Preparation and Evaluation of Sublingual Tablet of Ketoconazole

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Abstract

The objective of the study is to develop ketoconazole sublingual tablets. KTZ is an antifungal medication that is used to treat fungal infections. The direct compression approach was used to make ketoconazole sublingual tablets. Some of the substances are utilized in the manufacturing of sublingual tablets. SSG (sodium starch glycolate), MCC (microcrystalline cellulose), talc, Mannitol, M S (magnesium stearate), and sodium saccharine are among the components. The variation content of Microcrystalline, cellulose, magnesium stearate, and sodium starch glycolate were tested using a 23 factorial design. The varying concentration quantities of MCC, magnesium stearate, and SSG exhibit the distinct formulation results. Various evaluation tests, such as in-vitro disintegration time, in-vitro dispersion time, wetting time, and in-vitro drug release research, weight variation technique, thickness, friability, wetting time, water absorption time, and other methods, are used for the analysis of tablets. These studies reveals that the KTZ sublingual tablets have the optimum composition. According to their in-vitro drug release, the formulation F5 has been determined to be the optimal formulation. In-vitro drug release was reported to be 99.49%.Increased concentrations of SSG, which work as superdisintegrants in the formulation, causing in-vitro releases. Various approaches are used to calculate drug release kinetics.

Keywords: *Sublingual route, Oral Thrush, Ketoconazole (KTZ), Sodium Starch Glycolate (SSG), in-vitro disintegration time, in-vitro dispersion time, wetting time, and in-vitro drug release, weight variation technique, thickness, friability, wetting time, water absorption.*

Introduction

The onset of pharmacological effect of the drug is ensured when it is delivered this way. Infants who have difficulty swallowing, and elderly people who are mentally disturbed (Ishikawa T.et.al 2001). The drug is absorbed through this route based on the permeability of the mucosal membrane (Squier CA .et.al). The drug is readily absorbed into the veins observable under the buccal mucosa, and ultimately into the bloodstream (NarangN.et.al 2011). The small amount of saliva required for the tablet to dissolve in the oral cavity is sufficient. Sublingual drug absorption is fast and has a rapid onset of action (Patil VA.et.al 2014). In most cases, sublingual retention is quick in real life, but it also has a short duration. The basic system for assimilation of drugs into the oral mucosa via detachable distribution on lipoid layer (R.P Walton.et.al). Sublingual assimilation of the drug is 3 to 10 times more than oral absorption and is only accomplished through hypodermal infusion. A minimal amount of saliva is necessary to trigger tablet degradation in the oral cavity for this purpose (Kurosaki Y.et.al1991). Sublingual medications were developed for a variety of headache symptoms (which requires a quick start of exercise) and dysfunctional behavior (which demands subject consistency to unending symptoms, such as discouragement). Oral mucosal medication administration is an optional strategy of basic drug administration that has a few advantages over both infuse capable and enteral approaches (Birudaraj J.et.al 2005) Drug maintained through the oral mucosa enters the basic diffusion directly, passing through the gastrointestinal tract and first pass Metabolism in the liver, due to the unusual vascularization of the oral mucosa. This leads in a more comfortable and advantageous conveyance course than the intravenous course in the rapid onset of exercise for specific drugs. All medications not administered through this route are dependent on the oral mucosa and pharmacological characteristics. (H. Zhag, J. Zhag, et al., 2002).

ADVANTAGES

1. Initiation of action in a short period of time
2. The drug is protected from metabolism, which is carried out by a digestive enzyme.
3. It improves patient compliance.
4. Bypass the drug's first-pass hepatic metabolism.
5. It can be used in an emergency.

DISADVANTAGES

1. Possibilities of interacting while eating, drinking food, and other activities.
2. Doesn't function as quickly as parental formulations.
3. Cannot be used if the subject is recalcitrant or asleep.
4. Unsuitable for long-term release
5. The biggest issue is the drug's bitter taste

SUBLINGUAL GLAND

The salivary bodies, also known as sublingual bodies, are found beneath the tongue in the mouth. These organs create mucin and contribute in the formation of saliva. The interior of

the mouth is not greased up as a result of salivation emissions, which is important for biting and gulping food. Because of the emphasis of grease and restrictions, sublingual organs cannot be discounted (Singh M.et.al 2012). The texture becomes deceptive and gulping becomes difficult when spit is mixed with food to aid in biting. The nutrients can easily flow into the neck and on to the tract that leads to the abdomen due to the salivation component. These organs, along with the availability of oil, are important components in the development of good dental hygiene. (Kumar Bind A.et.al 2013). As the drug retention route moves from its organization site to the basic stream, assimilation is plainly on the double, corresponding to the thickness of the film layer. Sublingual mucosal thickness (100-200μm), buccal mucosal thickness (200μm), gingival mucosal thickness (250μm), and palatal mucosal thickness (500-600μm) are the several types of mucosal thickness. Because of the elevated porosity action and rich blood transmission, the sublingual course can develop a quick start of exercise, making it the best route for medicinal items with rapid conveyance and recurrence. Spit dissolves medication, allowing it to be absorbed through the mouth. (A.H. Shojaie et al., 1998).

Drugs for sublingual administration

Sublingual medication arrangement is associated to cardiovascular medicines, steroids, a few barbiturates, and substances. It has been a significant development in the administration of various supplements and minerals that can be resolved to be absorbed fundamentally and totally by strategies for this method. Sublingually consumed nutrients that avoid gastric device and liver introduction, a direct health benefits method that is explicitly essential for patients with gastrointestinal problems such as ulcers, hyperactive intestine, celiac disease, and people with negotiated assimilation, the elderly, and invalids. D. Boer et al., 1984 (AlGhananeem AM, et al., 2006). This course regulates antianginal medications like nitrites and nitrates, as well as hypertensive pharmaceuticals like nifedipine, analgesics like morphine, and bronchodilators like fenoterol.

Factors affecting the sublingual absorption (Katz M.et.al 1995)

Drug lipophilicity: Greater lipid solvency drug absorb by sublingual course.

Solubility in salivary secretion: Drug soluble in aqueous buccal fluids in addition of high lipid solubility, i.e. biphasic solubility is required for absorption

pH and pKa of the saliva: since saliva pH 6.8, this pH supports retention of medicina l products that remain unionized. In addition, the retention of medicinal products by or al mucosa occurs; pKa is more prominent than 2 for corrosive and less than 10 for bas e medicinal products.

Oral mucosal binding: Systemic drug availability poor with oral mucosa

Oral epithelium quantity: As the sublingual epithelium density is 100-200 μm lower when compared to buccal density. As a result, the assimilation of medicines faster due to slimmer epithelium and, in addition, flooding of medication in a shorter salivation quantity.

Coefficient of partitioning oil to water:

mixtures with large coefficients of the oil to water section are ingested quickly. Oilwat er parcel coefficient range 40-2000 considered ideal sublingual intake of medicines.

METHODS

DRUD RELATED STUDIES

Melting Point Determination

Ketoconazole melting point determined by digital melting device. And recorded, compared with reference literature value.

UV Spectrophotometry

10mg Ketoconazole was dissolved in dichloromethane and scanned in the range of 200-400nm, spectrum mode λ_{max} was recorded and compared with literature value.

CALIBRATION CURVE

Preparation of standard plot in phosphate buffer pH-6.8

10 mg Ketoconazole was correctly measure and place in hundred ml volumetric flask .few amount phosphate buffer mix until the complete dissolve and make up the volume until 100 ml help of phosphate buffer pH6.8.Standard stock solution thus obtained was the serially diluted by phosphate buffer pH6.8get to 10-60, µg/ml of KTZ solution. Abs of the sample determined using phosphate buffer pH6.8 as blank. The absorbance value was plotted against concentration (µg/ml) to obtain the standard calibration cure.

VALIDATION OF ANALYATICAL METHOD

The analytical method was validated according to USP requirements for assays in category 1 and ICH Q2A guidelines for assays in category 2. For absorbance (y) vs concentration (x) of KTZ in the range of 1-6g/ml, the linearity of the calibration curve was evaluated. The method's accuracy was confirmed by making a solution of known KTZ concentration and comparing the average measured concentration to the nominal concentration, reported as a percentage recovery. Samples were tested three times inside the day to determine the method's intra-day precision. The relative standard deviation (R.S.D) of measured concentration at each sample was used to assess precision. The calibration curves obtained in phosphate buffer pH6.8 were used to validate the analytical technique.

Table1-Formulation composition of Ketoconazole sublingual tablet

Formulation Code	Drug	Sodium starch glycolate	Micro crystalline cellulose	Magnesium stearate	Talc	Mannitol	Sodium saccharine
KST I	200	12	80	12	20	64	12
KST II	200	12	80	20	20	56	12
KST III	200	12	120	12	20	24	12
KST IV	200	20	120	12	20	16	12
KST V	200	20	80	12	20	56	12
KST VI	200	20	80	20	20	48	12
KST VII	200	12	120	20	20	16	12
KST VIII	200	20	120	20	20	8	12

Preparation of sublingual tablet of ketoconazole

Using various excipients, ketoconazole sublingual tablets formulated by direct compression. MCC (binding agent), mannitol (diluents), saccharine sodium (sweetener) and SSG (super disintegrate) excipients. Given table shows compositions of different formulations. All components of KTZ sublingual tablets were weighed and blended with pestle in mortar. The tablet punching machine then slightly compressed the blended material. The overall weight of the formulation was maintained at 400 mg. (Kumar M Karan et.al**)**

RESULT AND DISCUSSION

DRUG IDENTIFICATION TESTS

Melting point Determination

Melting point of KTZ was found 145^0c-147^0c which complies with the literature value of 146^0c indicating the identify and purity of drug sample (Lewis .R.J.S.R)

UV Spectrophotometry

UV Spectrophotometry study was carried out for the λ_{max} value of the ketoconazole in the phosphate buffer pH6.8. The λ_{max} of the KTZ was found 225nm. (U.S.P 2006)

FTIR Spectrophotometry

Compatibility study of drug and ingredients was performed by FT-IR technique. (FT-IR-Spectrum-2, Perkin). The IR spectra were indicated no interactions are present between the ketoconazole and formulation other excipients such as, MCC, Magnesium stearate, SSG and others. Ketoconazole (KTZ) and other excipients show the peak in the range 400-4000cm^{-1}. Peak 1647cm^{-1}due to stretching of C=N group. Peak 2964cm^{-1} show the stretching of the C-H group and peak 981cm^{-1} indicate the vibration of C-C stretching and C-O-C vibration are indentified at peak 1051cm^{-1}. Peak at 985cm^{-1} and 3221cm^{-1}were expected of C-C and O-H asymmetric stretching of MCC. Peak at 1157cm^{-1} and 3280cm^{-1} indicate the C-O-C and C-H groups. Peak at the 1658cm^{-1} and 3392cm^{-1} shown the vibration of C=O and O-H groups. Peak at 1101$cm^{-1}$are shows due to the C-C stretching which are present in the SSG. In the spectral studies no change are observe in peak of the KTZ excipients mixture. Same peak of the KTZ and excipients (MCC, SSG) was found in FT-IR spectra. The studies of FT-IR spectrum of the KTZ and other excipients shown the no interactions are presented in the mixture of the formulation.

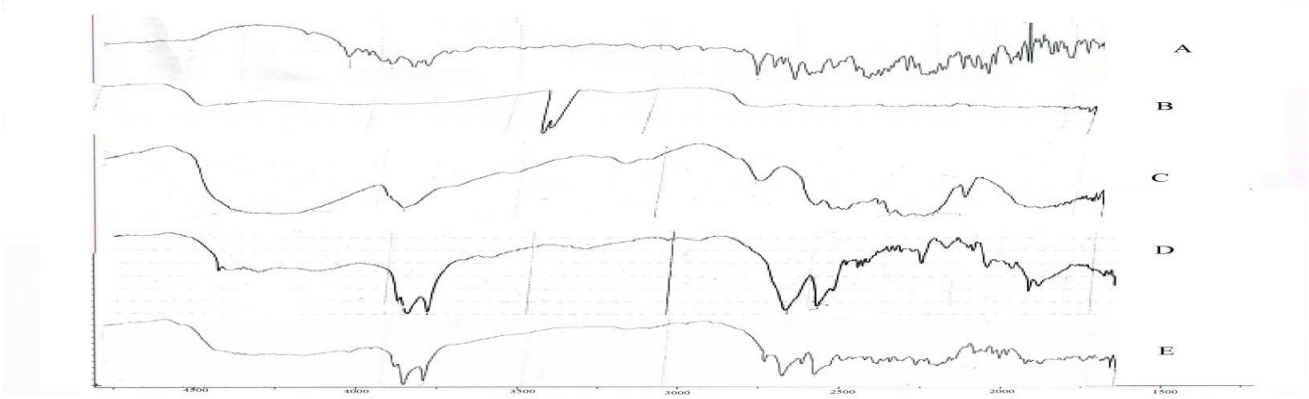

Figure 1: FT-IR Spectra Ketoconazole (A), Sodium starch glycolate (B), microcrystalline cellulose (C), Magnesium Stearate (D), Mixture (E)

VALIDATION OF ASSAY METHOD

Linearity

The calibration curve of ketoconazole were linear in the range 10-60µg/ml. Using least square regression, the calibration curve of absorbance against concentration of ketoconazole (µg/ml) was y= 0.016X+0.025 with r^2= 0.999 in phosphate buffer, pH6.8. The LOD 2.35µg/ml and LOQ 7.14 µg/ml in phosphate buffer, pH6.8, respectively.

Precision and accuracy

The value of %RSD between calibration curves within day at different time point was found to be less than two, which showed the intraday precision between calibration curves. The data indicated that he drug in phosphate buffer pH6.8 was stable during the entire study period and the analytical method used in reliable. The summaries of intra-day and interday precision/accuracy are listed in table 2.

Percentage Recovery

The mean of prevent recoveries in media are given in table. Percent recovery of ketoconazole for the calibration in phosphate buffer pH6.8 was in the range 103.12- 106.25.

Table 2-Accuracy and precision of the assay

Parameter	Phosphate buffer, pH6.8
Accuracy (% recovery)	103.12- 106.25
Intraday precision (% RSD)	>2
Interday precision (%RSD)	>2
LOD µg/ml	2.35
LOQ µg/ml	7.14
r^2	0.999

Preparation of sublingual tablets

Sublingual tablet of ketoconazole were prepared and evaluated for various parameters like hardness, weight variation, thickness, drug content, water absorption ratio, wetting time, in vitro dispersion time, in vitro drug release , friability, in vitro disintegration.

In-vitro drug release

USP Pharmacopoeia apparatus-II use for this study. In-vitro releases examine the release of drug under specific environments. In-vitro drug release of formulation ranged 99.49 – 3.15% at the end of 2 to 30 min. Higher amount of drug released was 99.49% observed in case of F5. These results showed that when concentration of sodium starch glycolate increased, increased percent drug release. The result of same found in all formulation in which F5 containing high amount of sodium starch glycolate having higher percent of drug release. (Tas c.et.al 2011)

Table 3 - % drug release of sublingual tablets of ketoconazole (F1-F8)

S.no.	2min %release	5 min %release	10min %release	15min %release	20min %release	30min %release
1	2.78	36.6	66.21	71.85	74.79	79.19
2	5.48	45.89	54.16	61.58	68.38	71.93
3	53.15	56.71	59.10	60.49	63.58	64.67
4	7.802	43.95	48.43	49.98	50.83	51.92
5	3.159	42.87	70.06	81.04	84.06	99.49
6	39.32	72.78	79.12	80.74	81.36	84.45
7	13.13	38.71	50.37	55.16	57.33	61.34
8	49.60	61.73	64.51	66.44	67.22	70.46

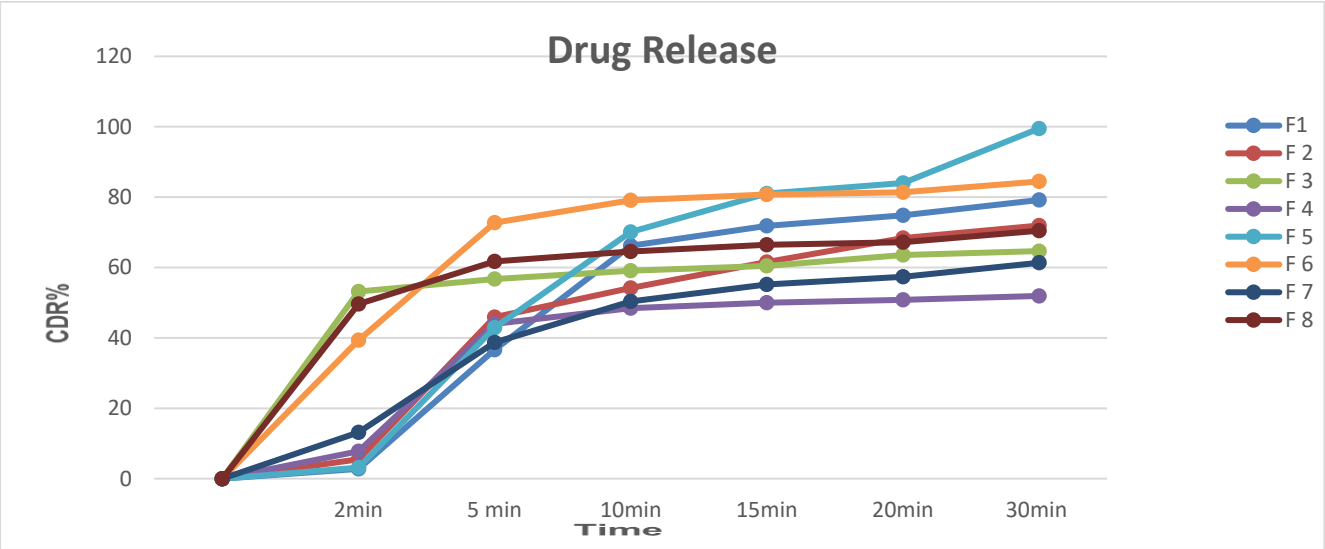

Figure 2 -In-vitro drug release profiles of ketoconazole sublingual tablets (F1-F8) in saliva

Drug release kinetic of tablets

First order, zero order, Higuchi, and Peppas model conducted drug release kinetic of tablets. The zero order, Peppas, first order, and Higuchi model determine coefficient (r^2) through curve. Formulation F1, F4 follow the Peppas kinetics and Formulation F2, F3, F5- F8 follows the Higuchi kinetics with maximum r^2 value.

Table 4 - Release Kinetic models of the formulations (F1-F8)

Formulation code	%CDR	Best fit Model	r^2 value
F1	79.19	Peppas	0.889
F2	71.93	Higuchi	0.892
F3	64.67	Higuchi	0.646
F4	51.92	Peppas	0.787
F5	99.49	Higuchi	0.929
F6	84.45	Higuchi	0.792

F7	61.34	Higuchi	0.911
F8	70.46	Higuchi	0.709

Accelerated Stability studies

Accelerated stability studies according ICH guidelines Q1A (R2) were performed at temp 40 ± 2^0c and humidity 75±5% RH. Sample withdrawn at 0 -3 months. Duration of time check the physical properties such as color, surface pH, weight loss. Zero time samples were used as controls (Bali et.al 2010). No variations observe during after storage. Formulations found to stable.

CONCLUSION

Sublingual tablets of ketoconazole were formulated for the sublingual application. According all those evaluation parameters formulation (F5) show better drug release. Because in formulation F5 increases the concentration of the superdisintegrants. Formulation F5 shows the 99.49% release of the drug in 30 min. Formulation stable at temp 40 ± 2^0c and 75±5% RH.

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