Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(9):4393-4399

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Influence of Storage conditions on Potency of different Iron Tablet in Libyan market

Arwa M. Elhagi[1], Tariq K. Almog[*1] and Mosbah A. ElMajri[2], Mssoud A. S. Anwair[1], Mohamed M. M. Sian[2]

[1]Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, Tripoli University, Tripoli Libya.
[2]Department of Industrial Pharmacy, Faculty of Pharmacy, Tripoli University, Tripoli Libya.

ABSTRACT

The objective of this study was to investigate the effect of moisture sorption on iron tablet brand and the morphological change, if any, resulting from moisture sorption. Four iron tablets of commercial brands, provided by different sources to Libyan market were examined. Accelerated stability testing was obtained at 40 ^{O}C and 75% relative humidity. Changes in physicochemical properties of tablet were determined by weight variation test, hardness test, friability test, disintegration time test, dissolution rate test, thickness & diameter determination and chemical assay by UV- visible Spectrophotometer. The ranking of the storage effect on dissolution test of brand B (slow-fe) was, three months > two month> fresh, while brand A (Tardyferon) two month> fresh > three months, and brand D (Fumafer) fresh > three months > two months, and brand C (Fumacure) three months > two months > fresh. Thus Fumacure had lower tensile strength and disintegration time value than Fumafer and Slow-fe, but Slow-fe showed better ability to protect abrasion (friability), brand. Fumacure brand could be useful as an alternative iron tablet brand to three brands especially when used in Libyan markets and the problem of storage and effect of environment condition temperature and relative humidity are of particular concern. The iron content results show that all fresh type samples were within the limit according to Birth pharmacopeia. The ranking of storage effect on the content of iron tablets after the chemical assay by UV-Vis spectrophotometer is for all brands the same, fresh > two months > three months, which indicates that the four brands are affected by the unsuitable storage conditions and being expired, so, furthermore, it will never given the desired treatment.

Keywords: Accelerated stability testing, iron, tablet

INTRODUCTION

Iron occurs in different pharmaceuticals form as tablet, capsule, drinking ampoule, injectable and syrup. Iron is added to multivitamin as one of essential mineral.

Requirement of iron by an adult male is only 13 µg/kg per day (about 1 mg) while a menstruating female requires about 21 µg/ kg per day (about 1.4 mg). In the last two trimesters of pregnancy, requirements increase as higher as 80 µg/kg per day (5-6 mg) and the infant has similar requirements due to its rapid growth.

The usual therapeutic dose of iron is about 200 mg per day (2-3 mg/kg). Children weighing 15 to 30 kg can take half the average adult dose, however small children and infants can tolerate relatively larger doses (5mg/kg) [1].

Consequent upon its as desirable effects, it is widely used in the treatment of anemic disease and it is considered as essential for the development and regeneration of peroxidase, catalase, myoglobin, and cytochomes. Iron deficiency reported to affect the metabolism in muscle independently due to effect of anemia on oxygen delivery. Its deficiency

has also been associated with behavioral and learning problems in children and with abnormalities in the catecholamine metabolism [2]. The therapeutic importance of iron has prompted many researchers to develop methods for its determination and assay in clinical as well as in pharmaceutical form. In pharmaceutical products iron normally exists as ferrous ions and different methods have been used for the determination of iron in a specific oxidation state including determination of iron using titrimetric [3], spectrophotometric technique [4,5], combination of spectrophotometric methods, high-performance liquid chromatography [6], and atomic absorption methods [7-9]. Comparison between the methods of analysis also has been investigated [10].

EXPERMENTAL SECTION

Apparatus:
UV-Visible spectrophotometer GE418725, England, Balance used made by Sartorius, BP 121S, Germany; Friabilator tester, made by Erweka, Germany; DT600 Dissolution tester, made by Erweka, Germany; ZT501 Disintegration tester, made by Erweka, Germany; TBH28 Hardness tester made by Erweka, Germany; Micrometer USP; and CG825 pH meter made in Germany.

Reagents and Material:
All chemicals were of analytical grade. Sodium acetate was obtained from BDH Limited Pool England; Hydroxylamine HCl was obtained from Riedel-de Haen A G, Germany, iron used for preparation standard solution obtained from Fisher Scientific, UK. Freshly distilled and deionized water was used throughout experiment.

Iron tablet tested were collected from Libyan local market and were named as A, B, C, and D. Two different brands of ferrous sulphate (A, film coated tablet, Tardyferon®) and (B, sustained release tablet, Slow Fe®). The other two different brands were ferrous fumarate tablet (convential compressed tablets, C, Fumacure® and D, Fumafer®).

Storage conditions:
The iron tablets to be tested were subjected to accelerated stability testing. The packed brand tablet in blister were placed in transparent desiccators and stored at $40^{o}C \pm 0.5$ and 75% relative humidity for a period of three months. The relative humidity (RH) of 75% was initiated and maintained in desiccators using saturated solution of sodium chloride and the desiccators were placed in an oven at $40^{o}C \pm 0.5$ sample were withdrawn after two and three months and were examined for chemical changes [11].

Tablet thickness and diameter:
The thickness and diameter of 20 tablets of the four different brands determined by using micrometer and the average value were recorded.

Uniformity of weight:
The weight of 20 tablets of the four different brands was determined according to the method described in USP [4]. Mean of the weight ± standard deviation was calculated.

Determination of tablet hardness:
The breaking strength of each tablet was tested using Hardness tester, a tablet was placed between the two jaws; the breaking point was determined by gradually increasing the force on tester [12]. The average value was recorded.

Tensile strength:
Tensile strength (T) carried out on 10 tablet of each brand [13]. (T) calculated from equation below and the average results were recorded.

$$T= \frac{2\,xN}{\pi xLxD}$$

N= hardness in Neutin, L= thickness of the tablet in meter and D= diameter of the tablet in meter.

Friability test:
Tablet friability was measured as the percentage of weight loss of 10 tablets in a friability tester. After 4 minutes of rotation at 25 rpm, the dust of fresh and stored tablets was removed, and the percentage of weight loss calculated [14].

Determination of disintegration time:
The disintegration times of the tablets were determined in 800 ml deionized water at $37 \pm 0.5\ ^{O}C$, using a USP disintegration tester. The 6 tablets were placed in tubes, which were then raised and allowed in the test solution, if 1

_____

or 2 tablets fail disintegrate completely after 30 minutes for film coated tablets or 45 minutes for sugar coated tablets, repeat the test on 12 additional tablet not less than 16 of the total 18 tablet tested disintegrate completely [14] .

Determination of dissolution rate:

The apparatus used was of as per USP specifications, the quantity of dissolution medium is 0.1 N HCl (900 ml) for ferrous sulfate tablets and 0.5 % sodium lauryl sulfate in 0.1 N HCl (900 ml) for ferrous fumarate tablets, was poured into the vessel maintained at 37 ± 0.5 ^{o}C with speed rotation at 50 rpm. One tablet of each brand was placed in the basket and lowered into the vessel containing the dissolution medium. Sample (5 ml) were withdrawn at timed intervals (5, 10, 20, 30 ,60, and 90 minutes), and replaced with fresh dissolution medium. The samples are treated with reagents (1ml 10% hydroxylamine hydrochloride, 3 ml phenanthroline reagent and 10 drops of acetate buffer) to produce a red colour that is measured by using UV-Visible spectrophotometer at 510 nm wavelength [4].

Determination of iron concentration:

Active ingredient of Iron concentration in each pharmaceutical brand name were determined using spectrophotometeric method [15] and for this purpose standard calibration curve firstly was constructed to give the final standard concentration from 0.05 to 1 mg ml^{-1}

The sample was prepared by weighted and powdered 10 tablets, and then 12.5 ml 8M HCl was added to 0.5g of sample powder. The sample was slowly boiled for 5 min then cooled. 10 ml of deionized water was added and the solution was filtered using Whatman No 1 filter paper. The filtrated transferred to 50 ml volumetric flask and completed to the mark by deionized water. The iron was determined by used this solution as a sample.

5 ml of sample was analysis by mixed with 10 drops of acetate buffer, 2ml 10% hydroxylamine hydrochloride and 3ml phenanthroline reagent. The absorbance of the colour developed after 15 minutes was measured at 510 nm. And the amount of iron content in each brand tablet was determined from constructed standard curve.

RESULTS AND DISCUSSION

Pharmaceutical and chemical analyses of four types of iron content available in Libyain market were done. Brand name, country of origin, present of primary and secondary package, generic name, number of tablets in single pack, dose amount in each tablet, manufacturing and expiry of the samples of are represented in Tab.1.

Effect of storage (moisture and temperature) of again on the weight variation, friability, disintegration, Tensil strength, dissolution rate as well as the concentration of iron content in each sample were tested and the result are summarized in Tab. 2.

The % of drug release during period of time (0-100 min) were determined and the results are represented in Figures 1-4.

Table 1. Specifications of brands Iron tablet

Name code	A	B	C	D
Brand name	Tardyferon	Slow-fe	Fumacur	Fumafer
Origin	France	England	Morocco	France
Primary package	Present	Present	Present	Present
Secondary package	Present	Present	Present	Present
Generic name	ferrous sulfate	Dried ferrous sulfate	Fumarate ferreux	Fumarate ferreux
No. of Tablets in one pack	30	28	80	100
Dose amount	80 mg	160 mg	200 mg	200 mg
Batch No.	G07023	U0632	0367	N134
Manufacture date	11-2005	10-2006	12-2005	01-2007
Expiry date	11-2010	09-2009	12-2008	01-2011
Manufacturer	Giencedex France	Novartis pharmaceutical UK LTD	Filiale pharmal DEB	Sanafi winhrop

This study reviews the effect of moisture and temperature on iron tablet. It was stated that the amount of moisture adsorbed by drugs or excipients and increased in temperature influences hardness, disintegration time, dissolution rate. These changes may alter bioavailability, and therapeutic efficacy, even though the drug potency. The influence of relative humidity and temperature depends on its chemical affinity for tablet and nature of excipient or additive. The physiochemical properties of tablet (such as hardness, disintegration and dissolution rate) are dependent on the presence of moisture and influence by storage conditions.

The changes of appearance of the all entire tablet in period of three months store are reported. The significance of weight variation test is to insure that the tablets in each lot are within appropriate weight range, all sample showed

an acceptable uniformity in weight, as none had percent deviation greater than ± 7.5% as stipulated by the USP. The significant of this test is to ensure that the tablet in each Lot is with in the appropriate size rang.

The thickness and diameter are calculated by statistical analysis of the results, we conclude that all four brands show no or slight variation in thickness and diameter which all are accepted.

The tablet properties related to crushing are hardness and friability. The limit of hardness of compressed tablet is 4-8 kg, the result shown that slow-fe and Fumafer are within the limit, while Fumacur (2 months) are out of the limit. For sugar coated tablet and sustained release tablet the limit range from 10-20 kg, so the Tardyferon brand (fresh,2 and 3 months) are out of the limit, so, it is not comply with the specification of USP. The results are represented in Tale 2.

Table2. Effect of aging on the, weight variation, friability, disintegration, Tensil strength, dissolution and iron content.

Tablet code	Storage condition	Parameters					
		Weight variation [gm]	Friability %	Disintegration Time [min:sec]	Tensile strength [x 10^6]	Dissolution %	Iron content %
A	Fresh	0.2485	0.15	256:00	0.521	15.1 (t_{45})	83
	Two months	0.656	0.15	392:00	>4.114	16 (t_{45})	72
	Three months	0.663	0.30	411:00	>1.134	13 (t_{45})	65
B	Fresh	0.2495	0.39	02:07	1.433	22 (t_{45})	98
	Two months	0.259	0.40	02:46	0.791	23 (t_{45})	89
	Three months	0.2485	0.40	04:30	0.787	45 (t_{45})	84
C	Fresh	0.248	0.41	01:08	0.889	45 (t_{45})	96
	Two months	0.2425	0.40	00:30	0.702	45 (t_{45})	89
	Three months	0.2485	0.65	00:15	1.008	46 (t_{45})	75
D	Fresh	0.3025	0.65	82:00	1.467	40 (t_{90})	101
	Two months	0.302	0.33	92:00	1.352	43 (t_{90})	91
	Three months	0.306	0.33	94:00	1.440	66 (t_{90})	69

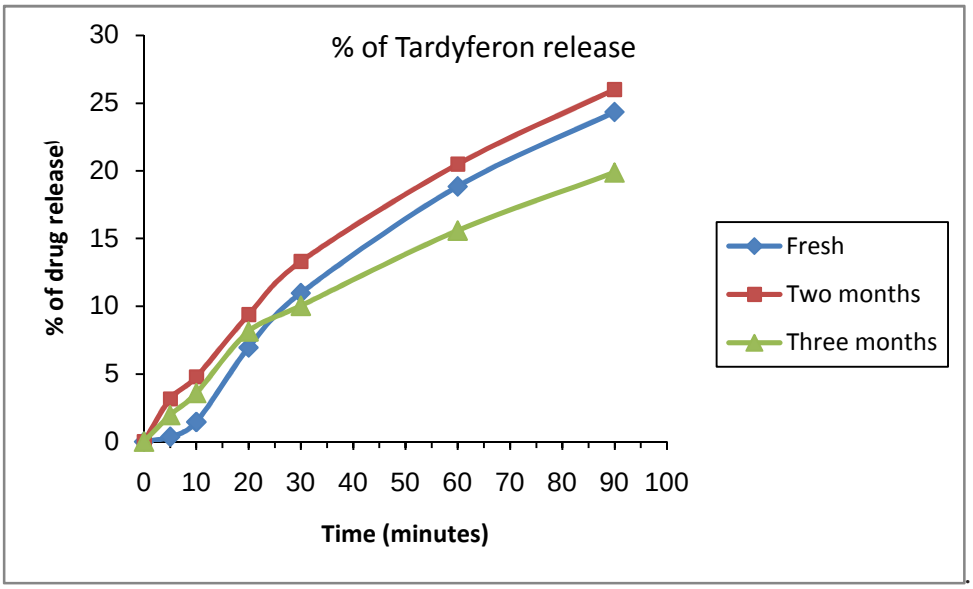

Figure 1. Release profile of Tardyferon Tablet

Friability was measured as the percentage of weight loss of 10 tablets in friability tester. For a convential compressed tablet and coated tablet the limit of loss should be less than 0.5%, All iron tablets brand from Libyan market showed unsatisfactory friability values and lower friability was obtained when increase time of storage and can be arranged in descending order when stored of three month at 40 ^{o}C/75% RH as follow: Fumafer-Fumacur> Tardyferon-Slow-Fe. Tensile strength (N.m^{-2}) results are calculated and presented in Table 2. From the results we see an obvious variation between tablets; this is due to high variation between each tablet of each brand in its hardness. The descending arrangement of the four brands as presented in Table 2. were Tardyferon> Slow-fe> Fumafer > Fumacur.

All types of tablet were examined for iron content as soon as transported to the laboratory. The results of iron was within the range, as stated by B.P 2004 (95-105% for ferrous sulphate tablet) and (90-105% for ferrous fumarate). Slow Fe found to have 95% which is the lowest as stated in B.P (Table 2).

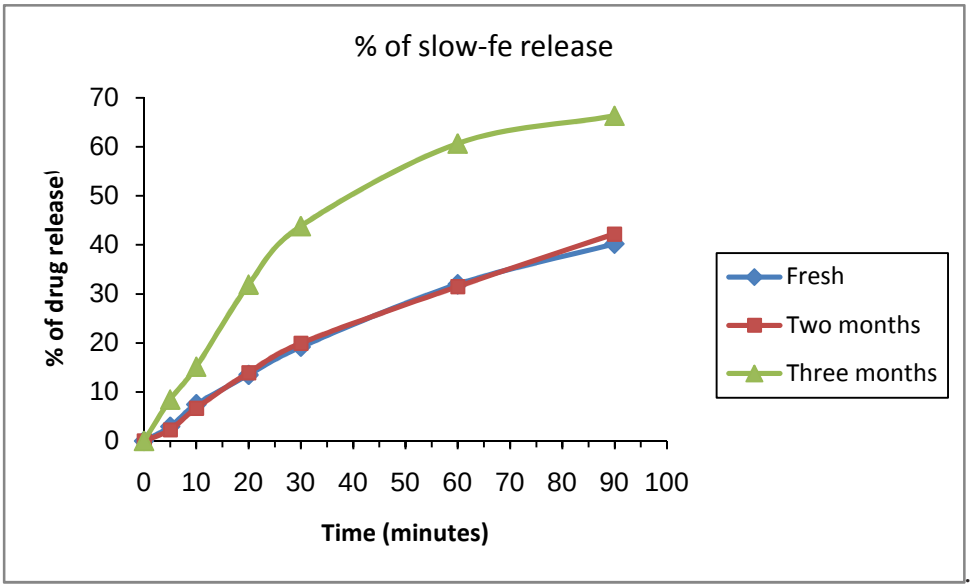

Figure 2. Release profile of slow-fe Tablet

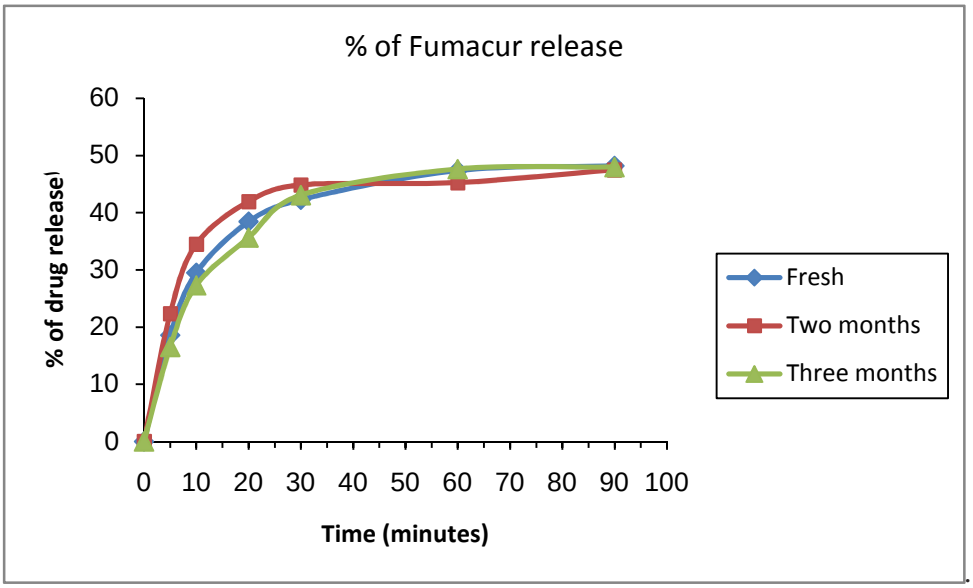

Figure 3. Release profile of Fumacur Tablet

From disintegration test, the shortest results time was achieved at fresh iron tablets, while upon the storage conditions at 40^{o}C and 75% relative humidity showed the highest values for all brands and can be arrange in descending order as follow: for slo-fe three months > two months > fresh; Tardyferon three months > two months > fresh; Fumafer three months > two months > fresh, and Fumacur fresh > two months > three months.

The maximum disintegration time it was for Tardyferon brand achieved at 392 min and 411 min when stored of two and three months respectively. The results in table 2 for uncoated convential tablets, the disintegration time should be within 30 min (1 to 30 min), the two brands Fumafer and Fumacur are within the limit of USP. and for coated and sustained release tablets the disintegration time should be within 1 to 2 hours, we found Slow-Fe are within the limit range, while Tardyeron brand is out of the limit.

According to USP stipulated that at 45 min all tablet should have release into dissolution medium an amount not less than 75% of labeled amount of ferrous salts. The results is summarized in table 2 and represented in figures 1-4, the release of all brand at fresh, two months and three months not reach to that level of release (75%) so all brand not comply with the specification of USP. Results increase in dissolution rate was observed for ferrous fumarate or sulfate tablet when they were subjected to stress storage condition (40^{o}C/75% RH) for prolonged period of time (3 months) where its found there is direct correlation between effect of stressed storage condition and dissolution rate.

The physical change of tablets mediated by moisture were the main cause for increase in dissolution according to stressed storage condition ferrous tablets brands could be arranged according to their t_{45} of dissolution as follow: Tardyferon: two months > fresh > three months; Fumafer: three months > two months > fresh and Fumacur: three months > fresh = two months. While Slow- Fe: three months > fresh = two months and three months > two months > fresh arranged according to its t_{60} and t_{90} respectively. It is worthy to note that T_{50} of ferrous salt dissolution from all the tested brands fresh and stored exceed 90 min. As shown in figures 1to 4, the dissolution of ferrous fumarate from its tablet in 0.1N HCl vary from one product to the other. After 5 min the percentage of ferrous fumarate dissolved in 0.1N HCl was found to vary from 13.7% - 18.58% and 4.7 – 16.5% for fresh and stored at three months respectively. These finding may be attributed to be effect of additive in the different formula as well difference in disintegration time of the core tablets.

The assay of iron in this in work is based on the method reported in USP, when we made accelerate storage condition for two month and three month. The results show decrease in percent of active ingredient as the time of storage increases. The most sample affected by changing in the storage conditions was Fumafer as the ferrous content reduced from 101% to 69%. This result gives evidence to the affect of temperature and moister on ferrous tablet, which convert ferrous to ferric form in tablet that is not soluble and not absorbed by gastrointestinal tract, that cause lose desired treatment or less effect to desired treatment.

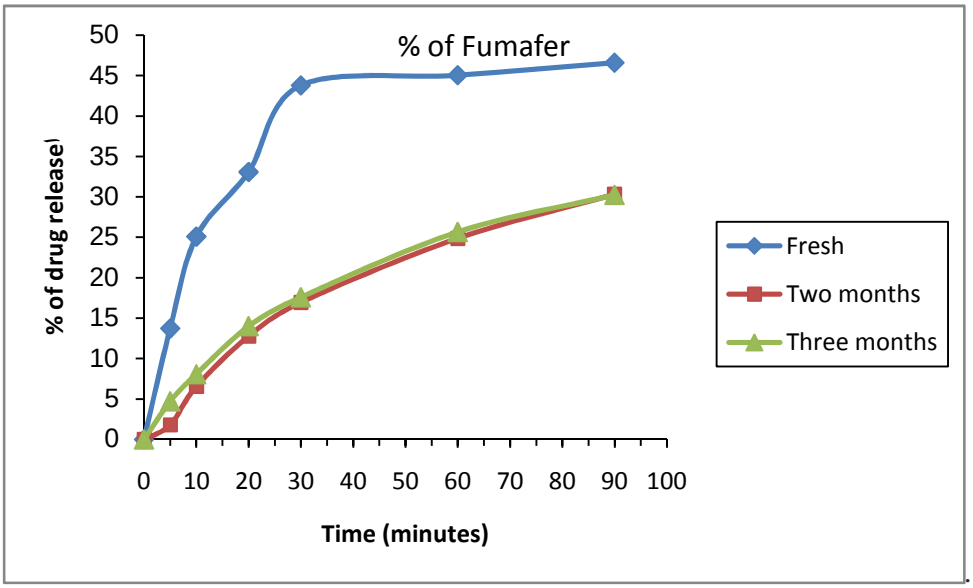

Figure 4. Release profile of Fumafer Tablet

CONCLUSION

From this work we can report that iron tablet with different salts, when stored in inappropriate storage condition especially in Libya weather that usually is in high temperature and humidity which cause acceleration changes on the physical and chemical properties leading to less effective drug.

REFERENCES

[1] E. Mutschler and H. Derendorf. *Drug Actions, Basic Principles And Therapeutic Aspects*, **1995**; 318-23, Stuttgart.
[2] A.G. Gilman, T.W. Rall, A.S. Nies and P. *Taylor. The Pharmacological Basis of Therapeutics*, 1282-92., 8th ed. Pergamon Press.
[3] British Pharmacopeia (BP) ; *Incorporating the requirements of the 6th edition of the European Pharmacopoeia*; **2009**, Vol. I, 845-850.
[4] The United States Pharmacopeia, 30 revisions, *National Formulary* 25; **2007**, 2: 1855-56.
[5] Shiki Masaharu and Yamamoto Koichi, , *Bunseki Kagaku*; **2006,** 55(9)**:** 727-732.
[6] Harrington CF, Elahi S, Merson SA and Ponnampalavanar P. *Anal. Chem;* **2001**, 73(18): 4422-4427.
[7] Kenduzer E and Turker AR. *Anal. Science*; **2002**, 18(8): 917-922.
[8] Giokas DL, Paleologos EK and Karayannis MI. *Anal. Bioanal.Chem*.; **2002**, 373(4-5): 237-243.
[9] Grotti M, Abelmoschi ML, Soggia F and Frache R. *Anal. Bioanal. Chem*; **2003**, 375(2): 242-247.

[10] Ramezani Zahra, Rahbar Nadere and Ghanaatian Azam, *Pak. J. Pharm. Sci.;* **2008,** 21(4): 396-399.
[11] Alfanso R Gennaro, Grafton D Chase and Glen R Hanson *Remington, 19th edition*, Mack publishing company**; 1995**, 594, 595.
[12] Carstenson JT. Stability and dating of solid dosage forms. In: Crstenson *JT.ed pharmaceutics of solids and solid dosage* form. New York, NY: Willy- Interscience. **1977**; 182-185.
[13] Fell JT and Newton JM. *J. Pharm. Sci*., **1970**; 59: 688-691.
[14] Lachman L and Lieberman HA (eds). *The theory and practice of industrial pharmacy;* Varghese publishing, 3ed edition. **1987**; 297-302.
[15] Jeffery GH, Bassett J, Mendham J, Denney RC. Vogel´s Textabook of Quantitative Chemical Analysis, Fifth ed. **1991**; Longman Scientific and Technical, Longman group UK-Limited, 691-692.