Republic of Iraq
Ministry of Higher Education and Scientific Research
University of Basrah

College of Pharmacy

Comparative evaluation of candesartan cilexetil brand and generic tablets

Agraguated project submitted by

Huda Jabar

Haneen Muslim

Supervised by:

Dr.mohammed sattar
Dr.Ahmed Abdul kareem

Dedication:

To…

My Supervisors

My family

My friends

List of content:

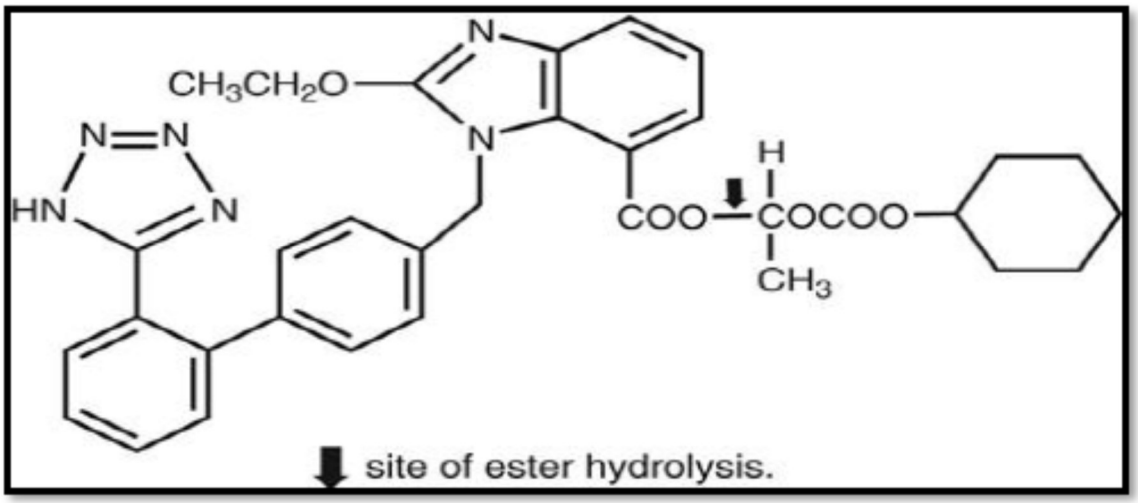
Chapter 1

1.1 Introduction

1.2 Candesartan Cilexetil

1.2.1 Chemical Name and Structure

Candesartan cilexetil is chemically 2-ethoxy-3-[21-cyclohexyl (1*H*-tetrazol-5-yl) biphenyl-4ylmethyl]-3*H*-benzoimiadazole-4-carboxylic acid 1-cyclohexyloxycarbonyloxy ethyl ester, with chemical formula $C_{33}H_{34}N_6O_6$ and molecular weight 610.67



chemical structure of candesartan cilexetil

1.2.2 Physicochemical properties

Candesartan cilexetil is white to off-white powder .The melting point of CC powder was 170˚C, which lies within the reported range that indicates the purity of the drug powder and its crystalline form

It is practically insoluble in water and sparingly soluble in methanol. The solubility of candesartan cilexetil in benzyl alcohol is 205mg/mL, and its solubility in water is less than 5×10^{-5}mg/ml. The partition coefficient (Coctanol/Caqueous) at pH 1.1, 6.9 & 8.9 is >1000 indicating high hydrophobicity character. It has apKa value of 6.0[3]. The dissolution enhancement by physical mixing with different carriers as compared to pure drug can be explained by increased solubility and surface area of the drug that comes in contact with the dissolution medium as the carrier dissolves. This might be due to the surface tension lowering effect of the polymers, resulting in the enhanced wettability of the hydrophobic drug having crystalline surface

1.3 Clinical Pharmacology

1.3.1 Mechanism of Action

Candesartan selectively blocks the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. This inhibits the AT1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in an overall decrease in blood pressure. Candesartan is greater than 10,000 times more selective for AT1 than AT2. Inhibition of aldosterone secretion may increase sodium and water excretion while decreasing potassium excretion

1.3.2 Pharmacokinetics :

1.3.2.1 General :

Candesartan Cilexetil is rapidly and completely bioactivated by an ester prodrug hydrolyzed to candesartan during absorption from the gastrointestinal tract, a selective AT1 subtype angiotensin II receptor antagonist[1]. Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by o-de-ethylation to an inactive metabolite. The elimination half-life of candesartan is approximately *9 hours*. After single and repeated administration, the pharmacokinetics of candesartan is linear for oral doses up to 32 mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing. Following administration of the candesartan cilexetil prodrug, the absolute bioavailability of candesartan was estimated to be 15%. Food with a high fat content has no effect on the bioavailability of candesartan from candesartan cilexetil.

1.3.2.2 Metabolism and Excretion :

Total plasma clearance of candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. When candesartan is administered orally, about 26% of the dose is excreted unchanged in urine. Following an oral dose of 14C-labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an intravenous dose of 14C-labeled candesartan, approximately 59% of radioactivity is recovered in urine and approximately 36% in feces. Biliary excretion contributes to the elimination of candesartan.

1.3.2.3 Distribution：

Candesartan Cilexetil The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. In rats, it has been demonstrated that candesartan crosses the blood-brain barrier poorly, if at all. It has also been demonstrated in rats that candesartan passes across the placental barrier and is distributed in the fetus.

1.3.3 Pharmacodynamics：

Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After 1 week of once-daily dosing with 8 mg of candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak with approximately 50% inhibition persisting for 24 hours. Plasma concentrations of angiotensin I and angiotensin II, and plasma renin activity (PRA), increased in a dose-dependent manner after single and repeated administration of candesartan cilexetil to healthy subjects and hypertensive patients. ACE activity was not altered in healthy subjects after repeated

candesartan cilexetil administration. The once-daily administration of up to 16 mg of candesartan cilexetil to healthy subjects did not influence plasma aldosterone concentrations, but a decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients. In spite of the effect of candesartan cilexetil on aldosterone secretion,

very little effect on serum potassium was observed. In multiple-dose studies with hypertensive patients, there were no clinically significant changes in metabolic function including serum levels of total cholesterol, triglycerides, glucose, or uric acid. In a 12-week study of 161 patients with non-insulin-dependent (type 2) diabetes mellitus and hypertension, there was no change in the level of HbA1.

1.3.4 Indication :

Candesartan is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions ,is widely used in treatment of hypertension, heart failure, myocardial infarction, diabetic nephropathy and given as prophylaxis to reduce the severity and duration of migraine[9].

1.3.5 Marketed Product of Candesartan Cilexetil :

Candesartan cilexetil is marketed under the trade names Atacand® available for oral use as tablets containing 4 mg, 8 mg, 16 mg, or 32 mg of candesartan cilexetil.

Chapter 2

Expremental work

Material used in this experiment:

Brand .Com

Generic A

Generic B

2.2 instrument

Instruments and their Manufacturers Used in the Study
Instrument
• Friabilator CS_II
• Hardness tester TBH 100
• Dissolution tester RC_3
• Disintegration tester BJ_2
• pH –Meter
• KERN Balanc
• UV-Visible Spectrophotometer PD_303
• Thickness of tablets

1.1.1 Quality Control (QC)

is considered as an essential operation in the pharmaceutical industry, including that the drug must be marketed as safe and therapeutically effective formulations whose performance is consistant and predictable. It is concerned with sampling, testing and documentation during manufacturing and also after completion of manufacturing. *Quality control is the monitoring process* through which manufacturer measures actual quality performance, compares it with standards and find out the causes of deviation from standard to ensure quality product not once but every time. In general terms, Quality control refers to a procedure or a set of steps taken during the manfacturing of a product to ensure that it meets requirements and that the product is reproducible .

1.1.2 Quality Control Tests for Tablets

General Appearance: Size, shape, and thickness:
This is important to facilitate packaging and to decide which tablet compressing machine to use. Organoleptic properties: include color and odor of the tablets. Weight uniformity and content uniformity: The tablet should include the correct dose of the drug

2.3.2.1 Uniformity of Dosage Units :

Table bellow shows that, all the CC brand tablet and generic tablet complied with USP specification which is 90-101% of CC content in each individual tablet indicating that the processing method was convenience[10]. dispersions ranged from 95.37±2.4 % to100 ± 1.82 % . This indicated that The percentage drug content of various CC was within the range of 92.49±2.2 % to 99.37±1.6 % while the percentage drug content in various CC solid CC was uniformly distributed in all these prepared tablets . The uniformly distribution of CC in prepared solid dispersion and physical mixtures may be due to using of microcrystalline cellulose as excipient which usually provides good dispersion and uniform mixing with drug .

2.3.2.2 Weight variation

20 tablets were selected at a random and then the average weight was determined. All the 20 tablets were weighed individually and compared with the average weight, the tablets meets USP specifications if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

2.3.2.3 hardness test The hardness of (3) tablets from each of the brand and generic companies was measured individually.The test is done using Erweka hardness tester used for measuring the hardness of the formulated porous Candesartan Cilexetil tablets , in which the hardness was expressed as a force in kg/cm2required to crush the tablet. The mean of three determinations ± SD was recorded

The friability test was performed for all the formulated porous CC tablets. 15 tablets were taken and their weight was determined.Then they were placed in the Roche friabilator at 25 for 4 minutes and allowed to make 100 revolutions. The tablets were then de-dusted and reweighed. Friability values below 1% are generally acceptable them and then operating the friabilator , re-weighting the tablets to determine the loss in their weight.

$$\%\text{Friability} = (W_1 - W_2) \times 100/W$$

Where,

W1= Initial weight of the 15 tablets.

W2 = Final weight of the 15 tablets after testing.

Friability values below 1% are generally acceptable.

.

2.3.2.5 Thickness of tablets :

Thickness is measured by using instrument called digital "vernier calipers". Randomly 10 tablets were taken and thickness was measured for each tablet by placing between two anvils and rotating sliding knob until the tablet was tightly fitted and the reading was noted on the digital scale.

2.3.2.6 disintegration test :

The disintegration time was determined in HCL solution (pH 1.2). Disintegration apparatus with a basket rack assembly containing six open-ended tubes and 10-mesh screen on the bottom was used. A tablet was placed in each tube of the basket and the time for complete disintegration of the six tablets was recorded.

2.3.2.7 Wetting Time：

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A water-soluble dye phenolphthalein was added to the petridish. The dye solution was used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of tissue paper in the petridish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in triplicates (n=3). The wetting time was recorded using a stopwatch.

2.3.2.8 drug content estimation :

An accurately weighed amount of 5crushed tablet of each company was dissolved in small volume of methanol and further diluted in phosphate buffer . the content of CC was determined spectrophotometrically at max of CC using UV visible spectrophotometer

2.3.2.9 invitro dissolution study :

The dissolution test was used to compare between cc (Brand.com) tablet, and (Generic c.A&B) companies. The USP paddle method was used for all the in vitro dissolution studies. In this method, phosphate buffer with 0.35% polysorbate 20, were used as dissolution medium. The rate of stirring was 50 ± 2 rpm. The amount of candesartan cilexetil was (16) mg in all formulations. The dosage forms were placed in both media

Th At appropriate time intervals (5, 10, 20, 30, 40, 50 and 60 minutes), 5 mL of the samples were taken and filtered through a 0.45-mm Millipore filter. The dissolution medium was then replaced by 5 mL of fresh dissolution fluid to maintain a constant volume. samples were then analyzed at □ max of CC by UV-spectrophotometer.

Company	Content uniformity range
Brand.com	100±1
Generic c.A	100±3.5
Generic c.B	100±4

3.1 Uniformity test :

3.2 Hardness test :

of tablets prepared by Hardness of the prepared tablets of all formulations are within the acceptable limit. Hardness direct compression was found to be from 5.04 to 6.7 kg/cm2.

company	Hardness range kg/cm^2
Brand.com	0.25±5
Generic c.A	0.42±5
Generic c.B	0.55±5

hardness measurement is to:

*Select the proper compression force:

-The very hard tablet has long disintegration time and reduced dissolution values

-The soft tablet may not withstand the subsequent process such as coating or packaging

So tablet hardness depend on :

-Compression force.

-Amount and type of binder.

-Type of material used .

3.3 Friability test :

.All CC of brand and generic company had acceptable friability as none of the tested tablets exceeded 1% loss in tablet weight as shown in table ,also no tablet was cracked, split or broken in either company. Since all the tablets met the standard friability criteria, so they are expected to show acceptable durability and withstand abrasion in handling, packaging and shipment . compress tablet less than *0.5 to 1.0%* of the tablet weight are consider acceptal .

The table below clarifies the results obtained from testing different companies , as thefollowing :

Table showing frinability percent %:-

% Friability	Brand.com	Generic c.A	Generic c.B
Tab1	0.13	0.5	0.7
Tab2	0.13	0.45	0.56
Tab3	0.13	0.65	0.55
Tab4	0.13	0.65	0.72
Tab5	0.13	0.40	0.64
Tab6	0.13	0.76	0.63
Tab7	0.13	0.23	0.27
Tab8	0.13	0.55	0.36
Tab9	0.13	0.51	0.52
Tab10	0.15	0.33	0.22
Tab11	0.13	0.41	0.55
Tab12	0.11	0.43	0.22
Tab13	0.13	0.58	0.42
Tab14	0.13	0.27	0.9
Tab15	0.13	0.29	0.6

Friability is affected by various external and internal factors like:

1) Punches that are in poor condition or worn at their surface edges, resulting in 'whiskering' at the tablet edge and show higher than normal friability values.

2) Friability test is influenced by internal factors like the moisture content of tablet granules and finished tablets. Moisture at low and acceptable level acts as a binder.

Chapter 3:

Result and discussion :

3.4 Disintegration Time :

The disintegration time for the candesartan cilexetil tablets of brand and generic was shown in table (1). It was found that, the mean of the disintegration times for all investigated tablets were less than 8 minutes, which fulfill the Pharmacopoeial requirements.

Table showing disintegration time variation:

Company	Disintegration time (min.) ±S.D
Brand.com	6±0.45
Generic c.A	6±1.54
Generic c.B	6±2

Disintegration is affected by compression and type & amount of binder, as binder amount increase or high compression force will cause strong tablet difficult to disintegrate and need more time.

3.5 Invitro study :

The dissolution profiles of CC of (brand.com) and (generic c.A&B)company in buffer medium with 0.35% of polysorbate 20 in the figure below.

Time (Minute)	Release%of Brand.com	Release % of Generic c.A	Release % of Generic c.B
5	2%	3%	1.5%
10	9%	7%	10%
20	25%	18%	20%
30	37%	28%	24%
40	53%	42%	47%
50	66%	58%	52%
60	78%	60%	55%

Buffer solution composed from dehydrogenase phosphate and potassium phosphate .

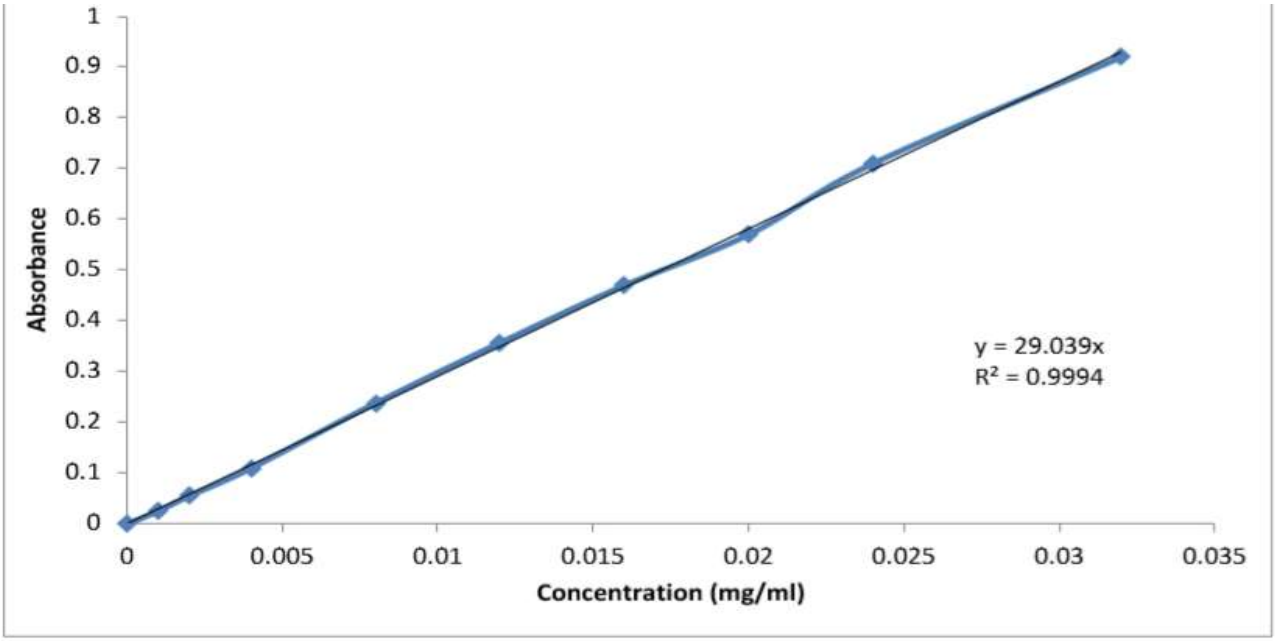
Up using the buffer solution,we don't obtain result because we need addition of twin in about 35% and then we obtain the calibration curve in poly sorbate.

In the addition can not use another solvent that we use it in the calibration curve so poly sorbate must be use.

We choose the buffer solution because we know the atacand is weak acid and it's of high dissolution in weak base so we must choose the buffer.

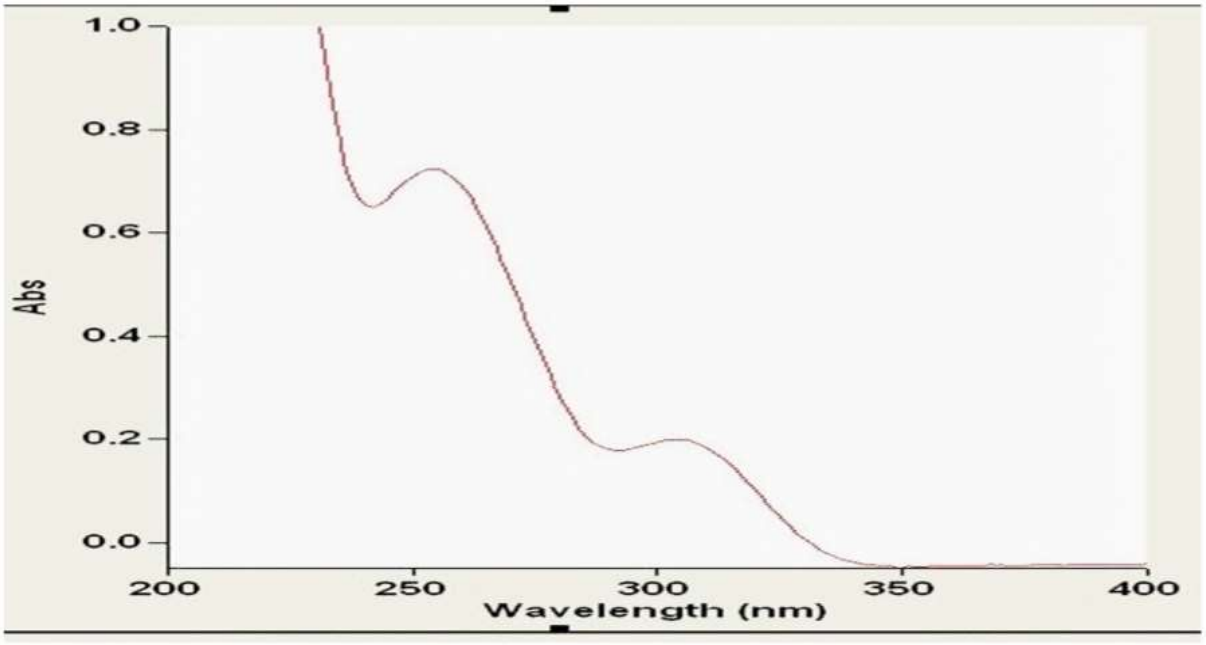
If we use Hcl for dissolutin should make the calibration curve in the Hcl and should use the twin.

The objective of the research is to identify the dissolution of the solubility of candesartan cilexetil.



Calibration curve of candesartan cilexetil in phosphate buffer solution (pH 6.8) with 0.35% polysorbate 20.

٣s •



UV spectra of candesartan cilexetil in phosphate buffer solution (pH 6.8) with 0.35% polysorbate 20

References :

(1) Sweetman S.C. (Ed.).Martindale: The Complete Drug Reference, 36th Ed. The Pharmaceutical Press, London, 2009.

(2). Moffat A., Osselton M., Widdop B. **Clarke's analysis of drugs and poisons.**12th ed. The pharmaceutical press. 2005.

(3) Vairappan K., Ayarivan P., Lakshmanan R. andSundaravadivelu J.Development and Validation of A Dissolution Test with Reversed-Phase High Performance Liquid chromatographic Analysis for Candesartan Cilexetil in Tablet Dosage Forms.Arabian Journal of Chemistry.2011; 67-78.

(4). Gaurav S., and Kimia F. **Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs.**Journal of Applied Pharmaceutical Science.2012; 2 (10): 170-175.

(5). Ghafourian T, Bozorgi AHA. **Estimation of drug solubility in water, PEG 400 and their binary mixtures using the molecular structures of solutes.** Eur J Pharm Sci. 2010; 40(5):430–40.

(6). Revathi T., Ethiraj Z., Jhansi L., Marreddy S. and Ganeshan V. **Development and validation of a dissolution test for Candesartan cilexetil in tablet forms using reverse phase – High performance liquid chromatography.** Journal of Pharmaceutical Education Reserch. 2011;2: 22-36.

(7). Shukla JB, Patel SJ. **Formulation and evaluation of self-microemulsifying system of candesartan cilexetin.** Int J Pharm Pharm Sci 2010; 2(4):143-146.

(8). Darwhekar G. N., Jain D. K. and Jitendra C.Biopharmaceutical Classification of Candesartan and Candesartan Cilexetil .Asian Journal of Pharmacy and Life Science.2012; 2

(9) Asif H., Sabir A., Moloy M., Parminder S. and Bhasin A. Review on Candesartan: Pharmacological and Pharmaceutical Profile.Journal of Applied Pharmaceutical Science.2011; 01 (10): 12-17.

(10) United States pharmacopoeia .The USP Convention. 2007, CD.

(11). Ravikiran N. **Design and evaluation of orodispersible tablet of piroxicam using different superdisintegrants.** International Journal of Drug Formulation & Reserch. 2010: 349-374.

(12). Spireas S. **Liquisolid systems and methods of preparing same,** U.S. Patent.2002; 6,423,339.

(13). Remon J P, Corveleyn S. Freeze-dried rapidly disintegrating tablets. US patent 6 010 719, January 4, 2000.

(14). Chandrasekhar Patro, S Sreenivas Patro, Bibhu Prasad Panda, M E Bhanoji Rao, Formulation and Evaluation of Cetirizine HCL Mouth Fast Dissolving Tablets, Der. Pharmacia Lettre, 2011, 3 (4), 63-70.

(15) British Pharmacopoeia 2009.

[16] British Pharmacopoeia. Appendix XII A. Disintegration Test for Tablets and Capsules. 2009;65-72.

[17]. Ravikiran N.Design and evaluation of orodispersible tablet of piroxicam using different superdisintegrants.International Journal of Drug Formulation&Reserch. 2010:349-374.

[18]. Spireas S., Bolton M. Liquisolid systems and methods of preparing same.U.S.Patent.1999;5:538-550.

[19]. Japanese pharmacopeia, 14th edition page-1327.

[20]. scholars research library.com/dpl-vol5.../DPL-2013-5-3-211-222.pdf