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Development of Dissolution Medium for Glipizide

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Glipizide, an antidiabetic drug is poorly water-soluble. Therefore *in vitro* dissolution testing of glipizide in water and buffered solutions is not possible. In present study, an attempt was made to develop a new dissolution medium for the *in vitro* dissolution testing of drug. The selection of the medium was made on the basis of solubility data of glipizide in different medium at 37 ºC. Solubility data revealed that phosphate buffer of pH 6.8 consisting of 0.75 % (w/v) sodium lauryl sulphate could be a suitable dissolution medium.

Key Words: Glipizide, Dissolution medium.

INTRODUCTION

Dissolution study has become the most important test as it determines product quality and drug release behaviour[1-3]. The rational behind this test is that a drug should be appropriately dissolved within the gastrointestinal tract in order to be absorbed.

Drug dissolution involves two important steps, drug release from the dosage form and drug transport within the dissolution medium. Several factors influence drug dissolution including: (i) Physico-chemical properties of drug (*e.g.*, solubility, crystalline forms, particle size, molecular structure, diffusivity in the dissolution medium), (ii) formulation characteristics (additives, coatings, manufacturing parameters), (iii) dissolution method (*e.g.*, apparatus type; volume, surface tension, ionic strength, viscosity and pH of the medium and hydrodynamic conditions)[4].

Dissolution study is particularly important for insoluble or low solubility drugs, where absorption is dissolution-rate limited (class II drugs in respect to Biopharmaceutical Classification System, BCS). At the same time, development of a dissolution method for this group of drug is quite challenging. Dissolution medium must provide sink conditions (*i.e.*, saturation solubility is at least 3 times more than the drug concentration in the dissolution medium as outlined in USP 28). According to some other references the drug concentration in the dissolution medium should not

exceed 15 to 20 % of saturation solubility of the drug in order to provide sink conditions[5,6]. Absence of sink conditions may result in unpredictable release kinetics and suppression of release profiles.

Various approaches have been suggested for designing dissolution tests for poorly water-soluble drugs. These include (a) use of large volumes of dissolution medium, (b) removal of dissolved drug, (c) mixed organic-aqueous solvents, (d) two phase dissolution media with an upper organic layer, (e) the inclusion of surfactants, (f) pH changes[7-10]. Moreover, the GI conditions must be simulated in a well-designed dissolution testing and any modification applied should be relevant to real GI conditions. Among the above-mentioned conditions, pH modification and surfactant addition appear to be the simplest and can be tailored to resemble GI fluid environment.

Glipizide, 1-cyclohexyl-3-[[4-[2-[[(5-methylpyrazin-2-yl)carbonyl]-amino]ethyl]-phenyl]sulphonyl]urea belongs to sulfonylureas group of anti-diabetic drug (Fig. 1). Its primary mechanism of action is enhancement of insulin secretion by binding to a specific sulfonylurea receptor on pancreatic β-cells[11]. It is a white, crystalline powder, practically insoluble in water[12]. Therefore, the knowledge of dissolution behaviour and the factors affecting such performance are of paramount importance in design, evaluation, control and therapeutic efficacy of solid dosage forms. The bioavailability of the orally administered drugs that are practically insoluble is usually less. Since the limiting step *in vivo* absorption process of such drugs is their dissolution rate, there is definite need for the development of an appropriate dissolution test.

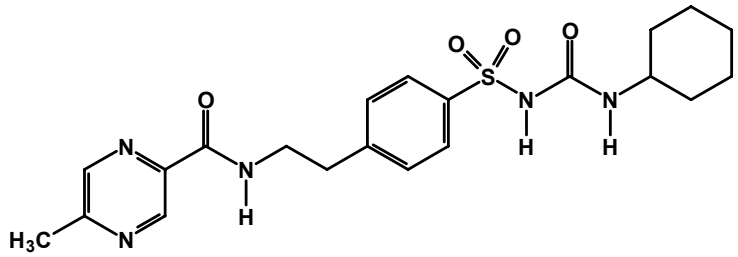

Fig. 1. Structure of glipizide

EXPERIMENTAL

Glipizide was obtained as a gift sample from Harind Pharmaceutical Pvt. Ltd., Mumbai, India. Three marketed brands of glipizide tablets were purchased from the local market. Sodium lauryl sulphate (SLS), Tween 80, methanol and Brij-35 were purchased from S.D. Fine-Chem Ltd., Mumbai. All other reagents used for the study were of analytical grade.

Deionized water was used in preparation of all test media. 10 mg immediate release tablets of glipizide (Glipicontin) were obtained from Modi Mundi Pharma, India.

Saturation solubility study: In this study, solubility data was used as a basis for the development of dissolution medium for glipizide. The apparent solubility of glipizide in water and in presence of co-solvent or surfactants in water was determined at 37ºC[13,14]. Glipizide (50 mg) was placed in each of the conical flasks, having teflon lined screw caps, containing 50 mL of the various solvents as shown in Table-1. The flasks were covered by aluminium foil to protect against light exposure and kept on a shaker incubator maintained at 37 ± 0.5 ºC for 24 h. The flasks were then kept in an incubator at 37 ± 0.5 ºC for equilibration for 12 h. The resulting solutions were filtered through 0.45 µm Millipore filter and the filtrates were assayed using UV-Vis spectrophotometer (Chemito Spectra Scan UV 2600) at 276 nm against respective blank solutions and the amount of drug dissolved was calculated using the calibration curve. The procedure was repeated until the maximum concentration of the glipizide was achieved.

Dissolution study: Dissolution experiments were performed using USP Dissolution Apparatus II (Electrolab, TDT-06P) at the temperature 37 ± 0.5 ºC and the paddle speed of 45 rpm. One 10 mg immediate release glipizide tablet was placed to each dissolution basket. Sample (5 mL) of dissolution medium was withdrawn at different time intervals and filtered through 0.22 µm Milipore filter. Same volume of fresh dissolution medium was added to maintain constant volume. The samples were then analyzed for glipizide using the above-mentioned UV method. Dissolution study was carried out on some selected dissolution media based on their solubility data. The experiment was conducted in triplicate and the average of the values was calculated.

RESULTS AND DISCUSSION

Glipizide is a weak acid with pK_a of 5.9. The solubility is expected to increase by rise in pH, but at higher pH it may not be biorelevant. Table-1 listed the saturation solubility (C_s) of glipizide at different dissolution media along with corresponding C_S/C_D values where C_D referes to concentration of glipizide after complete dissolution of tablet in 900 mL dissolution medium.

The solubility data as shown in Table-1, revealed that solubility of drug was found to be highest in the medium containing 0.75 % SLS in phosphate buffer of pH 6.8 (468.27 µg/mL). This data also indicated that the solubility of glipizide in 900 mL of 0.75 % SLS in phosphate buffer of pH 6.8 was *ca.* 4.89 times the solubility of the original dose of glipizide (10 mg).

TABLE-1
SATURATION SOLUBILITY (C_S) AND RELATIVE SINK CONDITIONS (C_S/C_D) OF GLIPIZIDE AT DIFFERENT DISSOLUTION MEDIA

Dissolution media	Saturation solubility (µg/mL)	C_S/C_D (10 mg tablet)
Water	33.13	0.58
0.1 N HCl (pH 1.2)	4.78	0.03
Acetate buffer (pH 4.5)	10.12	0.08
5% v/v methanol in water	21.84	0.17
10% v/v methanol in water	30.98	0.54
Phosphate buffer (pH 6.8)	245.40	2.21
Phosphate buffer (pH 7.2)	236.21	1.97
0.5% w/v SLS in water	179.06	1.31
0.75% w/v SLS in water	378.02	2.86
1% w/v SLS in water	216.25	1.43
2% w/v SLS in water	108.99	0.95
3% w/v SLS in water	218.67	1.73
4% w/v SLS in water	247.40	2.25
0.5% w/v SLS in phosphate buffer (pH 6.8)	260.12	2.32
0.75% w/v SLS in phosphate buffer (pH 6.8)	468.27	4.89
1% w/v SLS in phosphate buffer (pH 6.8)	283.71	2.41
2% w/v SLS in phosphate buffer (pH 6.8)	158.32	1.23
3% w/v SLS in phosphate buffer (pH 6.8)	295.43	2.47
4% w/v SLS in phosphate buffer (pH 6.8)	367.20	2.63
0.5% v/v Tween 80 in water	78.74	0.87
0.75% v/v Tween 80 in water	129.35	1.13
1% v/v Tween 80 in water	145.24	1.19
2% v/v Tween 80 in water	7.35	0.04
3% v/v Tween 80 in water	11.04	0.09
4% v/v Tween 80 in water	26.01	0.19
0.75% v/v Tween 80 in phosphate buffer (pH 6.8)	207.00	1.39

As 900 mL of 0.75 % SLS in phosphate buffer of pH 6.8 satisfied the sink conditions, it was considered to be a suitable dissolution medium. The results indicated that the dissolution rate of glipizide increased with increase in SLS content in phosphate buffer of pH 6.8 up to 0.75 % (w/v) and there after solubility of the drug decreased which may be due to attainment of critical micellar concentration at 0.75 % w/v. Addition of surfactant to the dissolution medium improves the dissolution of pure drug by facilitating the drug release process at the solid/liquid interface and micelle solubilization in the bulk. Pandit *et al.*[15] and Schott *et al.*[16] also described the justification for the usage of SLS in the dissolution medium.

The performance of selected dissolution medium *i.e.*, 900 mL of 0.75% (w/v) in phosphate buffer of pH 6.8 was confirmed by conducting dissolution study for commercially available drug formulations. Results of drug release in different dissolution medium is shown in Fig. 2. It was found that glipizide release in 0.75 % w/v in phosphate buffer of pH 6.8 more than 80 % after 45 min.

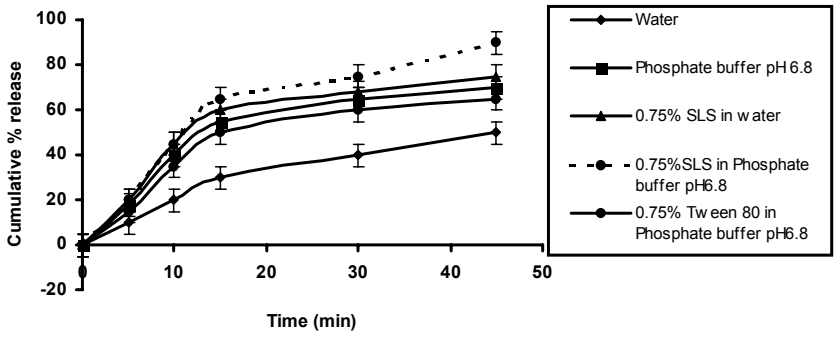

Fig. 2. Comparative dissolution profiles of glipizide (10 mg tablet) in different dissolution media. Bars represent ± SD (n = 3)

Conclusion

The results of present study clearly indicates that 0.75 % (w/v) SLS in phosphate buffer of pH 6.8, as dissolution medium was suitable for routine *in vitro* dissolution testing of conventional glipizide formulations.

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