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Comparative Dissolution and Disintegration Study of Different Brands of Linezolid 600 mg Tablets Available in Karachi, Pakistan

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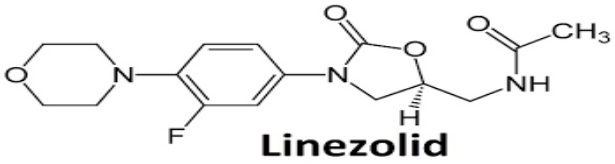
Abstract

The dissolution and disintegration tests (USP) are extensively useful for the determination of the safe and effective drugs as well as used for the stability and quality of the drug product. The purpose of the study was to observe the disintegration and dissolution profile (UV spectrophotometer), and estimation of the quality through weight variation and hardness test of different brands of Linezolid 600 mg tablets from Karachi, Pakistan. The weight variation test for all the brands was found to be under normal limits and the hardness of all the brands was also within normal limits. The tablet disintegration time was as per the specifications and all the tablets were disintegrated within 30 minutes except for brand C3, which disintegrates within 3.98 minutes and provided better disintegration time. Although, all the brands showed better dissolution rate, but the percent drug release of C1 was found to be the best, i.e. 100% drug was dissolved in 30 minutes in contrast to the different brands. Dissolution test is comparatively an efficient and cost effective *in vitro* approach that can be helpful in the assessment of the release attributes of formulation. It was found that brand C1 and C2 exhibited better dissolution profile as compared to other brands. Although, C3 and C4 were also found to be under the limits i.e. 80 % of the label amount of the drug.

Keywords: Linezolid; Spectrophotometer; Pneumonia; WHO

Introduction

Linezolid is very renowned synthetic antibacterial compound of the oxazolidinone derivatives and very helpful to treat Vancomycin-resistant *Enterococcus faecium* infections; *Nosocomial pneumonia*; complicated skin and skin structure infections including diabetic foot infections, without concomitant osteomyelitis; uncomplicated skin and skin structure infections and community acquired pneumonia. Linezolid should be taken two to three times per day [1].



Linezolid

Linezolid is reversible, nonselective inhibitor of monoamine oxidase. Therefore, Linezolid has the potential for interaction with adrenergic and serotonergic agents [2]. Basically Linezolid is completely a synthetic substance, which minimizes the tendency of naturally occurring resistance mechanisms. Linezolid has greater strength against gram-positive pathogens, including methicillin-resistant *staphylococci*, penicillin-resistant *pneumococci,* macrolides-resistant *streptococci,* and vancomycin-resistant *enterococci*. It was observed that the bioavailability of Linezolid (orally) is almost 100% so it can be taken orally or intravenously. Linezolid compound is permitted against various infections of skin and soft tissue; lower respiratory tract infections; and vancomycin-resistant *Enterococcus faecium* infections, including cases with concurrent bacteremia. Linezolid compound showed suitable portfolio of side effects, but on the other hand few patients, who take high doses beyond two weeks resulting reversible myelosuppression [3].

Absorption

Linezolid have fast absorption after oral dosing. Maximum plasma concentrations attained almost in one to two hours after dosing and the absolute bioavailability is almost 100%.

Metabolism

Initially Linezolid is metabolized by the morpholine ring oxidation and dual inactive metabolites are produced; i-aminoethoxyacetic acid metabolite, ii-the hydroxyethyl glycine metabolite. The hydroxyethyl glycine metabolite is produced by non-enzymatic chemical oxidation mechanism *in vitro* [4]. Linezolid never metabolized in terms of significant with cytochrome p450 (CYP) enzyme and neither suppress CYP isoenzymes and is not an enzyme inducer, revealed that the drug is rarely alter the pharmacokinetics of drugs metabolized by these enzymes (McEvoy).

Elimination

Basically linezolid is eliminated through urine with steady state situations in terms of PNU-142586 (40%), parent drug (30%) and PNU-142300 (10%). Practically in stool there is no patent drug is present and at the same time almost 6% (PNU-142586) and 3% (PNU-142300) of individual dose emerges. Generally, Linezolid elimination half-life is around 5-7 hours. Linezolid, non-renal clearance reported for almost 65% of the total clearance. By enhancing doses of linezolid a very minute intensity of non-linearity in terms of clearance was noted. This happens because of lower renal and non-renal clearance at greater linezolid strengths.

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Toxicity

The basic harmful effect of Linezolid is reversible hematologic which is commonly mild. Commonly indication which was observed almost with three per cent of patient courses is Thrombocytopenia especially if Linezolid is used for more than 14 days. The other harmful effect like Anaemia, neutropenia can take place in that patient who suffer with bone marrow suppression. Research of optic and peripheral neuropathy and lactic acidosis revealed adverse effects by the increase usage of linezolid like mitochondrial protein synthesis suppression. It is observed that combination of linezolid taken with serotogenic drugs (e.g. selective serotonin reuptake inhibitor) resulting serotonin syndrome developed [5].

Literature review

Nine formulations of Immediate Release Tablets of Linezolid were prepared with wet granulation technique using different disintegrants to achieve expected release according to the standards. They also studied different quality control aspects which were all within the limits [6]. Different immediate-release of BCS Class I drugs i.e. fluoxetine and linezolid and a Class III drug i.e. fluconazole generic drugs pursue the necessity of 85% or further release of drug in 15 or 30 min in various buffers i.e. pH 1.2, pH 4.5, and pH 6.8 with *in vitro* dissolution observation as per WHO. The two drugs i.e. Fluoxetine and Linezolid follow the specifications of biowaiver for BCS Class I drugs and can show *in vitro* equivalency, although fluconazole cannot accomplish the specifications of the protocols of WHO with respect to *in vitro* equivalency [7]. Dissolution test is comparatively an efficient and cost effective *in vitro* approach that can be helpful in the assessment of the release attributes of formulation as well as very effective *in vitro* assessment that can be used to asses and control variables relationship with formulation excipients, design and manufacturing [8]. So it is important to perform the dissolution test in order to forecast better *in vivo* evaluation of the drug product, which would be obtained if the gastrointestinal tract environment rejuvenates *in vitro* in better way [9]. *In vitro* dissolution depends upon the nature of the product, manufacturing technique and physicochemical properties of drug [10]. As 40% of compounds are lipophilic, so creating problem in dissolution. So, for this purpose FDA has published recommendations for single point dissolution and multipoint dissolution studies to evaluate immediate and modified release formulations [11].

Weight variation

Weight variation test is carried out to observe that the manufactured tablets have uniform weight (Babu). Weight variation test always describes that individual tablet of whole batch consists of accurate quantity of drugs (Reddy). This test is done to assure uniformity in the weight of tablets because variation in weight of tablets can cause difference in doses. So each tablet of a batch must be observed by weight variation test. Twenty tablets are selected randomly and their average weight is calculated [12]. For a tablet to pass the test not more than 2 tablets should lie out of the specified percentage and if no tablet differs by more than two times the percentage limit [13].

Procedure

From each brand twenty tablets were selected randomly and their weight was taken individually. The average weight was calculated and the results were tabulated on Microsoft Excel.

Hardness

Hardness is also referred to as crushing strength. Hardness of tablet is a very vital tool to observe the strength of splitting a tablet in a diametric compression test. Hardness can affect the disintegration [14]. With respect to the composition of tablets, including active ingredient, it is very essential to note down the precise tablet hardness [15]. Before discarding any tablet, if it is too soft or hard, then disintegration test must be performed. If the results are under the specified limits then the product can be approved. Hardness is very essential parameter in tablets because it estimates the capability of tablets to tolerate the impact of handling, packing and shipping or transportation [14].

Procedure

Ten tablets were selected randomly from each brand and their average hardness was calculated. The results were tabulated and analyzed graphically using Microsoft Excel 2016. The results should be within acceptable limits, i.e., 6-10 kg.

Disintegration test

"Disintegration is a fundamental demand of tablet to convert it into small particles thereby increasing the drug's surface area, which is very much vital for gastrointestinal absorption (GI)". Disintegration of tablets is very essential to classify the dissolution rate and many researchers revealed disintegration as a surrogate for dissolution [16]. The disintegration test is very advantageous to estimate disintegration of tablets or capsules within specified time when interact with a solvent which is according to standards [17]. In this method, six tablets from each batch are placed in each of the six tubes of the basket, immersed in appropriate medium and disintegration time is noted, which should be under the specified limits given in pharmacopeias. Disintegration of tablets has significant aspects throughout the production process. The greater powerful *in vitro* framework is to develop an indicator of drug bioavailability focused on disintegration. The first definite disintegration method was printed in the United States Pharmacopoeia [8]. The process of disintegration is renowned for the mechanical splitting of a compressed tablet into tiny granules and it is classified by the splitting of the interparticulate bonds, meanwhile counterfeit at the time of tablet compaction [18]. Tablet disintegration is an essential aspect in terms of drug release and altered by non-active ingredients known as disintegrants. These disintegrants provide various actions and the effectiveness of these disintegrants can be affected by many factors [19].

Methodology

0.6% v/v solution of HCl was prepared (16.2 ml of 37% HCl into 500 ml of distilled water and the volume was made up to 1000 ml with distilled water) and the vessel of disintegration test apparatus was filled with this solution up to the suggested point. The temperature was adjusted at 35°C and 39°C. One tablet was placed in each of the six tubes of the basket. The time was noted with the help of stop watch. All the tablets must be disintegrated within 30 minutes according to USP 2007 standards (Table 1, Figures 1 and 2).

Dissolution test

It is the most important quality control test, which determines the rate of release of the active ingredient from the drug product [8]. The strategy of drug characterization of bio pharmaceutics with the association of *in vitro* drug product dissolution and suggested *in vivo* bioavailability depend upon that dissolution of drug and permeability of GI are the basic tool to control the rate and extent of the absorption of drug [20]. The dissolution observation in pharmaceutical world can play as effective mechanism to manufacture and develop a quality drug. The basic perception and significance to observe the dissolution of oral solid dosage type will be useful for the observation of *in vitro* / drug release for special dosage forms [21]. Physico-chemical deviations

S. No.	Weight (mg) N=5	Hardness (kg) N=5	Disintegration (min) N=5
C1	948.52 ± 6.21	9.51 ± 0.09	3.16 ± 0.18
C2	854.46 ± 4.90	11.21 ± 0.02	3.38 ± 0.14
C3	796.48 ± 5.14	13.31 ± 0.20	3.98 ± 0.14
C-4	812.56 ± 2.91	8.22 ± 0.25	3.46 ± 0.22

Table 1: Weight and hardness of linezolid tablet 600 mg.

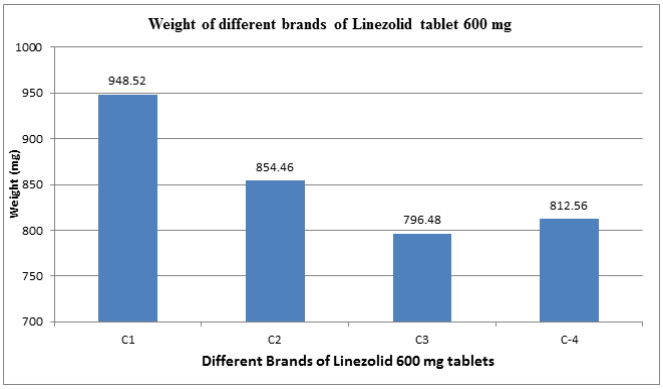

Figure 1: Weight of different brands of linezolid tablet 600 mg.

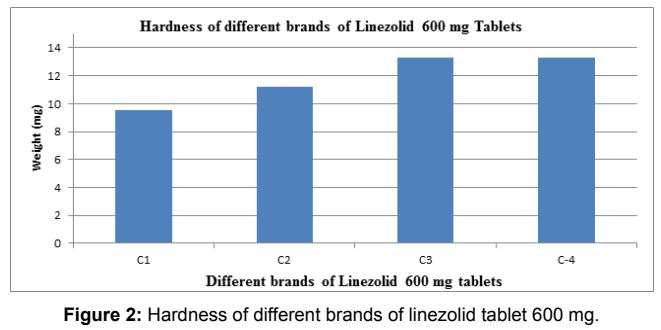

Figure 2: Hardness of different brands of linezolid tablet 600 mg.

like particle size diversity, excessive amounts of lubricant and coatings are reactive to dissolution testing therefore, dissolution tests are much essential in perceptive between batches of drug product(s) [8].

Equipment

Dissolution Apparatus II (ERWEKA, DT, Heusenstamm Germany), UV/VIS Detector (Shimadzu Corp., Japan), Linezolid Standard, Linezolid Tablets (Test) Different Pharmacies in Karachi, Pakistan.

Standard stock solution: 22 mg of Linezolid was accurately weighed in 100 ml volumetric flask. It was dissolved by adding approx. 40 to 60 ml of diluents. The mixture was shaken for 5 minutes. The volume was made up with diluents.

Working standard: 3 ml volumetric pipette was taken and rinsed with standard stock solution. Quantitatively 3 ml of standard stock solution was transferred in a 50 ml volumetric flask and the volume was made up with diluents up to mark and was shaken well.

Experimental condition: Dissolution medium: 0.1 N HCl, Time: 30 minutes, Temperature: 37°C Apparatus: USP II Paddle, RPM: 100 RMP ± 4.

Procedure: 900 ml of 0.1 N of HCl was taken in a cylinder of 1000 ml and transferred in dissolution vessels at 37°C ± 0.5°C. Each tablet was taken in each vessel and the apparatus was operated for 30 minutes (100 rpm). At the specified times, 20 ml of sample was withdrawn and filtered through whattman filter paper. The mixture was then transferred in 100 ml volumetric flask and the volume was made up with the medium. The absorbance of working standard and sample solution was observed at 243 nm (Table 2 and Figure 3).

Time (min)	C-1	C-2	C-3	C-4
0	0.00	0.00	0.00	0.00
5	79.66 ± 0.59	80.51 ± 0.23	71.16 ± 0.25	69.94 ± 0.16
10	89.85 ± 0.76	83.48 ± 0.64	78.54 ± 0.52	77.60 ± 1.04
15	93.78 ± 0.39	85.80 ± 0.32	83.84 ± 0.8	80.81 ± 0.93
20	95.56 ± 0.48	88.94 ± 0.89	85.03 ± 0.69	88.17 ± 1.27
25	97.68 ± 0.88	93.69 ± 0.76	91.88 ± 2.05	94.27 ± 1.25
30	99.55 ± 0.38	99.66 ± 0.57	97.39 ± 1.03	98.94 ± 0.95
40	100.66 ± 0.47	100.3 ± 0.60	98.33 ± 0.57	99.32 ± 0.56
45	102.29 ± 0.51	97.41 ± 1.56	99.66 ± 0.57	99.83 ± 0.19
60	103.03 ± 0.06	99.89 ± 0.78	101.66 ± 0.57	99.90 ± 0.16
90	103.8 ± 0.33	100 ± 1.11	102.25 ± 0.66	100.66 ± 1.52
120	104.36 ± 1.09	101.78 ± 1.61	105 ± 1.00	100.96 ± 0.04

Table 2: Dissolution profile of different brands of linezolid 600 mg tablets at 0.1 N HCl.

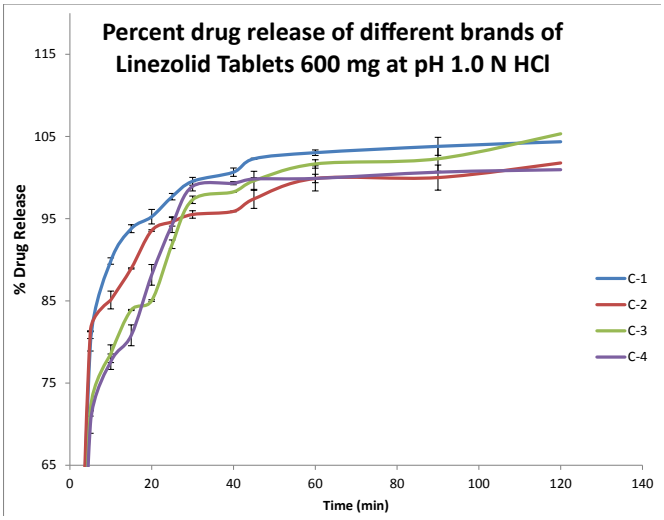

Figure 3: Percent drug release of different brands of Linezolid Tablets 600 mg pH 1.0 N HCl.

Result and Discussion

Disintegration of tablets has significant aspects throughout the production process. The greater powerful *in vitro* framework is to develop an indicator of drug bioavailability focused on disintegration. The first definite disintegration method was printed in the United States Pharmacopoeia [8]. The study performed by Vijaysinh. Chauhan et al., by preparing the taste masked tablet with Eudragit that disintegrates easily through microspheres forms of Linezolid and to prepare mouth disintegrating tablets of the formulated microspheres with superdisintegrant like sodium starch glycolate and sodium caramellose [22]. The tablets disintegration time was as per the specifications and all the tablets were disintegrated within 30 minutes except for brand C1, which disintegrates within 3.6 minutes and provided better disintegration time. Dissolution method is very effective *in vitro* assessment that can be used to asses and control variables relationship with formulation excipients, design and manufacturing. Pharmaceutical industries carry out the dissolution test for different purposes, for example the development of new entities, the quality control test in order to support the estimation of bioequivalence. The modern regulatory developments in which the Bio pharmaceutics Classification Scheme

(BCS) has emphasized the dissolution significance in the regulation of changes after the approval and utilizing the dissolution testing for clinical studies in some cases. For orally administered immediate drugs and other solid dosage forms, the dissolution test is very important, because the drug has to be dissolved in the dissolution medium very rapidly [23]. Multiple point dissolution was carried out for different brands of Linezolid 600 mg tablets and percent drug release was observed for every brand. It was found that brand C1 and C2 exhibited better dissolution profile as compared to other brands. Although, the other brands, C3, C4 and C5 were also found to be under the limits, i.e. 80 % of the labelled amount of the drug dissolved in 30 minutes. No significant difference was observed.

Conclusion

The results indicate that all the brands of Linezolid tablets 600 mg showed good overall quality and also the high dissolution rate shows that the drug is effectively bioavailable. It is concluded that in attempts of performing different tests, the overall result is satisfactory indicating that the proposed study is precise and accurate and can be used for the determination of Linezolid in tablet dosage forms.

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