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Review Article

TECHNIQUES IMPLEMENTED FOR SOLUBILITY ENHANCEMENT OF KETOCONAZOLE: A REVIEW

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ABSTRACT

Ketoconazole is a member of imidazole containing compound and commonly used as a broad spectrum antifungal agent. It used for treatment or prevention of systemic fungal infections. Ketoconazole is available as cream, oral tablet and dandruff shampoo formulations. Ketoconazole has a high permeability and low solubility, its solubility in aqueous media is not sufficient for the whole dose to be dissolved in the GI fluids under normal conditions. Now a day's different techniques are available to enhance the solubility of drug like co-solvent, chemical modification of drug, the present review deals in detail about the different techniques used for the improvement of solubility of poorly water-soluble ketoconazole includes, salt and co crystal formation, β-cyclodextrins complex formation, pHadjustment, hydrogel of ketoconazole and PAMAM dendrimer.

KEYWORDS: Antifungal agent, Ketoconazole, Low Solubility, High Permeability, Salt and Cocrystal Formation.

INTRODUCTION

There are many types of fungal germs (fungi) live mainly in the soil, on food, on our skin and in other places in the environment. However, some types of fungi can grow vigorously on the surface of the body, to cause infection of the skin, nails, mouth or vagina. General mechanism of action of ketoconazole is that, they inhibit C-14α-demethylase, thus blocking the demethylation of lanosterolto ergosterol. This inhibition disrupts membrane structure and function and therefore inhibits fungal cell growth. There are several different antifungal preparations that are used to treat various fungal infections. They are as creams, shampoos, tablets, injections and pessaries. Ketoconazole is developed for the first-choice treatment of human mycotic infections. It is poorly soluble in water; it is administered either topically or by mouth. Ketoconazole (KTZ)[(±)-cis-1-acetyl-4-(4-{[2-(2,4-dichlorophenyl0-2(1H-imdazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy}phenyl)piperazine], is an imidazole derivative with a wide antifungal spectrum and possesses some antibacterial activity. It is reported to be active in the treatment of systemic blastomycosis, candidiasis, coccioidimycosis, histoplasmosis, paracoccidioidomycosis and tinea of skin and nails .Ketoconazole is classified in the Biopharmaceutics Classification Scheme (BCS) as a class IIdrug, since it has a high permeability and its solubility in aqueous media (0.087mg/l at 25°c) is not sufficient for the whole dose to be dissolved in the GI fluids under normal conditions literatures are reported that poor water solubility and wet

ability of the drug can cause problems with drug release and bioavailability in various pharmaceutical forms. Ketoconazole is best absorbed at highly acidic levels, so antacids or other causes of decreased stomach acid levels will lower the drug absorption. Absorption can be increased by taking it with an acidic beverage. It is very lipophilic and tends to accumulate in fatty tissues. There are various techniques are available to increase the solubility of poorly water-soluble Ketoconazole i.e. salt formation, co crystal formation, pro-drug, co solvency, complexation, p^Hadjustment, miceller solublization. Among the various approaches, Pharmaceutical salt and co crystal formation techniques successfully improve the dissolution and bioavailability of poorly soluble, active Pharmaceutical ingredients because it is simple, economical and advantageous. Approximately 13% of dose of Ketoconazole is excreted; 2% to 4% is unchanged drug. The major route of excreation is through the bile into the intestinal tract. Plasma elimination is biphasic with a half-life of 2 h during the first 10 h and a half-life of 8 h after 10 h. (Papneja P. et. al. 2015)

SOLUBILITY ENHANCEMENT OF KETOCONAZOLE:-

It is well known that drug efficacy can be severally limited by poor aqueous solubility, leading to low Dissolution rate and thus results in low absorption in the gastrointestinal tract after oral administration. The ability to increase aqueous solubility is thus a valuable aid to increase the efficacy for certain drugs.

I.SALT FORMATION:-

Salt formation is an example of how crystal engineering concept can be utilized to address the poor solubility problem. Salt formation is one of the common approach in modifying the physicochemical properties of a drug. Salt formation is feasible only when the API has a suitable ionizable site. Salt formation of a KTZ (very weak base API) also presents a greater risk of disproportionation. Cocrystal formation is an alternative way to modify the physicochemical properties of API's, besides salt formation. Cocrystals are a multi component molecular complex in a definite stoichiometric ratio of solids that interact through noncovalent interactions, predominantly hydrogen bonds. A large number of pharmaceutically acceptable cocrystal formers exist, which potentially increase the scope of Cocrystallization over salt formation. Cocrystallization of pharmaceutical compounds may potentially be employed with all API's, including acidic, basic, and nonionizable molecule. (Hiendrawan S. et. al. 2015)

II.SALT AND COCRYSTAL PREPARATION:-

Salt and co-crystal of KTZ were prepared by slurry conversion method. Equimolar (1:1 mole ratio)quantities of KTZ and dicarboxylic acid (oxalic acid and fumaric acid) were added in 20 ml of ethylacetate and mixed under sonication at 40^{o}C for 1 h. The resulting slurry was filtered through whatman filter paper and the resulting solid was dried at 70^{o}C for 5 h. (Hiendrawan S. et. al. 2015)

III.β-CYCLODEXTRIN COMPLEX FORMATION:-

The antifungal drug ketoconazole were prepared with β-cyclodextrin and PEG-6000 by four different methods with an intention to improve its dissolution properties. Solubility of ketoconazole improves by Sonocrystallization, Solid dispersion, Hydrotropy and Inclusion complex. In vitro release profile were evaluated and compared with standard ketoconazole. (Patela J. et. al. 2012)

1) Melt Sonocrystallization technique:-

Drug was melted in a china dish on a paraffin oil bath at 148^{o}C (the melting point of ketoconazole), the molten mass was poured in a beaker containing deionized water at 60^{o}C and the content was sonicated for 15 min with a frequency of 1.5 MHz using bath ultrasonicator. The solidified dispersed droplets were separated by filtration and dried at room temperature. (Hasnain and Nayak ;2012)

2) Solid Dispersion technique:-

Carrier (PEG6000) was dissolved in 1:1 methanol and dichloromethane using magnetic stirrer to which the drug was added and allowed to dissolve, resulting mixture was transferred into petridish and evaporation of the solvents was carried out by keeping the petridish at room temperature. Obtained mass was crushed with the blunt end of a glass rod and passed through 44 mesh sieve. (Varagunapandiyan and Gandhi ;2008)

3) Hydrotropy technique:-

Hydrotrophy technique of ketoconazole and solution was prepared in evaporable organic solvent (ethylacetate) previously saturated with distilled water in a separating funnel to which hydrotrope (tri-sodiumcitrate) solution was added. Then, the separating funnel was sealed and immersed in a constant temperature bath and kept overnight for equilibration. After this, the aqueous layer was transferred into a beaker. (Ammar H et. al.2007)

4) Inclusion Complex Formation technique:-

Solid inclusion complex of ketoconazole and β-cyclodextrin were prepared by the co-evaporation method. This technique β-cyclodextrin and ketoconazole were taken in stoichiometric ratio and kneaded thoroughly with minimum amount of water to obtain a paste. This paste was dried under vacuum pump at room temperature using phosphorus pentoxide as a drying agent. (Parve B et.al. 2014)

IV.P^H ADJUSTMENT:-

Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid)may potentially be dissolved in water by applying a p^H change. P^H adjustment can in principle be used for both oral and parenteral administration.In the stomach the p^H is around 1 to 2 and in the duodenum the $p^H$is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines. Ionizable compounds that are stable and soluble after p^H adjustment are best suited. To adjust the microenvironmental p^H (p^H_M) of the matrix to a constant lower p^Hmodifier within the formulation seems to be the effective means to obtain a uniform weakly basic drug release from matrix type dosage forms(pellets, tablet). Several organic acids, such as fumaric, citric, succinic,ascorbic, adipic, sorbic, glutaric, tartaric, and malic were used to adjust p^H. The effect of organic acids on the dissolution profile of weakly soluble drugs is influenced by many factors connected with the drug such as solubility, molecular weight, pK_B. (Steubel A et. al. 2014)

V.HYDROGEL OF KETOCONAZLE AND [poly(amidoamine)] PAMAM DENDRIMERS:-

PAMAM-NH_2 and PAMAM-OH dendrimer generation 2 and generation 3 influence on the solubility and antifungal activity of ketoconazole. The surface charge of PAMAM dendrimers strongly affect their influence on the improvement of solubility and antifungal activity of ketoconazole. For this study ketoconazole hydrogel with PAMAM dendrimer are formed and evaluate. The MIC and MFC values obtained by broth dilution method indicate that PAMAM-NH_2 dendrimers significantly (up to 16-fold)increased the antifungal activity of ketoconazole against Candida strains. Lipophilic cavities in PAMAMdendrimers and hydrophilic surface groups provide the availability to encapsulated or conjugate with many guest molecules. So far dendrimer have been employed for enhancing the solubility of drug. (Savjani K et. al. 2012)

CONCLUSION

Ketoconazole is a BCS class II drug it has low solubility but high permeability. Various methods were employed to enhance the solubility of the ketoconazole. Salt and cocrystal formation, β-cyclodextrin complex formation, pH adjustment, hydrogel of ketoconazole formation is few methods which

enhance the solubility of ketoconazole. Salt and cocrystal formation is widely used method to enhance the solubility of ketoconazole.

REFERENCES

1. Papneja P, Kataria MK, Bilandi A, Yadav S(2015), Techniques implemented for solubility and dissolution rate enhancement of ketoconazole: A review, International Journal of Institutional Pharmacy and life sciences5(1):60-61.
2. Hiendrawan S, Hartanti AW, Veriansyah B, Widjojokusumo E, Tjandrawinata RR(2015), Solubility enhancement of ketoconazole via salt and cocrystal formation, International journal of Pharmacy and Pharmaceutical sciences;7:160-61.
3. Stephenson GA, Aburub A, Wood TA (2011). Physical stability of salts of weak bases in the solid-state. Journal of Pharmaceutical Science.100:1607-17.
4. Shanpui P, Goud NR, Khandavilli UBR, Nangia A(2011). Fast dissolving curricumin cocrystals, Cryst Growth Dec .11:4135-45.
5. Wenger M, Bernstein J (2008). An alternate crystal form of gabapentin: a cocrystal with oxalic acid.Cryst Growth Dec.8:1595-8.
6. Ansari S, Arora M, Azim S, Hussain A, Kumar G, Ali R (2014), Solubility enhancement of ketoconazole by different techniques and its comparison study, American Journal of Pharmacy and Health Research.2:1-11.
7. Patela JR, Carlton RA, Needhan TE, Chichester CO, Vogt FG (2012).Preparation, structure analysis and properties of tenoxicam cocrystal.Int J Pharm.436:685-706.
8. Chaudhari PD, Uttekar PS (2009). Melt-Sonocrystallization: A novel particle engineering technique for solubility enhancement. International Journal of Pharma Tech Research.1 (1):111-120.
9. Hasnain MS, Nayak AK (2012). Solubility and dissolution enhancement of ibuprofen by solid dispersion technique using PEG 6000-pvp k 300combination carrier. Bulgarian Journal of Science Education.21 (1):118-132.
10. Varagunapandiyan N, Gandhi NN(2008). Enhancement of solubility and mass transfer coefficient through hydrotropy. International Journal of Applied Science and Engineering.6:97-110.
11. Ammar HO, Salama HA, Ghorab M, Mahmoud AA (2007). Inclusion complexation of glimepiride in dimethyl-β-cyclodextrin. Asian Journal of Pharmaceutical Science.2 (2):44-55.
12. Parve B, Shinde P, Rawat S, Rathod S, Waghmode G(2014). Solubility enhancement techniques: A Review.3:405-06.
13. Parve B, Teli B, Birajdar A (2014). Solid Dispersion: an overview on solubility enhancement of poorly water soluble drugs. Int. J. Pharma Bio Sci.5 (3):7-25.
14. Steubel A, Siepmann J, Dashevshky A, Bodmeier R (2000). pH –independent release of a weakly basic drug from water insoluble nd soluble matrix tablet. J Control Release.67:101-10.
15. Padhy KK, Swain K, Chowdary KA (2010). Influence of organic acids on drug release pattern of verapamil hydrochloride pellets. J Adv Pharma Res.1:65-73.
16. Varma MVS, Kaushal AM, Garg S (2005). Microenvironmental pH modulation in solid dosage forms influence of micro-environmental pH on the gel layer behavior and release of a basic drug from various hydrophilic matrices. J Control Release.103:499-510.
17. Bolourchian N, Dadashzadeh S(2008). PH-independent release of propranolol hydrochloride from HPMC based matrices using organic acids.DARU.16:36-142.

18. Tatavarti AS, Hoag SW (2006). Microenvironmental pH modulation based release enhancement of a weakly basic drug from hydrophilic matrices. J Pharma Sci.95:1459-68.
19. Espinoza R, Hong E, Villafuerte L (2000). Influence of admixed citric acid on the release profile of pelanserin hydrochloride from HPMC matrix tablet. Int J Pharma. 201:165-73.
20. Winnicka K, Wroblewska M, Wieczorek P, Sacha PT, Tryniszewska E(2012).Hydrogel of ketoconazole and PAMAM dendrimers: Formulation and antifungal activity, molecules,17,4612-4624.
21. Savjani KT, Gajjar AK, Savjani JK (2012), Drug Solubility: Importance and Enhancement Techniques, ISRN Pharmaceutics, 1-10.
22. Wen X, Tan F, Jing Z, and Liu Z(2004), Preparation and study the 1:2 inclusion complex of carvedilol with β-cyclodextrin, Journal of Pharmaceutical and Biomediacal Analysis, vol.34, no.3, 517-523.
23. Papneja P, Kataria MK, Bilandi A (2015), Formulation and Evaluation of Solid Dispersion for Dissolution Enhancement of Ketoconazole, European Journal of Pharmaceutical and Medical Research, 990.
24. Meler j, Szczesniak M, Plta J, Grimling B(2014), Adsorption Studies of Ketoconazole with Ketoconazole, Progress on Chemistry and Application of Chitin and its Derivatives, VolXIX,22, 114-115.