days	120 Days	150 Days	180 Days
R.T. $\pm 2^{\circ}\text{C}$, 35 % RH $\pm 5\%$	107.65 4	106.44 1	105.35 4	104.97 0	104.87 0	104.61 0
40 $^{\circ}\text{C} \pm 2^{\circ}\text{C}$, 40 % RH $\pm 5\%$	107.64 5	106.42 5	104.92 5	104..8 60	104.68 3	104.52 8
50 $^{\circ}\text{C} \pm 2^{\circ}\text{C}$, 65 % RH $\pm 5\%$	107.58 1	106.40 8	104.88 4	104.77 9	104.64 8	104.50 4
60 $^{\circ}\text{C} \pm 2^{\circ}\text{C}$, 75 % RH $\pm 5\%$	107.48 8	106.07 2	104.76 7	104.66 5	104.55 3	104.02 8

Table-4: Stability data for Miconazole muco-adhesive tablets

Where: **R.T.** Is the room temperature
RH the relative humidity

Discussion:

The tablets used in this study have been prepared in three different batches with the same compositions percentages for accurate and active monitoring. The storage conditions were preformed according ICH conditions.⁽²¹⁾ The selection of ICH condition was because the drastic condition that could achieve on tablets stability and this could help us for monitoring any changes in the active ingredients during storage in pharmacies or hospitals^[22].

The weight variation of the studied tablet was found 2.245 %, this results predicts that the manufacturing tablets were within the limits. The initial assay was 108.630 (zero time storage).

The collected results showed efficiency of mixing and strong distribution of the Miconazole in the investigated tablets as well as suitability of the preparation formula for Miconazole. However, the assays were with the accepted limits of the United States pharmacopoeia^[17].

The preparation of the tablets have achieved by two steps: the first direct mixing of Miconazole, carbapol, sodium lauryl sulphate, carboxymethylcellulose lactose and magnesium stearate in 25 ml of ethanol with continues mixing for 25 minutes until removing of the ethanol the second step included the dissolve of sucrose with mint flavour and yellow colour. Mixing of two mixtures with sieving in 25- μm sieves to remove any aggregation that could formed during preparation steps^[15, 16]. Lauryl sulphate provided efficiency of release of the Miconazole from tablet matrix. The preparation was containers for stability study. Sodium lurylsulphate were used in this formula because of its antiseptic properties^[12, 17].

HPLC provided useful monitoring of Miconazole in the tablets. All obtain chromatograms showed base line separation without any fragments or abnormal

peak with complete matching with the corresponding standards^[17]. These results predicted no related substances were achieved during storage periods. However, the assays of the three batch showed non significant changes ($p > 0.05$) of the stored tablets.

Dissolution result provided information about the release of the active substance (Miconazole). The dissolution value was 88.22 which comply with USP -27. The disintegration of the prepared tabs was 2.33 mins which also comply with the USP-27.

In conclusion: the reported formula is very effective for manufacturing Miconazole tablets in mass products. The prepared tablets were very stable for hot and humidity weather. HPLC is very potential tools for monitoring of the Miconazole in muco-adhesive tablets; we recommended strongly using muco-adhesive Miconazole tablets in dentistry treatments.

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