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POST MARKETING QUALITATIVE DISSOLUTION TESTING FOR FIXED DOSE TABLETS WITH NEW DEVELOPED VALIDATED METHOD

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Abstract:

Fixed dose tablets are gaining value as they give a Fixed dose combination therapy (FDC) method for direction of contrary or synergistic drugs and decrease many doses. However, two different active ingredients or parts of active pharmaceutical ingredients with diverse liberate individually may be formulated as one unit, containing diverse potency. The maximum study is going towards substantial stability (avoidance of delamination), concurrent dissolution testing of dissimilar active pharmaceutical ingredients in fixed dose tablets has been ignored. In this study, a new developed validated method for concurrent analysis of dissolution study of glibenclamide and metformin from fixed dose tablets. Dissolution medium was chosen on the establishment of solubility, sink conditions for drugs. A variety of investigational conditions (kind of equipment, stir rate and volume of dissolution medium) were optimized, and the new method was validated according to ICH and USP guide lines. Investigation of dissolution samples was assessed by HPLC column: Merck LichroCART 250 x 4 C 18(Cat.1.51378) as the stationery phase. The composition of mobile phase was acetonitrile, phosphate buffer(pH5.3, 50:50, v/v). The flow rate of the mobile phase was 1 ml/min at 40^{0}C and the wavelength was set at 230 nm. The most excellent dissolution profiles were achieved with 900 ml dissolution medium of Phosphate buffer pH 7.4 at 37± 2^{0}C, stirred at 75 rpm utilizing apparatus -II. Total dissolution completed within 45 minutes. Validation criteria revealed accuracy, precession and robustness of the novel method with no any intrusion through sample analysis. Validated method would be useful in fixed dose tablets containing glibenclamide and metformin hcl at any stage of formulation development, quality control investigation and post marketing inspection studies.

Keywords: *Fixed dose tablets, glibenclamide, metformin ,dissolution, method validation.*

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INTRODUCTION:

Dissolution is the rate-limiting step used for absorption of drug and utilized to evaluate the value of dosage form at diverse steps in formulation life cycle, starting from formulation development and marketed sample examination [1]. This study is used to determine the drug liberate rate from a solid dosage form [2].Dissolution is a necessary equipment for assessing the result of formulation and methods variables on appearance of the final formulation all over its stability [3]. Fixed dose combination of oral anti diabetic drugs are slowly suitable to established an appropriate options in the healing of type 2 diabetic. Which can simply use, for patients particularly taking frequently different strength of doses. Fixed dose combination offer an expedience additional medication without further tablets.

Fixed dose combination (FDC) treatment is known as a combination of two or more drugs in a fixed share of doses, International Diabetic Federation (IDA), and American Diabetic Federation (FDA), be likely to propose if the single drug fails beside lifestyle alteration the patient must used fixed dose combination treatment. Combination remedy consist on the justification of a multi targeted approach that helps to get and continue the preferred curative targets. Advantages of fixed dose mixture are simple of using, synergistic effect convenience, balancing mechanism of action, through low dose less side effects, also economical as reduce the medication burden and thereby, get better fixed glycemic control, get better adherence to treatment, reduce the occurrence/severity of unfavorable drug effects, interruption the need for insulin treatment[4,5]. Currently, wide-ranging study has been done, to decide a variety of troubles associated to fixed dose tablets. Mostly the growth of structural dependability (avoidance of delamination), with mechanical strength to the tablet that is upper crushing power and lower friability time. Dissolution assessment of fixed dose tablets having diverse active pharmaceutical ingredients has been unnoticed via pharmaceutical study. Generally dissolution liberate rate of diverse APIs, enlisted in fixed dose tablets is assessed as for conventional tablet. Imperfect information is existing concerning development of dissolution analysis methodologies, valid for various drugs, having in fixed dose tablets.

Diabetes considered to be a chronic disease by high concentration of sugar in the blood. Diabetes mellitus often referred to simple as diabetes, which roughly translates to excessive sweet urine. Which is a noninfectious sickness, in the body systems affected by the endocrine and urinary systems, digestive, nervous, circulatory, but the entire body system are in some means affect. To get the beneficial anti-diabetic effect of poly drug combination on a single tablet with double release mechanism. To develop the patient compliance by giving the combination as a single dosage form. To decrease the dosing rate, the patient already getting the glibenclamide 5mg, metformin 500mg that two times a day to once daily dosage form. To give Safe, effective and stable pharmaceutical oral formulation containing both immediate release and sustained release of two or three anti-diabetic drugs with different mechanism of action to improve glycemic control [6].

Glibenclamide is a hypoglycemic an oral drug (sulphonylurea group), utilized in healing of non-insulin needy diabetes patients. The compound name for glyburide is 1- [p-[2-(5-chloro-o-anisamido)ethyl]phenyl]sulfonyl]-3-cyclo- hexylurea. It is a white to off-white crystalline chemical agent with a formula of C23H28ClN3O5S having a molecular weight of 494.01. It has less bioavailability, that is recognized to its weak dissolution nature [7]. however, as a weak acid with a pKa of 5.3, its solubility depends on the pH of the particle size and analysis medium [8].

Metformin is an antihyperglycemic agent utilized in the treatment of type 2 diabetes. Metformin hcl is not pharmacologically or chemically associated to sulfonylureas, α-glucosidase or thiazolidinediones inhibitors. Which is a white to off-white crystalline chemical compound having a molecular formula of C4H12ClN5 with a molecular weight of 165.63. Metformin hcl is completely soluble in water and almost not soluble in ether, acetone, and chloroform. The metformin pKa is 12.4. The pH of a metformin 1% aqueous solution is 6.68. Metformin HCl is an orally used as antidiabetic drug of the biguanide class. It is suggested as a choice of first line drug for the management of non- type 2 diabetes mellitus or insulin-dependent diabetes mellitus (NIDDM) or [9].

GLUCOVANCE has been marketed and used orally in tablets dosage forms containing 5 mg glibenclamide with 500 mg metformin hcl as fixed dose tablet. Dissolution study for single ingredient formulations of glibenclamide and metformine have been conducted through a variety of regulatory bodies. Developing a dissolution technique for combination formulation of two medication was required to decrease the analysis cost and time. In addition, to carry the formulation development efforts, an appropriate solitary dissolution testing was necessary. Glibenclamide is a BCS class-II, has a less

solubility outline, whereas glibenclamide is connected with stability and solubility troubles. [10,11].

It is hard to develop dissolution testing analysis situation without solubility or stability issues. This study demonstrates, development and validation with single dissolution testing method for fixed dose tablets having glibenclamide and metformine. Major confront was to discover dissolution medium to combine the two drugs and create robust outcomes without any solubility and stability problems. Furthermore, analysis of the sample by direct spectrophotometry method was inappropriate for mixture product, due to lacking of specificity, thus a high- performance liquid chromatography (HPLC) technique used for dissolution samples. A new developed method used to assess the potency of the commercial batches marketed for the period of 2016 and 2017 in Quetta, Balochistan.

MATERIAL AND METHODS:

Fixed dose tablets having metformin and glibenclamide were bought from a local market in Quetta, Balochistan . The metformin and glibenclamide reference standard were gifted by Merck Sereno Factory.(Quetta, Pakistan). Other Chemicals ($NaHPO_4$, acetonitrile, HCl etc) were purchase from chemical market of Pakistan. All the chemicals were used of analytical standard .

Dissolution tests were done in the dissolution analysis apparatus (Erweka DT-6) and analysis of the drug testing were performed by HPLC. The developed HPLC system (Agilent Technologies, 1100 Series, USA) was set with LC- 10 AT VP pump. Set with a DGU-AM 14 degasser, manual injector system and SPD-10 AVP UV–VIS detector, Merck Lichro CART 250x 4 C 18 (cat.1.51378) column. Agilent software 1100 Series, USA Chem Station Series 2001-2005 was utilized for qualitative and quantitative data collection and processing. The chromatographic mobile phase composed of acetonitrile and phosphate buffer pH:5.3 (50:50 v/v) Buffer solution pH 5.3 were used.

Transfer 28.8g Ammonium dihydrogen phosphate to 1 lit flask. Dissolve and dilute with water. Mix well and adjust pH with 1 N NaoH to 5.3 (Ammonium dihydrogen phosphate 0.25M).Inject volume 20 µl, detected at a wavelength of 230 n

Fig.1*:* Fixed dose tablet containing glibenclamide and metformin

Choice of dissolution medium

Dissolution medium was chosen on the criteria of solubility for (glibenclamide, metformin) and sink environment through dissolution analysis. Conical flask shaking technique was utilized for assessment of balance solubility of both samples (metformin and glibenclamide) in different dissolution medium [12,13]. The surplus of drug was used in test media, dissolved and sonicated for 10 minutes and continuously shaking for 24 h at 37 ± 2°C and filtered. Analyzed for drug content using HPLC. Processes typically utilized in the plan of dissolution medium, slightly soluble drugs comprise: bringing almost drug solubility by rising the aqueous sink volume otherwise removing the dissolved drug, change of pH and improve the solubility of ionizable drug compounds [14,15].

Both metformin and glibenclamide tablets have official monographs in USP. every dissolution tests conducted utilizing an Erweka DT-6 dissolution tester of (6 vessels) in agreement with (USP) general method <711>. Dissolution testing on (3), commercially accessible formulation tablets of GLUCOVANCE were assessed using USP apparatus 2 (paddle method). Analysis dissolution media was 500 and 900 ml of monobasic potassium phosphate USP buffer (pH 7.4 and 8.0) stirred at 50 and 75 rpm.

The guidelines for metformin dissolution media is USP-39/NF-34, independently the dissolution rate of dissolution parameter of metformin: (pH 7.4 Phosphate buffer, 1000 ml, Apparatus: Paddle, 50 rpm), in each case, analysis samples are drawn after 30 minutes, assessed for drug constituents [16].

In the current research study, dissolution rate as of

Fixed dose tablets, containing metformin and glibenclamide assessed in dissolution medium suggested for both drugs individually and media prepared on the foundation of solubility, ratio of different dissolution media, utilized in this study, are given

- SLS Phosphate buffer (pH 7.2).
- Phosphate buffer (pH 5.8).
- Sodium Phosphate buffer (pH 7.4-8).
- Acetate buffer (pH 4.0).
- 0.1 N Hcl

Dissolution medium given that sink conditions (Cs/ Cd ≥3) was used to further study.

Experimental condition optimization

The choice of optimal experimental conditions for different investigational parameters such as, kind of shaking rate, apparatus, and quantity of dissolution medium were assessed at various stages, as mentioned by USP monographs, with the result on dissolution rate was assessed [16]. The USP suggested different sort of dissolution testing instruments for conventional tablets:

- Apparatus-II: Paddle technique

The choice of type-II apparatus, speed of dissolution was assessed and outcomes compared in conditions of time in use for entire drug liberate. Equipment showing faster liberation was chosen for dissolution testing of fixed dose tablets.

Dissolution also affect by rotation speed procedure, rotation speed observed at 50 and 75 rpm in this method, result liberation was assessed. Dissolution solution quantity is an essential aspect for solubility, dissolution solution quantity optimized via observing dissolution volume utilizing 450ml, 900 ml of dissolution medium, and assessed the results.

Dissolution studies rate

The rate of dissolution for metformin and glibenclamide from fixed dose tablets were assessed utilizing dissolution USP apparatus- II (paddle method), with optimized investigational situation. Earlier to dissolution analyzing, dissolution medium were sonicate for 5 minute at 37 ± 2°C. Placed One FDC tablet in dissolution vessel containing dissolution medium at 37 ± 2°C. Samples (five ml) were taken at particular time (0, 5 10, 15, 30, 45, and 60 minutes), after removing filtered, analyzed for the drug liberate in triplicate. After every sample dissolution volume corrected by dissolution medium.

Assessment of the drug content in samples

For the period of dissolution assessment, samples were together at particular time period and assessed for drug liberate by HPLC. Merck Lichro CART 250x 4 C 18 (cat.1.51378) was utilized as a stationary phase. Liquid phase composed of acetonitrile and phosphate buffer pH:5.3 (50:50 v/v), flow rate of pump was 1 ml/min , temperature 40^0 C, wavelength of detector was set at 230 nm. Inject volume 20 µl, drug constituents of sample was analyzed by evaluation of peak height and area of standard in sample solutions. Both samples were analyzed in triplicate .

Stock standard solution

Stock standard solutions, (1 mg/ml) of glibenclamide and metformin were prepared in 50% v/v (water +Acetonitrile) solvent. Daily basis working solutions were prepared with dissolution medium from prepared stock standard solution. All solution were filtered properly before analysis.

Standard solution

Accurately weigh approximately 55.55 mg of glibenclamide in to 100 ml volumetric flask. Dissolve and prepare the volume with 50% v/v (water +Acetonitrile). Dilute 1 ml of this prepared solution in a 100 ml V. flask containing 55.55 mg. Metformin Hcl and make up the volume the volume with (Buffer solution pH:7.4).Dissolve 6.53g of monobasic potassium phosphate and 1.5g of sodium hydroxide in 1000ml purified water. measure the pH it must be in the range 7.35-7.45.Dilute 1 ml of this prepared solution in to a 100 ml V. flask with 50 % v/v (water + Acetonitrile)

Sample preparation

Place one tablet in each of 6 dissolution vessels and at the specified sampling time with draw 10 ml sample and filter dilute 1 ml further diluted in to 100 ml 50 % v/v (water + acetonitrile)

VALIDATION OF NEW DISSOLUTION METHOD

As per ICH guidelines and USP, new method of dissolution validated for different conditions; accuracy, specificity, precision and stability, given below [17-20].

Specificity

Dissolution validated method specificity was assessed via probing the outcome of dissolution medium peak results (retention time, area, tailing factor and height). Dissolution medium was assessed with (blank) and recognized quantity of drug, and outcomes were compared.

Accuracy

Determination accuracy of the projected dissolution technique was assessed through percent recovery. A solution having 5 mg/mL of glibenclamide drug and 500mg/ml of metformine was arranged in acetonitrile and water. Aliquots (0.8, 1 and 1.2 ml) of each solution were added to dissolution media to get the drug concentration in the range of 80–120% of the nominal dose. Dissolution medium was maintain at 37 ± 2°C and stirred at 75 rpm for 15 minutes. Drawn samples (5 ml) were assessed for drug concentration, and percent recovery was assessed .

Precision

The precision of dissolution method was assessed in conditions, repeatability and intermediate precision. Dissolution test was done in six basket of the dissolution analyzing equipment at the same time below same situation, and outcomes were compared for changeability. Intermediate precision assessed on condition of intraday and interday observation. Intraday analysis was done by re observing, dissolution studies three times in a day, and compared the results. Interday dissolution study was repeated on a every day basis for 3 days in the similar situations, results compared for changeability, SD and % RSD .

Stability assessment of solutions

Dissolution solutions stability assessment was done at three situations temperature at 2–8°C; ambient temperature, 24 ± 3°C; and high temperature, 40 ± 3°C. for three days. standard reserve solution of each one drug (glibenclamide and metformin), prepared dilution with dissolution medium (Phosphate buffer pH 7.4) at particular concentration (20 µg/ml). The solution was separated into three parts, stored at particular temperatures for three days. Drawn samples assessed for drug concentration on every day basis, percent recovery of analytes were assessed in triplicate. Observation were showed as mean ± SD; % RSD (n = 3).

Comparative study of the dissolution profiles

For comparison of similarity and dissimilarity factors an independent model approach was used

RESULTS AND DISCUSSION:

Glibenclamide is BCS class-II drugs, consisting less water solubility but metformin has good water solubility. These drugs are official and dissolution observation has been mentioned in the USP official monographs, separately [16]. Solubility parameter of PH indicates the solubility is pH reliant. It showed considerable solubility at pH 1.2, 1.5, and 8.0. Highest solubility showed in phosphate buffer at pH 7.4. Solubility of pH raises while the pH decreases (Table. 1). Since pH is a weak base and present in ionized form at a pH low than its pK_a of 12.06 [17].

The purpose of this research study, to develop a single dissolution testing technique for Fixed dose tablets having glibenclamide and metformin which could be used for both the APIs, concurrently, with no one solubility and stability problems.

Choice of dissolution medium

Solubility shows important function in dissolution study, and its relationship is well recognized [21]. In current research study, sink conditions development on the foundation of solubility to-dose ratio (Cs/Cd) utilized as essential parameter for the choice of dissolution medium. A developed sink condition observed while the concentration of drug which can be soluble into the dissolution medium in three times larger than the concentration of drug to be dissolved [22]. A small solubility to-dose ratio indicates presence of non-sink situation through later lower dissolution rates and vice versa. Solubility of glibenclamide and metformin were assessed with various medium (phosphate buffer at different (pH 7.4-8), acetate buffer and 0.1 NHcl and acetate buffer, its dose-to-solubility ratios assessed, indicated in Table 1. Solubility of drugs was accountable for non-sink conditions in medium. Utilize of surfactants in dissolution medium is physiologically applicable and can better to enhance the GIT surroundings [23]. Furthermore, little quantity of surfactant addition , under its serious micelle concentration, is frequently enough solubilize some drug formulations.

In contrast to 0.1 N Hcl, solubility of glibenclamide were very low as compared to pH 7.4 Phosphate buffer increased as shown in Figure 2. Use of 0.1 N Hcl, because dissolution medium was not measured further as the sink situation were not predictable due to lesser solubility-to-dose ratio (< 3). In addition, utilize of the maximum solubility of drugs and sink conditions were observed in Phosphate buffer (pH 7.4) as indicated in Fig. 2.

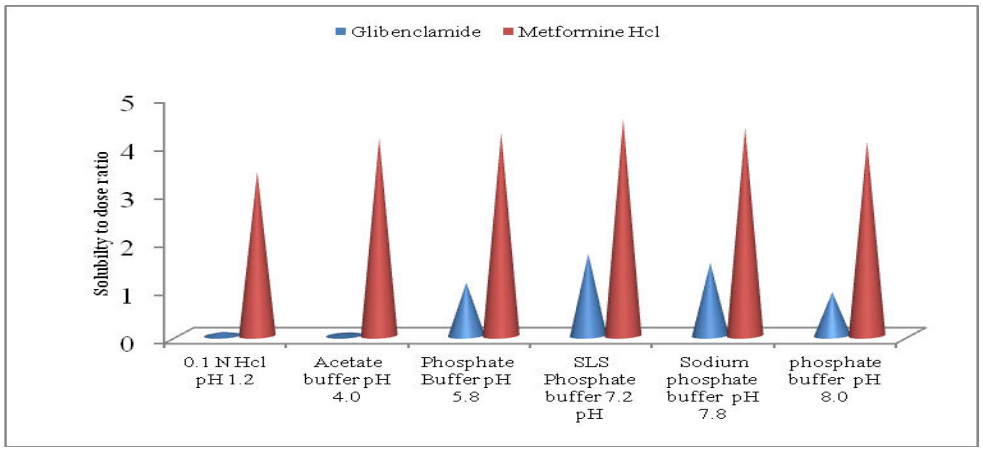

Fig. 2: Solubility of the dose ratio of glibenclamide and metformin in various dissolution medium and association among sink conditions

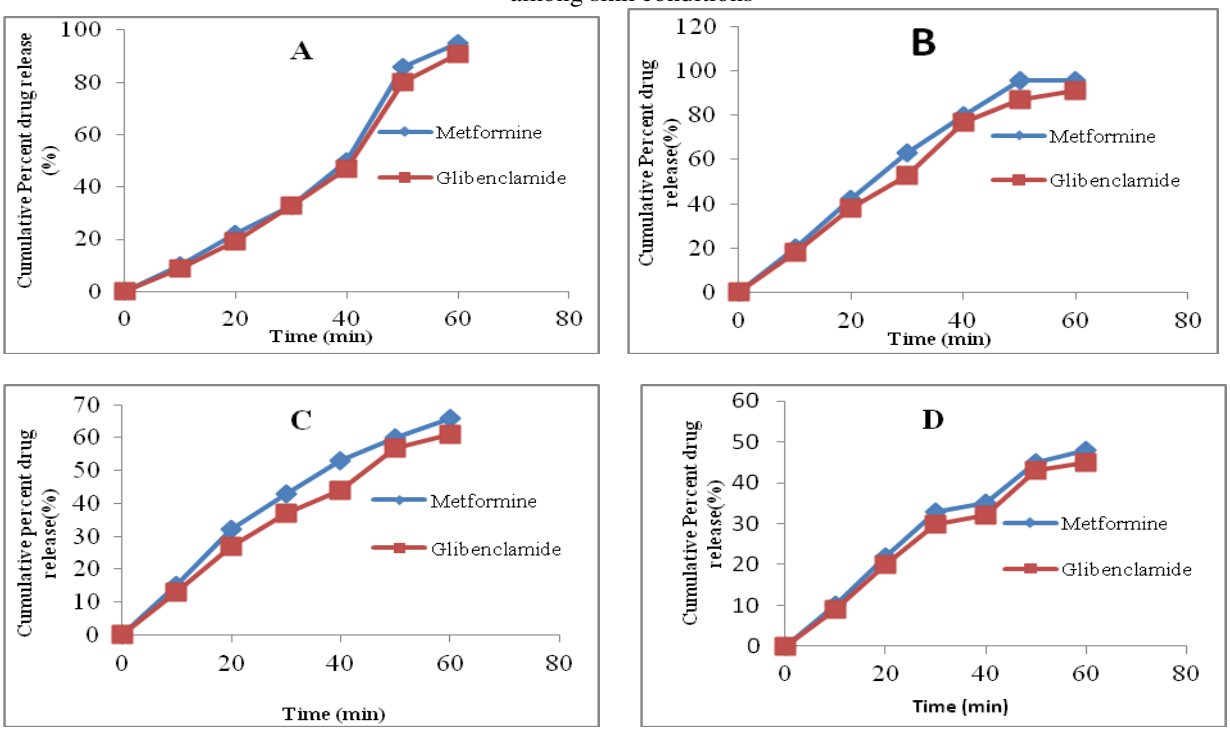

Fig.3: Effect of rotation of speed of the dissolution study at various volumes of dissolution medium (phosphate buffe pH 7.4) (A) 75 rpm,900 ml,(B) 50 rpm,900 ml,(C) 75 rpm,450 ml,(D)50 rpm,450 ml.

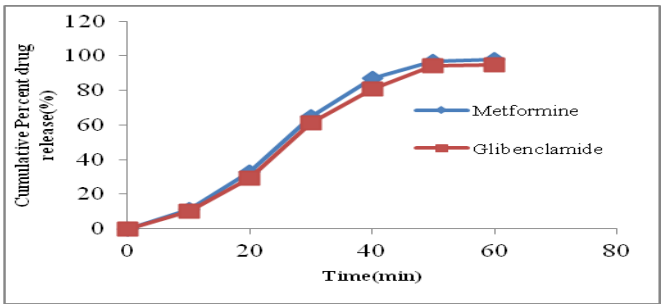

***Fig. 4**:* Dissolution profile of glibenclamide and metformin from Fixed dose tablets.

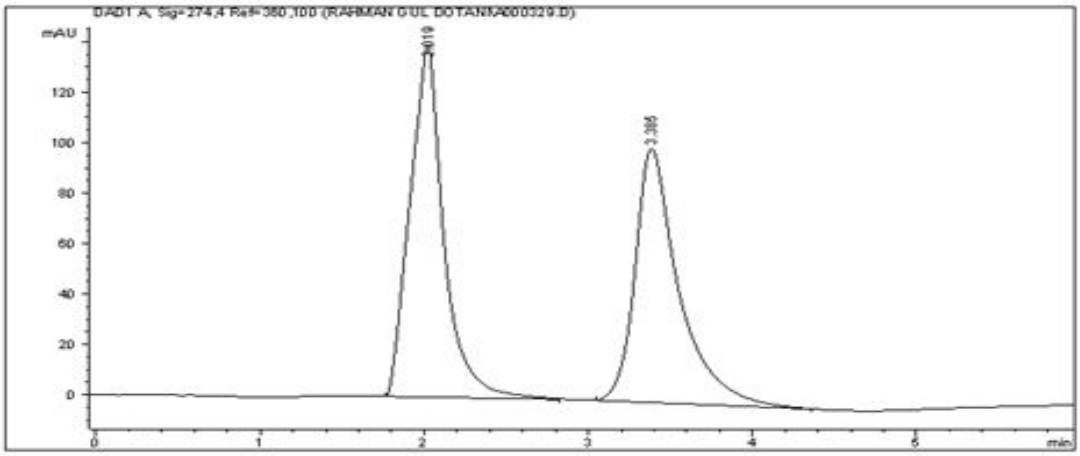

***Fig.5**:* HPLC results chromatogram of glibenclamide and metformin ,in dissolution medium consisted of SLS Phosphate buffer pH 7.2 metformin retention time 2.019 glibenclamide 3.315

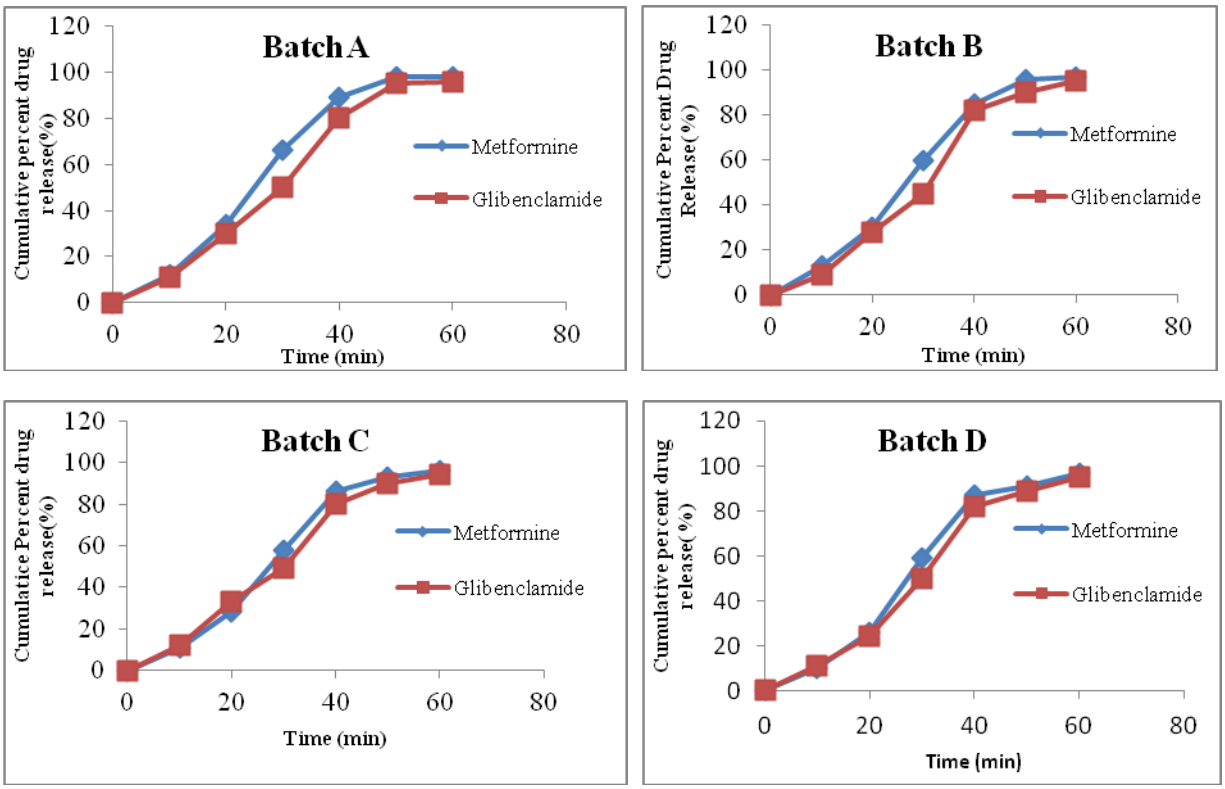

Fig. 6: Dissolution study of four marketd batches (Batches A-D), of fixed dose tabltes containing glibenclamide and metformin.

Table: 1, Glibenclamide and metformin solubility in various dissolution medium among pH

Dissolution medium	**Glibenclamide**		**Metformine Hcl**	
	Solubility (mg/mL)	**C_s/C_d**	**Solubility (mg/mL)**	**C_s/C_d**
0.1 N Hcl pH 1.2	0.08	0.4	3.40	1700
4.0 pH Acetate buffer	0.04	0.2	4.10	2050
5.8 pH Phosphate Buffer	1.10	5.5	4.21	2105
7.2 pH SLS Phosphate buffer	1.70	8.5	4.50	2250
7.8 pH Sodium phosphate buffer	1.51	7.55	4.31	2155
8.0 pH phosphate buffer	0.90	4.5	4.04	2020

Table: 2, Parameters of validation for developed dissolution method

Parameters	**Metformine Hcl**	**Glibenclamide**
Accuracy		
60 mg (80%), (n=30	100.0 ±0.51	98.42±0.36
75 mg (mg)(100%)	99.51±0.41	99.08±0.13
90mg(120%) (n=3)	99.11±0.19	99.01±0.49
Precession		
Repeatability		
Dissolution vessel 1 (n=3)	100.10±0.51	99.18±0.17
Dissolution vessel 2 (n=3)	99.46±0.32	99.68±0.27
Dissolution vessel 3 (n=3)	99.10±0.56	99.98±0.20
Dissolution vessel 4 (n=3)	99.01±0.23	99.99±0.67
Dissolution vessel 5 (n=3)	100.11±0.23	99.08±0.28
Dissolution vessel 6 (n=3)	98.16±0.33	99.93±0.67
Intermediate precession		
Intraday reproducibility.		
8h(n=3)	99.13±0.32	99.09±0.76
16h(n=3)	99.03±0.11	99.01±0.69
24h(n=3)	99.99±0.32	99.05±0.78
Interday reproducibility		
Day 1(n=3)	99.90±0.11	99.00±0.32
Day 2(n=3)	99.99±0.32	98.79±0.87
Day 3(n=3)	99.83±0.21	99.01±0.54

Table: 3, *Stability study of glibenclamide and metformin since solutions arranged in acetonitrile + water and dissolution medium different storage situations for 3 days*

Analytes	Mixture of the solvent	Recovery (%)		
		Room Temperature	Refrigerator ($2\text{-}8^0$ C)	high temperature (40 ± 3^0 C)
Glibenclamide	Stock solution (Acetonitrile + water 50%v/v)	98.01±0.69	99.12±0.69	96.02±0.69
	Developed dissolution media	97.32±0.69	98.32±0.69	94.32±0.69
	Official dissolution media	98.32±0.69	99.32±0.69	98.32±0.69
Metformine hcl	Stock solution (Acetonitrile + water 50%v/v)	99.22±0.69	99.10±0.69	97.30±0.69
	Developed dissolution media	98.12±0.69	98.01±0.69	96.10±0.69
	Official dissolution medium	99.32±0.69	99.11±0.69	97.32±0.69

Results are showed as means ± SD (n=3).
Developed dissolution medium , 0.75% SLS Phosphate buffer pH 7.2; glibenclamide official dissolution media ; metformin official dissolution media, (Phosphate buffer pH 7.4)

Experimental condition optimization

The experimental situation were optimized, by the recognized procedure [9,10].with the composition of dissolution medium, it is based upon different experimental situation similar to sort of dissolution analysis testing equipment (USP apparatus II), volume, speed and stirring conditions. Using USP monographs, for the dissolution rate of glibenclamide and metformin are assessed using apparatus-II (paddle method) . Dissolution parameters of both drugs from fixed dose tablets indicated alike results, by slighter difference in time to get the majority drug liberate. The data of similarity (f_1) and dissimilarity (f_2) factors also recognized of drugs.

At upper level dissolution medium (900 ml), sink situation were recognized (Cs/Cd > 3) for glucovance tablets, result of stirring rate was assessed in the foundation of time necessary for highest drug liberate. Drugs release showed various dissolution profiles through changeable rate of the paddle (50 and 75 rpm), elevated speed (75 rpm), highest liberate of drugs was resulted in less time (45 min) via 900 ml of dissolution medium, whereas, at slow speed rate (50 rpm), 60 minutes necessary for total drug liberate. With lesser volume (450 ml), paddle rate (50 rpm), highest liberate of drugs was less than 55%. Through rising the stirring rate, 12.6% and 11.1% raise in highest release resulted for glibenclamide and metformin , respectively. Decrease in dissolution of drugs observed due to lack of sink situation via lessening volume of dissolution medium, the drugs decreased, considerably. Result of paddle speed in dissolution at various concentration of volume is showed in Fig. 3. Phosphate buffer (pH 7.4) indicated best dissolution profile for glibenclamide and metformin at maximum volume (900 ml) with paddle speed (75 rpm). Drugs released up to 100%, in 45 minutes showed in Fig. 4.

Validation for the Developed dissolution testing Method

It was selected on the bases of observed outcomes, 900 ml, phosphate buffer pH 7.4 through a paddle rate of 75 rpm was chosen, while dissolution test situation for fixed dose tablets constitutes glibenclamide and metformin. Developed dissolution testing technique validated in agreement through ICH guidelines and USP.

Specificity

The developed technique Specificity was observed through chromatographic result, dissolution medium as a blank having various contents of glibenclamide and metformin. Dissolution medium chromatogram showed free of any interfering peak, whereas various concentrations of both analytes showed peaks among concentration-dependent area with stable retention time. Drugs Chromatograms in dissolution medium shown in fig. 5.

Accuracy

The method accuracy was done by percent recovery. Suggestion for greatest precision is method of the

percent recovery inside limit of 95.0– 105.0%. Analysis experimental mean result for glibenclamide was in limit of 98.42-99.08%, while that of metformin was 99.11 to 100% shown in (Table. 2). Representing the dissolution method accuracy of glibenclamide and metformin .

Stability studies of solutions

The Stability studies of dissolution medium of both analytes arranged in (SLS phosphate buffer pH 7.2) was assessed for 3 days. Glibenclamide constituent of the drugs samples was degraded considerably, particularly at high temperature (40 ± 3°C), as indicated in (table. 3).Which has been reported. Results showed dissolution samples having glibenclamide must be assessed in 24 hours [24]. Metformin content was within the range of 96.10 to 99.32%.

Appliance of the method

Fixed dose tablets having glibenclamide and metformin , marketed in Quetta, Pakistan, throughout 2016 and 2017 were assessed, quality depends in drug liberate parameters utilizing developed dissolution analyzing technique. The only batches having accepted minimum 6 to 9 months shelf life incorporated in the research, moreover, the entire batches were tested prior to expiry date. Sum of four batches were chosen of which two batches formulated during 2016 and two were during 2017. The release of drugs from every one batches were alike, within the official monograph limits [17]. Dissolution study criteria of the analyzed batches shown in fig. 6. Regular quality control analyzing, post-marketing surveillance were conducted.

CONCLUSION:

The current study was a robust, perfect dissolution analyzing technique was developed for Fixed dose tablets having glibenclamide and metformin furthermore, validated according to ICH guidelines and USP official monograph. Drugs solubility was assessed in various dissolution medium, along with sink situation were determined. The dissolution study medium was chosen on the criteria of solubility and sink environment for the drugs, moreover different test circumstances optimized. Utilization of dissolution medium 900 ml phosphate buffer (pH 7.4) fixed at 37 ± 2°C at 75 rpm stirred constantly and given acceptable results. The dissolution testing of fixed dose tablets having glibenclamide and metformin was assessed in the chosen dissolution medium under validated test situations, the entire drug released in 45 min. Procedures of validation showed precision, accuracy, and robustness of method lacking any hindrance among analysis. Developed validated method will be supportive in dissolution analyzing fixed dose tablets having glibenclamide and metformin with in the stage of formulation development and regular quality control testing and marketed sample analysis studies.

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