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COMPARATIVE *IN-VITRO* EVALUATION OF COMMERCIAL SIMVASTATIN TABLETS (20 MG)

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ABSTRACT: The availability of several brands of Simvastatin tablets in Libyan pharmacies today places health practitioners in a problem of generic substitution. The aim of the present study was the evaluation and comparison between four different Simvastatin brands, which are commercially available in the Libyan market produced by various pharmaceutical companies with different trade names. The physicochemical equivalence of four brands of Simvastatin tablets was investigated through the evaluation of both official and non-official standards according to the USP pharmacopoeia including uniformity of weight, thickness, hardness, disintegration time, drug content as well as dissolution rate. Acceptable external features as well as uniformity in diameter and thickness revealed for all the tablets. The entire brands complied with the official specifications for uniformity of weight where no tablet showed a deviation more than ±7.5%. Brand B had the highest crushing strength and highest disintegration time compared to the other brands. All the brands had values within the range specified for assay in the BP. The dissolution profiles showed that none of the brands had dissolution less than 75% within 30 minutes, dissolution efficiency at 30 minutes (DE30) more than 85%. All the four brands could be regarded as bioequivalent and therefore can be interchanged in the clinical practice. This sort of study is good indicator for the evaluation of the idealness of commercial products.

INTRODUCTION: The marketing of drug product from multisource registered by national agencies in developing countries with competitive pricing, has its attendant dilemma of ascertaining their quality and inter changeability[1]. Unacceptable trends of different clinical responses to drugs presented as generics and batch - to batch inconsistencies have been reported [2].

The oral route is most frequently used for introducing drugs into the body, and in fact the vast majority of drug dosage forms are designed for oral ingestion [3]. Tablets are the most frequently administered oral solid dosage form. The increases in the number of generic drug products from multiple sources has placed people involved in the delivery of health care in a position of having to select one from among several seemingly equivalent products [4].

Tablets are solid dosage forms, containing medicinal substances with or without suitable diluents. They may be classed, according to the method of manufacture, as compressed or molded tablets [5]. The properties of tablets are usually

evaluated with respect to various physicochemical parameters such as appearance, hardness, friability, uniformity of active ingredients, disintegration and dissolution [6].

Quality of pharmaceutical product is the most important for efficacy and safety of product. Quality control tests are performed on tablets during manufacturing and on the final product batches. Generic drugs are chemically equivalent to their brand-name counterparts in terms of active ingredients but may differ in other aspects such as color, shape, excipients employed, and manufacturing process.

Drug products that are chemically and bio-pharmaceutically equivalent must be identical in strength, quality, purity, active ingredient release profile and should be in the same dosage form, for the same route of administration [7]. Therefore, analysis of these parameters for the generic product to ensure that they can be used interchangeably, where the observation is that most of the generic products have lower shelf prices than the innovator, which raises the problem of possibility of unequal product performance [8, 9].

Dissolution testing of drug products play an important role as quality control tool to examine batch to batch consistency of drug release in addition can be used as a qualitative and a quantitative tool, which can provide important information about biological availability of a drug [10]. Therefore, in order to ensure the required quality, drug manufacturers are required to test their product during and after manufacturing and at various intervals during the shelf life of the product. As such they require to ensure that the generic and branded drugs products are pharmaceutically equivalent cannot be overemphasized and the requirement to select one product from several generic drug products of the same active ingredients during the course of therapy is always a cause for concern to health practitioners [11, 12].

Dissolution tests are used nowadays in the pharmaceutical industry in a wide variety of applications [13], to help identify which formulations will produce the best results in the clinic, to release

product to the market, to verify batch- to- batch reproducibility [14], to help identify whether changes made to formulations or their manufacturing procedure after marketing [15].

The increase level of use of Simvastatin tablets in clinical practice creates the need to monitor and ascertain the quality of the various brands available in the drug market for quality control assessment and for purpose of generic substitution. Simvastatin is a cholesterol lowering drug of the group called statins to lower cholesterol used when diet and exercise are not enough. In patients with coronary heart disease and elevated cholesterol, Simvastatin is used to reduce the risk of death, stroke, and heart attack. It reduces the amount of cholesterol produced and increases the rate it is removed from the body [16]. Its chemical formula $C_{22}H_{38}O_5$, with chemical name Butanoic acid, 2,2-dimethyl-1,2,3,7.8,8a-hexahydro-3, 7 – dimethyl – 8 - [2-(tetrahydro-4hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, and its structural formula is as shown in **Fig. 1**.
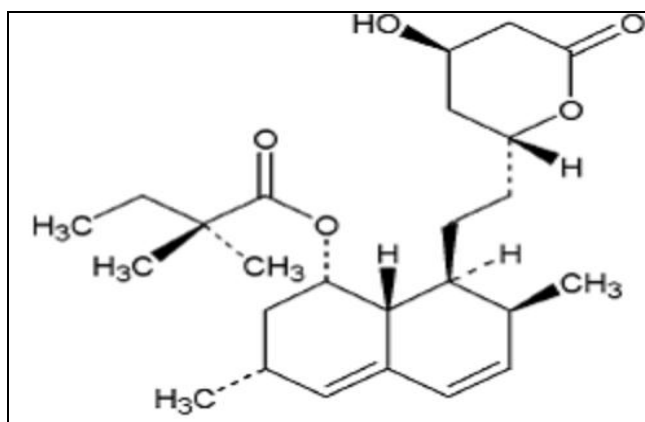

FIG.1: STRUCTURE OF SIMVASTATIN [17]

Simvastatin is a white to off white, non-hygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol. Simvastatin is categorized as a class II drug by the biopharmaceutics classification system (BCS), which implies that Simvastatin has low solubility in aqueous media but high permeability characteristics through the gastrointestinal mucosa. BCS serves as a guide for predicting intestinal drug absorption based on solubility and permeability parameters. Based on the above BCS classification for Simvastatin, drug release from the dosage form

and its solubility in the physiological fluids of the gastrointestinal tract (i.e., its dissolution) are the rate- limiting step for its actual *in-vivo* absorption [18-19].

The present study has been undertaken to evaluate and compare various quality control parameters along with dissolution profile of four marketed Simvastatin tablet brands prior to determining their inter changeability. Drug should be regularly checked to ascertain that their quality meet the standards and to identify counterfeits, where nowadays, drugs can be obtained from more than one source and might be chance of presence of some superiors along with sub-standard drugs, that makes the patients conscious about the selection of safety, effective as well as economical medicine.

MATERIALS AND METHODS:
Simvastatin tablets having a label strength of 20 mg of four different brands were purchased from local pharmacies in Tripoli Libya. The products were coded as A, B, C and D as illustrated in **Table 1** and the study was performed within product expiration dates as shown in **Table 2**. Hydrochloric acid 0.1 M, 0.01 M Sodium dihydrogen orthophosphate, 0.5% w/v Sodium dodecyl sulfate, Sodium hydroxide, Glacial acetic acid and freshly prepared distilled water were used throughout the work.

TABLE 1: LIST OF THE COMMERCIAL SIMVASTATIN BRANDS UNDER INVESTIGATION

Sample No.	Product code	Brand Name	Manufacturer
1	A	Simvastatin®	Bristol laboratories Ltd UK.
2	B	Simvastatin-1APharma®	1A Pharma GmbH, Germany
3	C	Vascor®	Laboratoires adwya route de la Marsa Tunisia
4	D	Simvastatina Normon®	Laboratorios Normon, S.A. Madrid Spain

TABLE 2: LABEL INFORMATION OF FOUR DIFFERENT BRANDS OF SIMVASTATIN TABLETS (20 MG)

Product code	Batch No.	Manufacture Date	Expire Date	Price LD* per tablet
A	HU3001	6-2013	5-2016	0.20
B	DB3304	Nile	12-2015	0.30
C	005 UT AV	11-2013	11-2015	0.53
D	H17X1	4-2013	3-2016	0.22

*LD: Libyan dinar

Visual Inspection:
The general appearance of tablets, their visual identity and overall elegance are essential for consumer acceptance [20]. Samples of 20 tablets from each brand were randomly selected and visually inspected for their external characters such as color, shape, size, presence of grooves, monograms and surface defects.

Uniformity of Weight:
Samples of 20 tablets from each of the 4 brands were randomly selected, their individual weights were measured and recorded using sensitive digital balance. The average weight of each sample was calculated and the deviation of each tablet weight from the average weight was determined in percent [21].

Hardness Test:
Hardness is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength [21]. The hardness, thickness, and diameter of samples of 10 tablets were determined using tablet combination tester (Erweka TBH 320 WTD Multi-Check tester, Germany). In the hardness test, pressure was applied on the tablet and the force caused the tablet to break up was recorded. The values were expressed in Kg/cm^2.

Disintegration Test:
The disintegration time of randomly selected six tablets of each of the four brands was determined at 37^0C in 0.1 M hydrochloric acid using (Pharma test) disintegration tester apparatus. The basket was raised and lowered at a fixed frequency of 30 cycles / min. The disintegration time was taken to be the time no particle of any tablet was left on the basket. The average disintegration time was recorded.

Calibration curve:

A calibration curve was plotted over a concentration range of 4-20µg/mL Simvastatin. Accurately measured standard stock solution of Simvastatin (4,6,8,10,12, 15 and 20µg/ml) were transferred to a separate series of 10 ml of volumetric flasks and diluted to the mark with methanol and water in the proportion of 40:60. The absorbance of each solution was measured at the wavelengths of 238 nm. Calibration curve was constructed for Simvastatin by plotting absorbance versus concentrations. Reading was average of six determinations. Regression equation ($y = ax + b$) where (a) is the slope = 0.063, (b) is the intercept = 0.109, from that Regression coefficient $R^2 = 0.911$.

Estimation of Simvastatin in Dissolution:

UV spectrophotometric method based on the measurement of absorbance at 238 nm in Phosphate buffer pH 7 was used for estimation of simvastatin.

Dissolution Rate Determination:

Dissolution is defined as the amount of substance that goes into solution per unit time under standardized conditions of liquid/ solid interface, solvent composition and temperature [22]. Dissolution test was carried out on four different brands of Simvastatin tablets (20 mg). The reference was coded Vascor® and the three test brands as Simvastatin®,Simvastatin-1A Pharma® and Simvastatina Normon® the test was carried out with four units of each brand using USP apparatus II (Paddle) at 37 ± 0.5 ^{0}C in 900 ml phosphate buffer medium pH 7.0 with 0.5% SLS at 50 rpm. Samples of 10 ml were withdrawn from the dissolution medium at 5, 10, 15, 30, 45 and 60 min intervals, followed by immediate replacement of fresh dissolution medium for the acquisition of sink condition.

The sample was filtered through Whatman filter No. 41. The quantity of Simvastatin released in the dissolution test was assayed for simvastatin at 238 nm. All the dissolution experiments were conducted in triplicate (n=3), for the sample and standard. The absorbance of the blank solution was used to correct the readings on the standard and sample. Preparation of standard solution Simvastatin (reference powder) equal to 10 mg was accurately weighed and dissolved in 10 ml of Methanol in the ratio of 40: 60 (Methanol : water). The prepared solution was sonicated for 5 minutes and filtered through the filter. From this stock solution, 1ml was diluted up to 50 ml with dissolution medium, making the final concentration equivalent to 20µg/ml.

The dissolution test determined the percentage of the active agent released into the dissolution medium, in relation to the value declared on the product label, within the period specified on the monograph. In the first stage, each tablets was expected to release not less than 80% Simvastatin (Q=75% +5%) [23]. The chemical adequacy test on the dissolver (Pharma test) was performed before carrying out the dissolution test, using calibrating tablets of prednisone and acetylsalicylic acid from the same pharmacopoeia [23, 24].

Assay of Simvastatin Tablets:

High performance liquid chromatographic method was used to determine the potency of related tablets. The test for assay is done to determine the actual amount of the active ingredient present in the tablet and it is the same as the labeled amount.

RESULTS AND DISCUSSION:

Table 3 shows the visual inspection of tablets, **Table 4** shows the evaluated physicochemical parameters, while **Fig. 2** represents the dissolution profiles of all the four brands. All investigated brands were within their shelf life at the time of study. Four different brands of Simvastatin tablets obtained from different pharmacies within Tripoli were subjected to a number of pharmacopoeial tests in order to assess their biopharmaceutical equivalence.

The assessments involved the evaluation of uniformity of weight, hardness, disintegration and dissolution as well as chemical content determination. The USP uniformity of weight determination for all the brands gave values which complied with official book specifications for weight uniformity as none of the brands deviated by up to $\pm 7.5\%$ and none of tablets differ by more than double that percentage limit, from the mean value. Where tablets weighting more than 130 mg but less than 324 mg.

Crushing strength test shows the ability of tablets to withstand pressure or stress during handling, packaging and transportation. It is a property of a tablet that is measured to assess its resistance to permanent deformation. The result indicates that all brands passed the test while brand B had the highest crushing strength of all the four brands with hardness of 19.76 Kg/cm^2. Thickness and diameter are non pharmacopoeial requirements but naturally they will have an effect on packaging [25] as well as they are used in calculation of tensile strength of tablets [26].

The rate of disintegration is directly proportional to the rate of dissolution. The rate of disintegration is influenced by the rate of influx of water into the tablets. The results showed that all the brands passed the disintegration test according to the pharmacopeia which specifies 30 minutes for film coated tablets. According to the monographs in the pharmacopoeia specification USP 34, for each tablet tested for dissolution, the amount of active ingredient in solution is not less than 75% of Simvastatin is dissolved in 30 minutes. The results obtained from the study revealed that all the brands passed the general standard specifications for dissolution rate test for conventional release tablets. The difference in the result can be correlated to all factors which affect the dissolution rate from the raw material (purity) which can affect solubility, and all diluents which were used in the formulation of each brand [27-30]. The results obtained from the assessment of the percentage content of active ingredient in the four brands showed that all brands gave values within the specification which is average weight content between 95-105% of Simvastatin [31]. **Fig. 3**-**8** shows the HPLC chromatogram of different commercial brands of Simvastatin and the standard.

TABLE 3: APPEARANCE FEATURES OF THE DIFFERENT BRANDS OF SIMVASTATIN 20 MG TABLETS

Parameter	Brand A	Brand B	Brand C	Brand D
Shape and color	White, oblong	Pink, oblong	White, oblong	Pink, round
Surface texture and Convexity	Smooth, Biconvex, coated tablet	Smooth, Biconvex, coated tablet	Smooth, Biconvex, coated tablet	Smooth, Biconvex, coated tablet
Monograms and score lines	Split by break line on one side, embossing SVT on the other side	Split by break line on one side, embossing SIM20 on the other side	Split by break line on one side	Grooved, Split on one side

Physicochemical Properties of Simvastatin Tablets: Weight variation, hardness, disintegration time as well as thickness and diameter are shown in **Table 4**. The drug content was assessed and also shown in **Table 4**.

TABLE 4: PHYSICOCHEMICAL PARAMETERS OF THE FOUR BRANDS OF SIMVASTATIN TABLETS

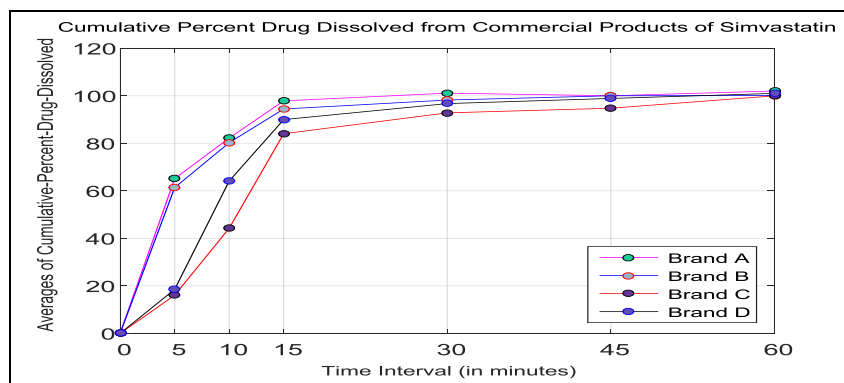| Brands	Average weight g	Weight variation %	Hardness (kg/cm^2)	Disintegration time (sec)	Assay (%)	Diameter (mm)	Thickness (mm)
A	0.2098	±3.43	9.39	366	93.43	10.93	3.979
B	0.2885	±1.80	19.76	981	95.51	11.68	4.354
C	0.2034	±2.21	9.98	283	94.65	11.04	3.581
D	0.2060	±3.39	6.66	38	94.28	8.59	3.456

FIGURE (2) -DISSOLUTION PROFILE OF THE FOUR COMMERCIAL PRODUCTS OF SIMVASTATIN TABLETS

The dissolution efficiency at 30 minutes (DE_{30}) for the brands can be arranged in descending order according to their area under the curve brand A 100 % < brand B 97.81 % < brand D 91.04 % < brand C 85.59 %.
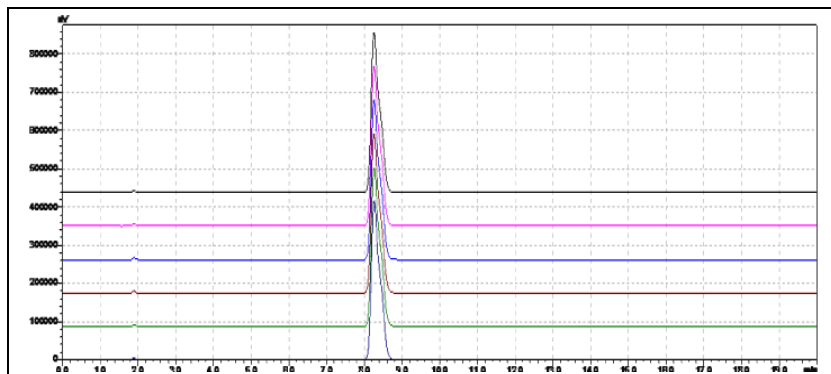

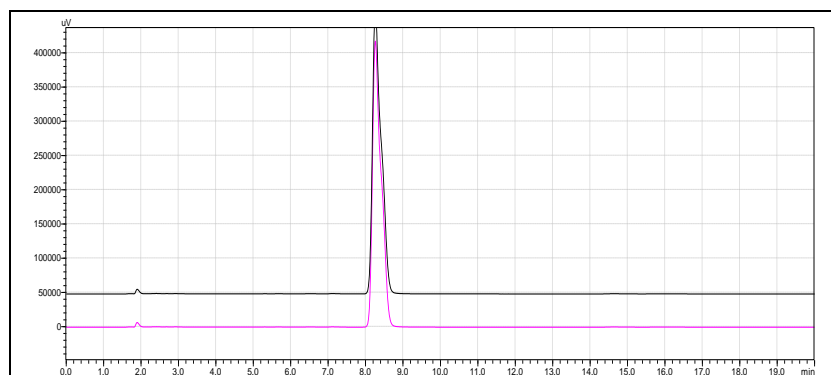**FIG.3: HPLC CHROMATOGRAM OF STANDARD NUMBER 1 OF SIMVASTATIN IN 20 MINUTES**

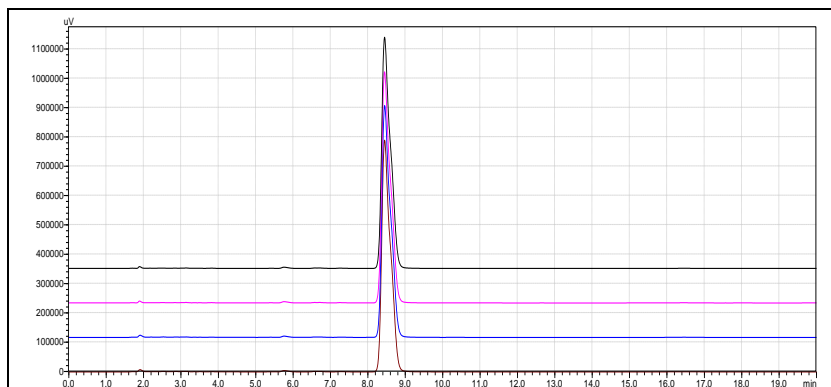**FIG.4: HPLC CHROMATOGRAM OF STANDARD NUMBER 2 OF SIMVASTATIN IN 20 MINUTES**

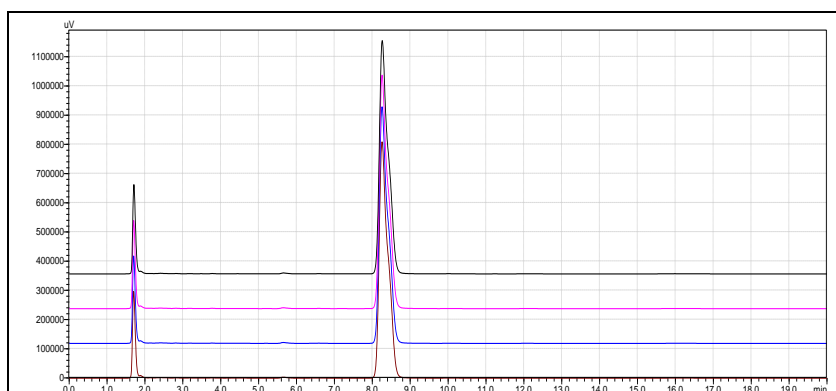

FIG.5: HPLC CHROMATOGRAM OF BRAND A IN 20 MINUTES
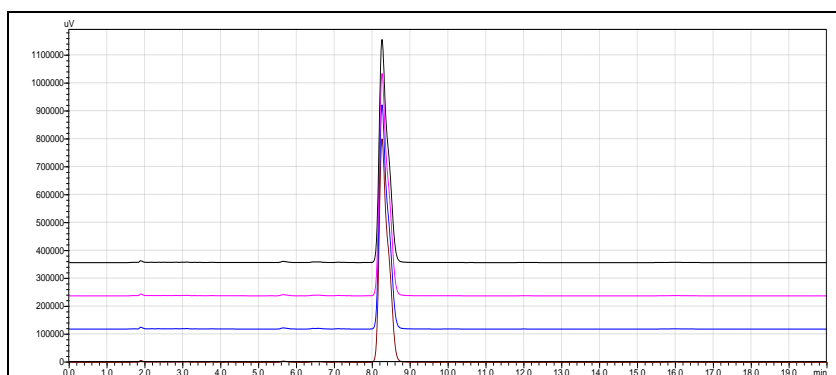

FIG.6: HPLC CHROMATOGRAM OF BRAND B IN 20 MINUTES

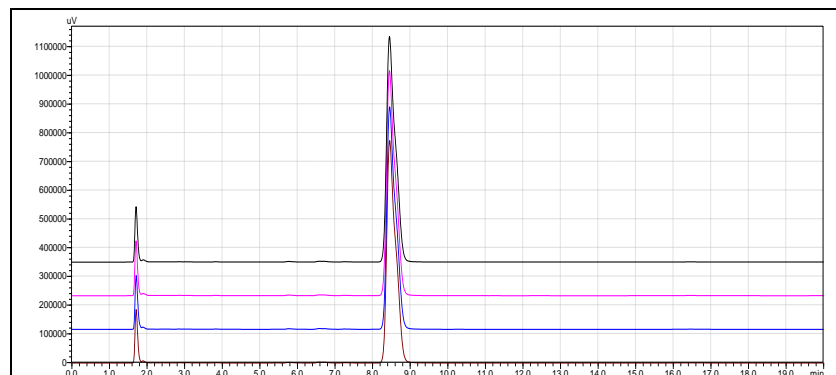**FIG.7: HPLC CHROMATOGRAM OF BRAND C IN 20 MINUTES**

FIG.8: HPLC CHROMATOGRAM OF BRAND D IN 20 MINUTES

CONCLUSION: Four brands of Simvastatin 20mg tablets have been subjected to analysis according to the Pharmacopoeia. The results have shown that all the tested brands satisfied the requirement in term of weight uniformity, hardness, disintegration and content uniformity and their dissolution curves and dissolution efficiency were similar thus could be considered bioequivalence and therefore can be substituted with each other in clinical practice. According to the present study patients can safely switch from one brand to another. This study emphasized the need of constant inspection on marketed drug product by the government, manufacturers and independent research groups to ensure supply and availability of quality medicines for the patients and *in vitro- in vivo* bioequivalence.

REFERENCES:

1. Yashavant A. Chikate, Kundan P. Chaudhari, Umesh T. Jadhao, Vinod M. Thakare, Bharat W. Tekade, Vijay R. Patil: Formulation and *in-vitro* evaluation of simvastatin buccoadhesive tablets. International journal of biophrmaceutics 2014; 4 (3):156-163.
2. Reem Khamis Al Naimi and Shah Alam Khan. Comparative *in-vitro* Pharmaceutical Evaluation of Four Brands of Metronidazole Tablets Marketed in Gulf Region. Jordan Journal of Pharmaceutical Sciences 2014; 7(2).
3. P. Amsa, S. Tamizharasi, M. Jagadeeswaran, T. Sivakumar. Preparation and solid state characterization of simvastatin nanosuspensions for enhanced solubility and dissolution. International Journal of Pharmacy and Pharmaceutical Sciences 2014; 6(1).
4. Delina Xhafaj, Ledjan Malaj, Migena Mileti. A comparative quality control study of cetirizine hydrochloride 10 mg tablets on the albanian pharmaceutical market. International Journal of Pharmacy and Pharmaceutical Sciences 2015; 7(1).
5. Linda A. Felton. Remington- essentials of pharmaceutics. First edition 2013.
6. Ashim K. Mitra, Deep Kwatra, Aswani Dutt Vadlapudi. Drug delivery 2014.
7. A.K. Azad, Mohd. Aminul Islam, W.S. Wan Mohd Azizi . Appraisement of Ranitidine Hydrochloride Tablet (USP150mg) Preparations from Few Selected Companies in Bangladesh. Pakistan Journal of Nutrition 2013; 12 (11): 966-972.
8. Ahmed M. A. Masaad, Majed Al robaian. Post market monitoring of Five Marketed Brands of Ciprofloxacin. IOSR Journal of Pharmacy 2016; 6(2): 14-19.
9. Sing Gajendra and Khinchi M.P. An approach for Poorly Water Soluble Drug, ijpls 2012; 3(9):1991-1996.
10. Ganesh K. Derkar, Rajshekhar M. Chimkode, Priti Bhoite, Ankita Desai, Mayuri Gatade. Comparative *in-vitro* bioequivelence evaluation of different brands of indomethacin capsule Am. J.Pharm Tech Res. 2016; 6(1): 356-363.

11. N. Srujana, Venkata Nitin Chilukuri, Valluru Ravi, Balamuralidhara. V. Pramodkumar. T.M. Comparative study of in-process and finished product quality control test's of IP.BP.USP, EP, JP for parenterals. Am. J. Pharm Tech Res. 2012; 2(3): 305-325.

12. J.C. Rivera-Leyva, M. Garcia-Flores, A. Valladares-Mendez, L. M. Orozco-Castellanos and M. Martinez-Alfaro. Comparative studies on the dissolution profiles of oral ibuprofen suspension and commercial tablets using biopharmaceutical classification system criteria. Indian J Pharm Sci. 2012; 74(4): 312-318.

13. David Attwood, Physical Pharmacy. Alexander T Florence 2007:154, 156, 163.

14. Alfonso, R.G. Remington the science and practice of pharmac, 2000: 20th Ed., Philadelphia.

15. Ahmed M. A. Masaad, Majed Al robaian. Post market monitiring of five marketed brands of ciprofloxacin. IOSR Jornal of pharmacy 2016; 6(2): 14-19.

16. Swamy KS. Goud BA. Kumar PV. Bioadhesive buccal tablets of simvastatin. Journal of advance Pharm Sci. 2011; 1(1): 29.

17. Graham L. Patrick. An introduction to medicinal chemistry. Fifth edition 2013

18. Rao, M., Mandage, Y., Thanki, K, & Bhise, S. Dissolution Improvement of Simvastatin by Surface Solid Dispersion Technology. Dissolution Technologies 2010; 27-34.

19. Sharma A, Saini S. Process validation of solid dosage form: a review. International journal of research in pharmacy and science 2013; 3(2): 12-30.

20. Aulton ME, Wells TI, Pharmaceutics, The Science of Dosage Form Design, Churchill Livingstone, Vingstone, London, 1988; 168.

21. Rudnic E, Schwartz JB, Oral Solid Dosage forms In: Remington's Pharmaceutical Sciences, 18th edition, Mack publishing Company. Easton, Pennsylvania, USA; 1990; 1633-1665.

22. I.E. Shohin, J.I. Kulinich, G.V. Ramenskaya and G.F. Vasilenko. Evaluation of *in-vitro* equivalence for drugs containing BCS Class II compound ketoprofen. Dissolution technology. 2011;(2): 26-29

23. The United States Pharmacopeia. 34[th]ed. Simvastatin, Simvastatin Tablets. Rockville: United States Pharmacopeial Convention, 2011.

24. Ibide dissolution procedure: development and validation *<1092>*. Rockville: United States Pharmacopeial Convention, 2011a.

25. Sarfaraz, N. (1979) Text Book of Biopharmaceutics and Clinical Pharmacokinetics. Appleton- Century- Crofts, New York.

26. Gunsel, W.C. (1980) Tablets. In: Pharmaceutical Dosage Forms (ed. H.A. Liberman, and L. Lachman), 198. New York: Marcel Dekker.

27. European Pharmacopoeia. 7 ed. Simvastatin. Strasbourg: Directorate of Quality of Medicines of the Council of Europe, 2011.

28. Kapur NK. Musunuru K. Clinical efficacy and safety of statins in managing cardiovascular risk. Vasc. Health Risk Mana 2008; 4(2): 341-353.

29. Marques- Marinho FD, Zanon JCC, Sakurai E, Reis IA, Lima AA, Yianna-Soares CD. Quality evaluation of simvastatin compounded capsules. Braz. J. Pharm. Sci.2011; 47(3): 495-502.

30. Hofer, Jeffrey D., Gray Vivian A. Examination of Selection of Immediate Release Dissolution Acceptance Criteria, Dissolution Technologies 2003; 10(1): 16-20.

31. British Pharmacopeia. *Simvastatin preparation*, volume III, 2009.