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A COMPARATIVE STUDY WITH EFFECT OF SURFACTANT AND DEGASSING TECHNIQUES ON EXTENT AND RATE OF DISSOLUTION OF GLICLAZIDE MODIFIED RELEASE TABLETS

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ABSTRACT

The class II drug has very poor aqueous solubility, which leads to variability in in-vitro dissolution profile. This research paper relates to the impact of surfactants and a comparative study with some physical parameter on Extent of dissolution rate on extended release dosage form Gliclazide, the release being sensitive to variations in the pH of the dissolution medium. Gliclazide is a hydrophobic weak acid, insoluble in acidic pH and soluble towards neutral to alkaline pH. Variation in pH results in inconsistent and irregular release of drug from the dosage form, which is not a desirable feature .Extended release dosage form. Therefore, the aim of the study was to impact study on enhance the rate of dissolution of the drug in a Extended release Tablet by adding appropriate concentration of surfactants in dissolution media for proper dissolution profiling and other physical parameters like deaeration by different methods e.g. conventional and non conventional methods . The variability in the dissolution profile gets reduced substantially by increasing the localized solubility of the drug by maintaining the pH of the formulation.

Key words *Surfactants ,Gliclazide MR Tablet ,Dissolution Deaeration Extended release tablets.*

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INTRODUCTION

Gliclazide, 1-(4methylbenenesulphonyl) 3-(3azabicyclo [3.3.o] octyl) urea, is a second generation sulphonylurea oral hypoglycemic agent used in the treatment of non-insulin-dependant diabetes mellitus (NIDDM). It improves defective insulin secretion and may reverse insulin resistance observed in patients with NIDDM or known as type two diabetes. These actions are reflected in blood glucose level which is maintained during short and long term administrations, and is comparable with that achieved with other sulphonylurea agents (Palmer and Brogden, 1993). Gradually accumulating evidence suggests that gliclazide may be useful in patients with diabetes retinopathy, due to its hematological actions, and that addition to insulin therapy enables insulin dosage to be reduced (Schernthaner, 2003).

Gliclazide is an effective agent for the treatment of the metabolic disorder associated with NIDDM and may have the added advantage of potentially slowing the progression of diabetic retinopathy. These actions, together with its good tolerability and low incidence of hypoglycemia, allow gliclazide to be well placed within the array of oral hypoglycemic agents available for the control of NIDDM. The objective of this study was to a comparative study with effect of surfactant and deaeration techniques on extent and rate of the Gliclazide MR Tablets to retard the drug release. The Gliclazide content was 30 mg per tablet. The Deaeration method chosen was the conventional and automated mechanical System.

EXPERIMENTAL

MATERIAL AND METHOD

A gift sample of Gliclazide MR Tablet Received from Ranbaxy Laboratories Limited(Gurgaon,india),Sodium dodechyl Sulphate(spectrochem),Tween 20(Merck),distilled water used in study and all analytical works were performed on Water Alliance HPLC 2695 equipped with waters 2996 photo diode array detector, Empower Software, RP C8 column(250*4.0)mm,5um,A calibrated single pan balance Sartorius ME 5 model ,pH meter of Labindia,Diamicron MR purchased from market as a reference material. All chemicals and reagents used were HPLC\AR grade.

Preparation of mobile phase and standard stock solution

The mobile phase was prepared by mixing 600 mL of pH 2.45 orthophospheric acid buffer (pH adjusted to 2.45 with Triethyl amine) buffer with 400 mL of ACN. The mobile phase was sonicated 10 minutes and then it was filtered through a 0.45 µ membrane filter paper. An accurately weighed quantity of Gliclazide working standard 41 mg was transferred to 25 mL volumetric flask, which was then dissolved in ACN and made up to volume with dissolution media phase to give about 35 µg/mL

Prepration of dissolution medium:

sodium dihydrogen orthophosphate media prepared in distilled water pH adjusted 7.4 with diluted sodium hydroxide solution and used as degassed ,as such ,with adding surfactants e.g.Tween 20,Sodium dodechyl sulphate .

MEDIA DEGASSING STUDY VS SURFACTANTS

Solubility study of Gliclazide is carried out in various pH buffer Media e,g,0.1 N HCl, 4.5pH buffer 6.8pH buffer, 7.4 buffer and solubility is described graphically as figure given below as per solubility study Gliclazide is very low soluble in 0.1 N HCl and pH 4.5 acetate and hence does not meet sink condition criteria for dissolution and permeable in pH 7.4 sodium phosphate buffer due to high solubility rather than other media like pH 4,5 acetate buffer,0.1 N HCl, pH 6.8 buffer .seven media was prepared in which first three media was prepared in pH 7.4 buffer treated by different deaeration technique, four representative surfactant-containing dissolution media were prepared in pH 7.4 sodium phosphate buffer :0.5% sodium dodecylsulfate (Spectrochem),1.0% sodium dodecylsulfate and 0.5% Tween 20 (Merck).1% Tween 20 The **first** treatment of pH 7.4 sodium phosphate buffer media was placed in dissolution vessels immediately after preparation, the media were agitated at 100 rpm using USP Apparatus I. A **second** treatment of pH 7.4 sodium phosphate buffer media was filter and degassed by conventional degassing &filtration technique after preparation placed in dissolution vessels and agitated at 100 rpm using USP apparatus I . **Third** treatment of media was prepared according to the USP degassing procedure, placed in dissolution vessels and agitated at 100 rpm using Apparatus I. The drug dissolved of all three media was measured upon placement in the vessels, and at predetermined time points. Only the USP method of degassing required preheating of the media, all other treatments were placed in the vessels at room temperature.

EFFECT OF DISSOLVED GASES CONTENT ON DISSOLUTION RATE

To determine dissolved gases affects media differently, the series of experiments described below was conducted. The experiments were

conducted using media that had been treated by degassed and filter media by conventional filtration technique other was left untreatreated without degassing .and other one treated(heated and degassed) by new mechanical technique as per USP method of degassing To examine if any effects from dissolved gases were dependent upon dosage form,a series of experiments was conducted using predetermined time point for dosage forms. **First** experiment for tablet with a untreated dissolution media was performed This method utilizes pH 7.4 sodium phosphate buffer (100 rpm ,USP Apparatus I,900 mL) and The % of Gliclazide released was monitored by HPLC-with UV detector at 2,6,16 hour. **second** ,Experiment was conducted for tablet with media treated by helium sparging and filter by conventional method media treated pH7.4 sodium phosphate buffer.(100rpm,USP Apparatus I) . The percent of Gliclazide released was monitored by HPLC-UV detector at 2,6,16 hour minutes. **Third** experiment was done with dissolution media treated by latest mechanical technique as per USP, media was preheated and degassed effectively. The percent of Gliclazide released was monitored by HPLC-UV at 2,6,16 hours.

A second set of experiments was conducted to examine the effect of surfactant containing media parallel on a product that was known to be influenced by drug dissolved in aqueous media. This experiment involved the Gliclazide MR Tablets formulation. Although the standard dissolution method does not call for surfactants to be used, the experiment was performed with very low levels of surfactant ,0.5% and1 % SDS in pH 7.4 sodium phosphate buffer and 0.5%and 1% tween 20 in pH 7.4 sodium phosphate buffer. Also amount of surfactant can minimize as desirable to obtain proper drug release pattern. The aerated or non degassed media were generated by bubbling air through the media .The media were heated prior to placing them in the dissolution bath to minimize the time the media in the vessels before beginning the experiment. The percent of Gliclazide released was monitored by direct HPLC-UV at 2,6 and 16 hours. .observation showing influence of degassing results data significantly according to techniques or method use for that and shown a correlation between appropriate quantity of surfactant and degassing effect.

DISCUSSION

The results from the media study show that media prepared with surfactant provide a significant extent and rate of dissolution of Gliclazide MR tablets . and also in the three media(without Surfactants) which is used for comparative study between surfactant content media and degassed media shows also a significant effect on extent and rate of dissolution. Media deaerated with advance deaeration technique provide proper deaeration of media to minimize chance of improper deaeration. in the dissolution bath dissolved gases were caused bubble form and which is created blocked pore of the baskets during the middle and final time points .improper deaerated media have high surface tension and dissolved gases create a barrier between drug and media equilibration .hence also create a big impact on real data. deaeration by conventional techniques which can affect results significantly with respect to true vales or actual drug release. data obtained from degassed media experiments shown significant extent and rate of dissolution of Gliclazide MR Tablets.

CONCLUSIONS

The level of dissolved gases present in the dissolution media can have an effect on the release profile of a Extended Release dosage form e.g. Gliclazide MR Tablets. An experiment performed in media containing a high level of dissolved gases or non degassed media has not given proper and consistent release of drug and could cause difficulties during method validation or method transfer at Quality control . However, the influence of dissolved gases is less of a concern when using surfactant containing dissolution media because of the rapid equilibration time compared with aqueous media. This increase in equilibration rate is most likely due to the decrease in surface tension caused by the addition of surfactant .hence this

study also shows correlation between surfactant impact and use proper degassing technique for true observations and results. and also provide a model to initiate investigation of any inconsistent or improper drug release profile.

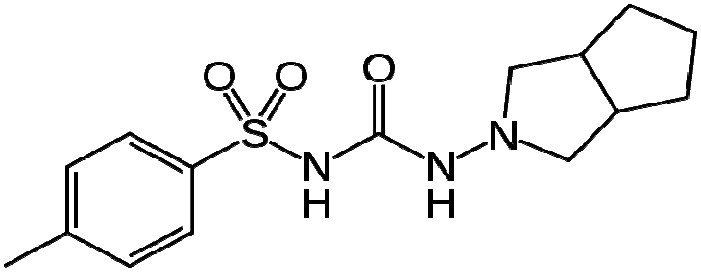

Figure 1 Chemical structure of Gliclazide

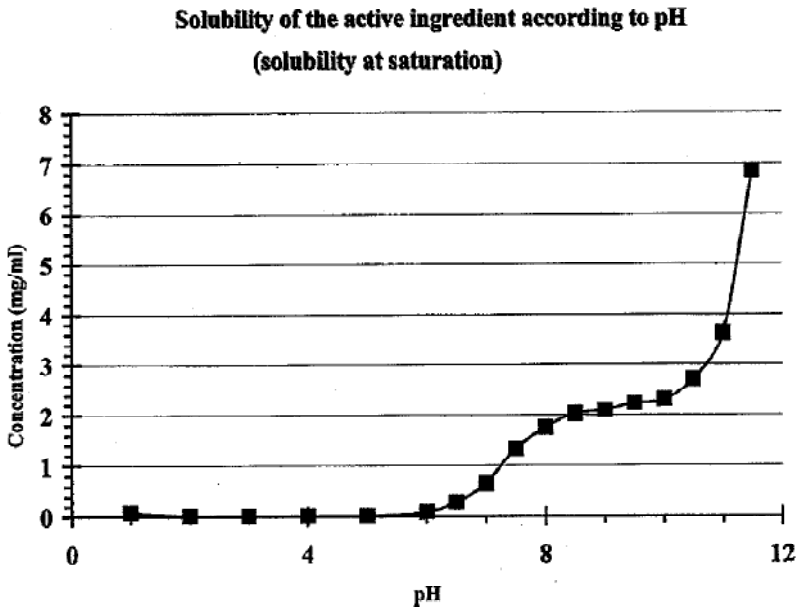

Figure.2 solubility of Gliclazide Active pharmaceutical ingredients

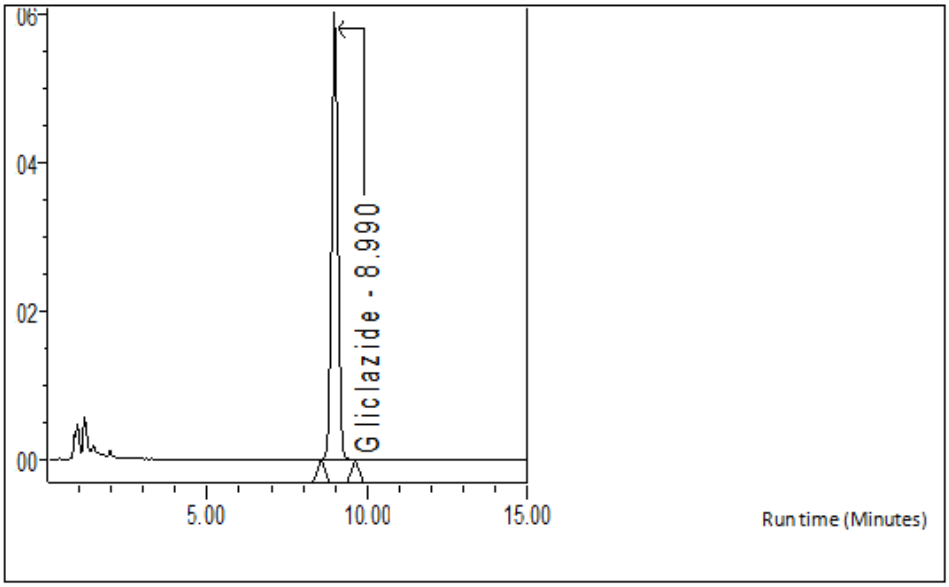

Figure:3 sepration of Gliclazide Modified released tablets using a sodium phosphate buffer .sepration conditions :RP C8(250*4.0) mm ,wavelength 230 nm at 30°C

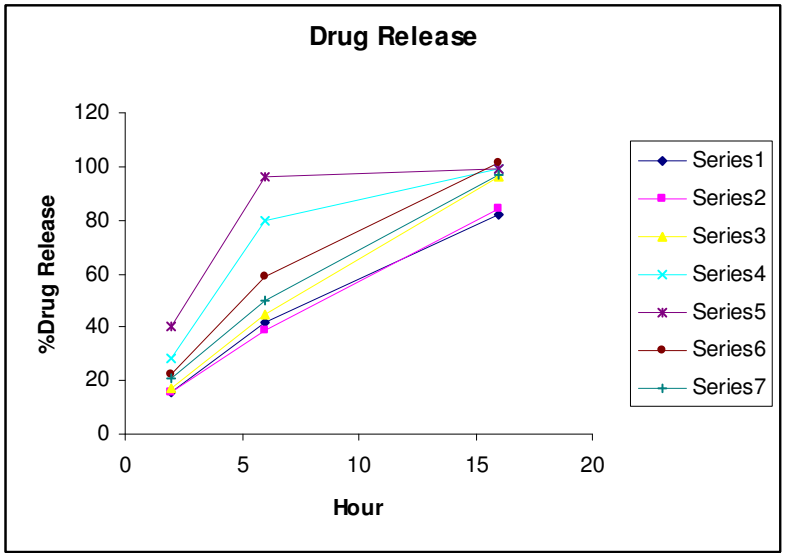

Figure :4: A diagramatic correlation between results obtained from various (degassed/non degassed/with surfactants media)

Non-Degassed Media				Degassed Media				Degassed Media			
				Conventional method				By Mechanical degasser			
#	2Hr	6Hr	16Hr	#	2Hr	6Hr	16Hr	#	2Hr	6Hr	16Hr
1	16	40	79	1	17	41	86	1	17	46	95
2	16	43	83	2	15	39	83	2	18	47	98
3	15	40	81	3	14	37	81	3	19	48	95
4	16	41	83	4	15	38	86	4	17	44	94
5	18	47	82	5	15	38	81	5	15	40	95
6	15	40	83	6	17	40	86	6	17	43	96
Mean	**16**	**42**	**82**	**Mean**	**16**	**39**	**84**	**Mean**	**17**	**45**	**96**
SD	**1.1**	**2.8**	**1.6**	**SD**	**1.2**	**1.5**	**2.5**	**SD**	**1.3**	**2.9**	**4.4**
Min	**15**	**40**	**79**	**Min**	**14**	**37**	**81**	**Min**	**15**	**40**	**85**
Max	**18**	**47**	**83**	**Max**	**17**	**41**	**86**	**Max**	**19**	**48**	**98**

pH 7.4 buffer+0.5%SDS				pH 7.4 buffer+1%SDS				pH 7.4 Buffer+0.5% Tween 20				pH 7.4 Buffer+1% Tween 20			
#	2Hr	6Hr	16Hr	#	2Hr	6Hr	16Hr	#	2Hr	6Hr	16Hr	#	21	6Hr	16Hr
1	29	81	99	1	41	97	101	1	22	59	100	1	21	55	97
2	28	80	99	2	39	95	98	2	23	59	100	2	21	53	98
3	26	80	96	3	38	95	98	3	21	58	104	3	21	49	95
4	28	80	99	4	38	97	101	4	22	59	100	4	21	49	97
5	26	81	99	5	41	95	98	5	23	59	100	5	21	44	98
6	29	80	99	6	41	95	98	6	21	58	104	6	21	47	95
Mean	**28**	**80**	**99**	**Mean**	**40**	**96**	**99**	**Mean**	**22**	**59**	**101**	**Mean**	**21**	**50**	**97**
SD	**1.4**	**0.5**	**1.2**	**SD**	**1.4**	**0.9**	**1.4**	**SD**	**0.8**	**0.5**	**1.9**	**SD**	**0.0**	**3.6**	**1,2**
Min	**26**	**80**	**96**	**Min**	**38**	**95**	**98**	**Min**	**15**	**40**	**85**	**Min**	**21**	**44**	**95**
Max	**29**	**81**	**99**	**Max**	**41**	**97**	**101**	**Max**	**19**	**48**	**98**	**Max**	**21**	**55**	**98**

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