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Comparative in Vitro Evalution of Five Different Brands of Ketoconazole Tablets.

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ABSTRACT
The qualities of five different brands of ketoconazole tablets commercially available inIndia were assessed. The weight uniformity, hardness, friability, disintegration time, absolute drug content and dissolution rate of the were determined using official or standard methods, as applicable. The five brands passed the uniformity of weight test with the range of 0.351 – 0.676 g, hardness test with a range of 4.00 – 7.70 kgF, friability test with a range of 0.146 – 0.268 % and absolute drug content with a range of 98.82 – 107.02 % andconformed to the pharmacopoeias specifications. However, all the tested brands had poor dissolution profiles. None of the brands was bioequivalent with the innovator brand.

I. INTRODUCTION:

Ketoconazole, is a class of Imidazole and sold under the brand name Nizoral. Its IUPAC name is **1**-[4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4 yl]methoxy]phenyl]piperazin-1-yl]ethanone. It is used as an antiandrogen and antifungal medication for the treatment of number of fungal infections such as cutaneous candidiasis, pityriasis, dandruff, and seborrheic dermatitis. The chemical structure of ketoconazole is showed in fig 1

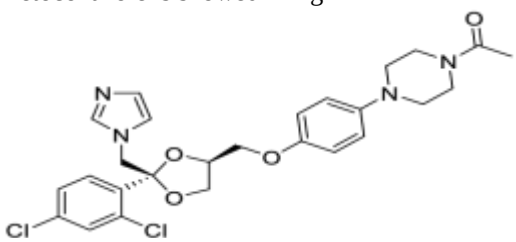

Fig. 1 : Chemical structure of Ketoconazole

II. MATERIAL AND METHOD:

a) Uniformity of weight test

Five different tablet are selected from each brand, were weighed individually and collectively using an analytical weighing balance. The mean weights, as well as the deviations (standard error of mean), of the individual tablets from the mean weight were calculated.

b) Hardness test (crushing strength)

Five tablets were randomly selected from each brand and their hardness determined using the Mosanto Stokes hardness tester. Each tablet was placed between the spindle and anvil and pressure applied by turning the knob sufficiently to hold the tablet in position. The pointer on the scale was adjusted to zero reading and pressure gradually and steadily increased until the tablet breaks. The pointer reading from the scale was taken as the pressure required to break the tablet. The above procedure was repeated for the five different brands of ketoconazole tablets.

c) Disintegration: Disintegration of ketoconazole tablets occurred within 5 minutes in each buffer solution and was unaffected by pH. At pH 2 and 3and stirred at 500 rpm at 37 degrees C, dissolution of ketoconazole was greater than 85% complete after five minutes**.** According to IP the disintegration time of tablet is 15 minute.

d) Dissolution: The veego tablet dissolution apparatus was used. The tablet was placed in a wire-mesh basket suspended in a dissolution medium of 500 ml of 0.1N HCl maintained at 37 ± 1 O C in a water bath. The wire-mesh basket was rotated at a speed of 50 rpm and the experiment allowed to run for 60 minutes for each tablet tested.

e) Friability test: Five tablets from each brand of ketoconazole tablets were de-dusted, weighed and subjected to vibration and shock in a Roche Friabilator rotating at 25 rpm for 4 minutes

$$\% \text{ weight loss} = \frac{W2-W1}{W1:} \times 100$$

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III. RESULT AND DISCUSSION

The ketoconazole tablets were all circular in shape and had colours that varied between white and off white color. The identity profiles of the different brands of ketoconazole tablets marketed in Nigeria are presented in While three of the brands (representing 60 %) were imported from Asia, the other two brands (representing 40 %) were imports from Europe. None of the brands was manufactured in Nigeria. This implies that the indigenous pharmaceutical industries in Nigeria are yet to meet up to the challenges of tableting some of the needed drug products. The results of the quality control parameters of the different brands of ketoconazole tablets are shown in relevant tables

The five brands of ketoconazole tablets passed the weight uniformity test since they all had low coefficient of variation in line with the specifications for compressed uncoated tablets (Lund, 1994). Tablet weight variations are attributed to various formulation factors which are dependent on the manufacturer. The hardness and friability tests results revealed that the five brands complied with the crushing strength (2.0 - 7.9 kg) and friability (0.8 – 1.0 % loss in weight) specifications (British Pharmacopoeia, 1998; Ofoefule, 2002; USP, 2005). According to Ofoefule, 2002, friability is a measure of the resistance of tablets and granules formulations of pharmaceutical products to abrasion. The results confirm that the ketoconazole brands could withstand the stress of handling and transportation.

Table:1 Uniformity of weight test

Name	Weight
Ketofly 200mg	0.4 gm
Ketocip 200mg	0.2 gm
Nizol 200mg	1.1 gm
Ketrich 200mg	0.3 gm
Ketomac 200mg	0.2 gm

Table:2 Values of disintegration test of different brands of Ketoconazole

Name	Times
Ketofly 200mg	2.0 minute.
Ketocip 200mg	1.45 minute.
Ketrich 200mg	1.55 minute.
Nizol	1.17 minute.
Ketomac	2.1 minute.

Table:3 Values of dissolution test of different brands of Ketoconazole

Name	Solution	Temperature	Time
Ketofly 200mg	Buffer	37 ± 2^{o} c	17.30 minutes.
Ketocip 200mg	Buffer	37 ± 2^{o} c	20 minutes.
Nizole 200mg	Buffer	37 ± 2^{o} c	18.55 minutes.
Ketrich 200mg	Buffer	37 ± 2^{o} c	19 minutes.
Ketomac 200mg	Buffer	37 ± 2^{o} c	16 minutes.

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Table: 4 Friability test

Name	Initial weight (w1)	Final weight(w2)	Friability %
Ketofly 200 mg	0.3 gm	0.2 gm	33.33 **%**
Ketocip 200mg	0.6 gm	0.4 gm	33.34 **%**
Nizol 200mg	0.4 gm	0.3 gm	25 **%**
Ketrich 200mg	0.5 gm	0.4 gm	20 **%**
Ketomac 200mg	1 gm	0.7 gm	30 **%**

The results of the disintegration time (DT) test showed that the five brands of ketoconazole tablets had disintegration times ranging between 0.49 and 8.51 minutes. The test tablets are considered to have satisfactory DT values since the obtained values are in agreement with the mean disintegration time specification for uncoated tablets which should not exceed 15 minutes (British Pharmacopoeia, 2004). In the context of tablet technology, disintegration implies penetration of the tablet by an aqueous liquid, disruption of internal bonds and subsequent breakdown of the tablet. Factors that can affect disintegration time of the tablets include the rate at which a liquid penetrates a tablet, the nature and method of incorporation of lubricants, the action of disintegrates, and the degree of compaction and reduction of inter-particle bond strength in the presence of water (Rawlins, 1970). All the brands of ketoconazole tablets had active ingredient which fell within the USP, 2004 acceptable limit of 90 - 110 %. The chemical qualities of ketoconazole tablets marketed in Nigeria were assured and are independent of the drug´s country of origin. The dissolution profile of the different brands of ketoconazole tablets revealed poor drug release. In vitro dissolution studies help in predicting biological drug release pattern in terms of rate and extent of release. No universal dissolution tests has been designed that gives the same rank order for in vitro dissolution and in vivo bioavailability.

Similarly, the five brands of ketoconazole tablets complied with the friability test specification of 0.8 – 1.0% loss in weight for pharmaceutical products, and that no tablet caps, laminates, or breaks up in the course of the test (Ofoefule, 2002; USP, 2005; BP, 1998).

IV. CONCLUSION

The present study showed that the weight uniformity, hardness, friability, disintegration time, absolute drug content, melting point, dissolution rate and antifungal activity of the five brands were determined using official method as applicable. The five brands passed the uniformity of weight test with the range of 0.351-0.676g, hardness test with range of 4.00-7-70kgF, friability test with range of 0.146-0.268%, absolute drug content a range of 98.82-107.02% and melting point tests and conformed with pharmacopeia specifications. However, all the tested brands failed the dissolution test requirements. With the exception of brand E, the other brands A,B,C and D showed appreciable activity against the test organism candida albican and Apergillus niger. Brand C and D, at the concentration of 20mg/ml exhibited identical activity against Aspergillus niger, Brands A, B and D inhibited C. albicans to similar extent and are therefore interchangeable with one another in the treatment of candidiasis.

REFERENCE

[1]. Piérard-Franchimont C, De Doncker P, Cauwenbergh G, Piérard GE (1998). "Ketoconazole shampoo: effect of long-term use in androgenic alopecia". Dermatology. 196 (4): 474–7. doi:10.1159/000017954. PMID 9669136. S2CID 30635892.

[2]. Piérard-Franchimont C, Goffin V, Henry F, Uhoda I, Braham C, Piérard GE (October 2002). "Nudging hair shedding by antidandruff shampoos. A comparison of 1% ketoconazole, 1% piroctone olamine and 1% zinc pyrithione formulations". International Journal of

International Journal of Pharmaceutical Research and Applications
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Cosmetic Science. 24 (5): 249–56. doi:10.1046/j.1467-2494.2002.00145.x. hdl:2268/11902. PMID 18498517.

[3]. Khandpur S, Suman M, Reddy BS (August 2002). "Comparative efficacy of various treatment regimens for androgenetic alopecia in men". The Journal of Dermatology. 29 (8): 489–98. doi:10.1111/j.1346-8138.2002.tb00314.x. PMID 12227482. S2CID 20886812.

[4]. Marks DH, Prasad S, De Souza B, Burns LJ, Senna MM (December 2019). "Topical Antiandrogen Therapies for Androgenetic Alopecia and Acne Vulgaris". Am J Clin Dermatol. 21 (2): 245–254. doi:10.1007/s40257-019-00493-z. PMID 31832993. S2CID 209331373.

[5]. "MedScape". Ectopic Cortisol Production Derived From Malignant Testicular Masses: Treatment and Management. Nature Publishing Group. Archived from the original on 13 May 2018. Retrieved 18 April 2015.

[6]. Jump up to:[a] [b] Loose DS, Kan PB, Hirst MA, Marcus RA, Feldman D (May 1983). "Ketoconazole blocks adrenal steroidogenesis by inhibiting cytochrome P450-dependent enzymes". The Journal of Clinical Investigation. 71 (5): 1495–9. doi:10.1172/JCI110903. PMC 437014. PMID 6304148.

[7]. Zelefsky MJ, Eastham JA, Sartor OA, Kantoff P (2008). DeVita VT, Lawrence TS, Rosenberg SA (eds.). Cancer: Principles & Practice of Oncology (8th ed.). Philadelphia: Lippincott Williams & Wilkins. p. 1443. ISBN 9780781772075.

[8]. Loli P, Berselli ME, Tagliaferri M (December 1986). "Use of ketoconazole in the treatment of Cushing's syndrome". The Journal of Clinical Endocrinology and Metabolism. 63 (6): 1365–71. doi:10.1210/jcem-63-6-1365. PMID 3023421.

[9]. Thompson IM (2001). "Flare Associated with LHRH-Agonist Therapy". Reviews in Urology. 3 Suppl 3: S10–4. PMC 1476081. PMID 16986003.

[10]. Jump up to:[a] [b] [c] [d] [e] [f] [g] [h] [i] "Ketoconazole tablet". DailyMed. 26 June 2018. Retrieved 5 January 2020.

[11]. Jump up to:[a] [b] [c] [d] [e] "Nizoral (Ketoconazole): Side Effects, Interactions, Warning, Dosage & Uses". RxList. Retrieved 7 April 2019.

[12]. Deepinder F, Braunstein GD (September 2012). "Drug-induced gynecomastia: an evidence-based review". Expert Opinion on Drug Safety. 11 (5): 779–95. doi:10.1517/14740338.2012.712109. PMID 22862307. S2CID 22938364.

[13]. Duret C, Daujat-Chavanieu M, Pascussi JM, Pichard-Garcia L, Balaguer P, Fabre JM, et al. (July 2006). "Ketoconazole and miconazole are antagonists of the human glucocorticoid receptor: consequences on the expression and function of the constitutive androstane receptor and the pregnane X receptor". Molecular Pharmacology. 70 (1): 329–39. doi:10.1124/mol.105.022046. PMID 16608920. S2CID 21455699.

[14]. Shaw JC (November 1996). "Antiandrogen therapy in dermatology". International Journal of Dermatology. 35 (11): 770–8. doi:10.1111/j.1365-4362.1996.tb02970.x. PMID 8915726. S2CID 39334280.

[15]. Jump up to:[a] [b] [c] [d] [e] [f] Sonino N (August 1986). "The endocrine effects of ketoconazole". Journal of Endocrinological Investigation. 9 (4): 341–7. doi:10.1007/BF03346939. PMID 3537102. S2CID 9148909.

[16]. Jump up to:[a] [b] Wheeler CJ, Keye WR, Peterson CM (2010). "Polycystic Ovary Syndrome". Reproductive Endocrinology and Infertility. pp. 147–182. doi:10.1007/978-1-4419-1436-1_11. ISBN 978-1-4419-1435-4.

[17]. Jump up to:[a] [b] [c] Drobnis EZ, Nangia AK (2017). "Antimicrobials and Male Reproduction". Advances in Experimental Medicine and Biology. 1034: 131–161. doi:10.1007/978-3-319-69535-8_10. ISBN 978-3-319-69534-1. PMID 29256130.

[18]. Feldman D (November 1986). "Ketoconazole and other imidazole derivatives as inhibitors of steroidogenesis". Endocrine Reviews. 7 (4): 409–20. doi:10.1210/edrv-7-4-409. PMID 3536461.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 361-365 www.ijprajournal.com ISSN: 2456-4494

[19]. Gal M, Orly J, Barr I, Algur N, Boldes R, Diamant YZ (May 1994). "Low dose ketoconazole attenuates serum androgen levels in patients with polycystic ovary syndrome and inhibits ovarian steroidogenesis in vitro". Fertility and Sterility. 61 (5): 823–32. doi:10.1016/S0015-0282(16)56691-6. PMID 8174717.

[20]. Jump up to:[a] [b] Lønning PE (2009). "New endocrine drugs for treatment of advanced breast cancer". Acta Oncologica. 29 (3): 379–86. doi:10.3109/02841869009090018. PMID 2194539.

[21]. Tarbit MH, Robertson WR, Lambert A (1990). "Hepatic and Endocrine Effects of Azole Antifungal Agents". Chemotherapy of Fungal Diseases. Handbook of Experimental Pharmacology. Vol. 96. pp. 205–229. doi:10.1007/978-3-642-75458-6_10. ISBN 978-3-642-75460-9. ISSN 0171-2004.

[22]. Philippaert K, Kerselaers S, Voets T, Vennekens R (April 2018). "2+-Activated Monovalent Cation-Selective Channels". SLAS Discovery. 23 (4): 341–352. doi:10.1177/2472555217748932. PMID 29316407.

[23]. Chin TW, Loeb M, Fong IW (August 1995). "Effects of an acidic beverage (Coca-Cola) on absorption of ketoconazole". Antimicrobial Agents and Chemotherapy. 39 (8): 1671–5. doi:10.1128/AAC.39.8.1671. PMC 162805. PMID 7486898.

[24]. Jump up to:[a] [b] [c] [d] [e] Elks J (14 November 2014). The Dictionary of Drugs: Chemical Data: Chemical Data, Structures and Bibliographies. Springer. pp. 720–. ISBN 978-1-4757-2085-3.

[25]. Jump up to:[a] [b] [c] [d] [e] [f] Index Nominum 2000: International Drug Directory. Taylor & Francis. 2000. pp. 586–. ISBN 978-3-88763-075-1.

[26]. Heeres J, Backx LJ, Mostmans JH, Van Cutsem J (August 1979). "Antimycotic imidazoles. part 4. Synthesis and antifungal activity of ketoconazole, a new potent orally active broad-spectrum antifungal agent". Journal of Medicinal Chemistry. 22 (8): 1003–5. doi:10.1021/jm00194a023. PMID 490531.

[27]. William Andrew Publishing (22 October 2013). Pharmaceutical Manufacturing Encyclopedia (3rd ed.). Elsevier. pp. 1997–. ISBN 978-0-8155-1856-3.

[28]. Jump up to:[a] [b] Golan DE (2008). Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy. Lippincott Williams & Wilkins. pp. 624–. ISBN 978-0-7817-8355-2.

[29]. "Ketoconazole HRA". European Medicines Agency (EMA). 17 September 2018. Retrieved 1 April 2020.

[30]. "Levoketoconazole - Strongbridge Biopharma - AdisInsight".

[31]. Fleseriu M, Castinetti F (December 2016). "Updates on the role of adrenal steroidogenesis inhibitors in Cushing's syndrome: a focus on novel therapies". Pituitary. 19 (6): 643–653. doi:10.1007/s11102-016-0742-1. PMC 5080363. PMID 27600150.

[32]. Jump up to:[a] [b] Morton IK, Hall JM (6 December 2012). Concise Dictionary of Pharmacological Agents: Properties and Synonyms. Springer Science & Business Media. pp. 159–. ISBN 978-94-011-4439-1.

[33]. Jump up to:[a] [b] [c] "Ketoconazole".

[34]. Press Release. European Medicines Agency. 26 July 2013. Archived from the original on 14 January 2014.

[35]. KuKanich B (January 2008). "A review of selected systemic antifungal drugs for use in dogs and cats". Veterinary Medicine. Archived from the original on 5 October 2013.