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EFFECT OF SODIUM LAURYL SULPHATE AND TWEEN^{R}80 ON THE THERAPEUTIC EFFICACY OF GLIBENCLAMIDE TABLET FORMULATIONS IN TERMS OF BSL LOWERING IN RABBITS AND DIABETIC HUMAN VOLUNTEERS

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ABSTRACT

Glibenclamide has limited gastrointestinal absorption. Therefore, different concentrations of sodium lauryl sulphate and tween^{R}80 were included into the tablet formulations to increase the absorption of the drug and hence, to enhance the BSL lowering in rabbits and human volunteers suffering from maturity onset diabetes mellitus. It was found that the surfactants had enhanced both the rate and extent of BSL lowering in rabbits as well as in diabetic patients in higher concentrations present in the tablet formulations.

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INTRODUCTION

Glibenclamide (HB 419), a hypoglycaemic sulphonyl urea group of drug, has been used successfully for the treatment of patients suffering from maturity onset diabetes.[1] The drug is official in B.P.[2] and also found in detail elsewhere.[3,4] It possesses potent hypoglycaemic properties both in man and animals.[5-7] The drug is almost insoluble in water and only 45% of the oral dose is absorbed through the gastrointestinal tract.[8]

In order to increase the aqueous solubility and absorption of this drug through gastrointestinal tract various concentrations of sodium lauryl sulphate and tween® 80 have been included in tablet formulations. Nymcel ZSB-16 was used as tablet disintegrant. Tablets were evaluated for in-vivo availability of the drug in terms of its therapeutic effect by measuring the blood sugar level (BSL) in rabbits.

A report chiefly concerned with the acute effects of the drug over 24 hour periods in diabetic patients and its value as a hypoglycaemic agent in clinical practice has been discussed.[9] Therefore, clinical trials of the best formulations of the drug were performed for their therapeutic effect over 24 hour periods by measuring the lowering in BSL in volunteers suffering from maturity onset diabetes mellitus.

MATERIALS

Glibenclamide B.P. - Hoechst Pharmaceutical Pvt. Ltd., Bombay; Dicalcium phosphate - Albright and Wilson (Mfg.) Ltd. England; Nymcel ZSB-16 - Nyma b.v. Holland; Sodium lauryl sulphate - B.D.H. England; Tween^{R}80 - Koch-light Laboratories Ltd. England; Sodium sulphate, sodium tungstate, copper sulphate, sodium carbonate, potassium oxalate and phosphoric acid were obtained from B.D.H. England; Sodium bicarbonate, molybdic acid, sodium hydroxide and potassium - sodium tartrate were received from Sarabhai M. Chemicals, Baroda. All other chemicals and solvents used were obtained from B.D.H., Bombay.

METHOD

Glibenclamide Tablets using different concentration of surfactants.

Formula - Each batch contains the following ingredients and the respective amount of surfactant shown in table 1.

Ingredients	Per tablet	Per batch (200 tablets)
Glibenclamide	5 mg	1.0 gm
Dicalcium phosphate	90 mg	18.0 gm
PVP, 10% W/V solution equivalent to	2 mg PVP	0.4 gm
Nymcel ZSB-16	5 mg	1.0 gm
Talc	2 mg	0.4 gm
Magnesium stearate	1 mg	0.2 gm

TABLE 1

Amount of Each Surfactant and Their Respective Batch

Batch	Surfactants	ml of 1% W/V aqueous solution of surfactant per batch
GSLS-1	Sodium lauryl sulphate	6
GSLS-2	-do-	8
GSLS-3	-do-	10
GSLS-4	-do-	20
GT-1	Tween^{R}80	6
GT-2	-do-	8
GT-3	-do-	10
GT-4	-do-	20

Preparation of Tablets

The drug and dicalcium phosphate were mixed intimately and uniformly on a Labaid vortex vibrating mixer for two hours. The drug-dicalcium phosphate mixture was transferred into the mortar and the specified amount of 1% W/V aqueous solution of surfactant was added and triturated with pestle to get uniform mixture. The mixture was dried in hot air oven for one hour at 60^{o} and passed through sieve no. 80. Dough mass of the mixture was prepared with 10% W/V PVP solution and passed through sieve no. 12. The granulation was dried

at 60° for one hour in hot air oven and passed through 20 sieve. The granules were mixed with the specified amount of Nymcel ZSB-16, talc and magnesium stearate and compressed into tablets of 105 mg in a Manesty E-2 type single punch tablet machine using 7/32" die and punch set at 15 unit compression pressure. Similarly plain tablets were also prepared without using the surfactants.

Glibenclamide content in Tablets

Glibenclamide content in tablets was determined by the method of B.P. 1973.

Physical characteristics of Tablets

Weight and thickness of tablets were determined by single pan balance (K. Roy and Co., Varanasi) and screw-gauge micrometer, respectively. Average compression ratio (C.R.) was calculated as

$$C.R. = \frac{\text{Average weight (gm)}}{\text{Average thickness (cm)}}$$

The hardness, friability and disintegration time (D.T.) were determined with the help of Monsanto type Tablet Hardness Tester, Thermonik Friability Test Apparatus and Thermonik Tablet Disintegration Test Machine B.P. standard, respectively and all the three machines were from Campbell Electronics, Bombay.

BSL studies in Rabbits

White male Albino rabbits of 1.5-2.0 kg body weight were selected for biopharmaceutical evaluation

of glibenclamide tablets. They were kept on fast for 12 hours before the experiment began. Rabbits were divided into control and treated groups and each group was consisted of seven rabbits. Placebo was fed to each rabbit of the control group and glibenclamide to each of the treated group. 0.1 ml of blood samples were withdrawn before tablet/solution administration and at 1, 2, 3, 4, 5, 6, 8 and 24 hours afterwards from the ear marginal vein.

The blood sugar was estimated by the alkaline copper reduction method of Asatoor and King.[10] The lowering in blood sugar level at different intervals was calculated by substracting the blood sugar level of treated group from the control group.

Clinical studies of Glibenclamide Tablets

Clinical trials were performed in the S.S. Hospital, B.H.U., Varanasi, India on the recently diagnosed and previously untreated patients of maturity onset diabetes mellitus. Patients were divided into control and treated groups. Each group was consisted of seven patients. The patients were kept on fast overnight and then at 8 A.M. in the morning 1.0 ml of blood sample was withdrawn from each one of the two groups. Placebo was then fed to each one of the control group while the glibenclamide tablet/ solution to each one of the treated group. 1.0 ml blood samples were withdrawn at 1, 2, 3, 4, 8 and 24 hours after feeding the tablet/solution from each group of patients.

The patients of both the groups were allowed to take standard diabetic meals at 5th and 12th hours after feeding the tablet/solution.

The blood sugar and its lowering were determined similar to BSL studies in rabbits as described previously.

Data Evaluation - Fortran computer program was used for in-vivo data evaluation.[11]

Area under the lowering in BSL-Time Curve (AUC):

Cubic spline interpolation was used to find the A.U.C.[12]

$$\int_a^b f(x)\,dx$$

let the points be (x_i, f_i), $i = 1,2,\ldots, n+1$

For $x_1 \leq x \leq X_{i+1}$

Let,

$S(X) = f_i + b_i(x-x_i) + c_i(x-x_1)^2 + d_i(x-x_i)^3$ be the cubic spline which interpolates $f(x)$ at the points

$$X_1, X_2, \ldots, X_{n+1}$$

$$\int_a^b f(X)\,d_X \simeq \int_a^b S(X)\,d_X$$

$$= \sum_{i=1}^{n} \left(h_i f_i + \frac{1}{2} h_i^2 b_i + \frac{1}{3} h_i^3 c_i + \frac{1}{4} h_i^4 d_i\right.$$

The coefficients b_i, c_i and d_i were obtained using the subroutine SPLINE.

Maximum mg % reduction in BSL (C_{maxl}), times to achieve the maximum mg % reduction in BSL (t_{maxl}) were also determined. % bioavailability (% Frel) was established by the formula -

$$\% \text{ Frel} = \frac{AUC_{tablet}}{AUC_{solution}} \times \frac{\text{Dose solution}}{\text{Dose tablet}} \times 100$$

Statistical Analysis - The results have been expressed as mean ± S.D. of seven determinations. Significance of differences in the bioavailability of tablets from the solution for C_{maxl} and % Frel have been determined by paired 't' test.

RESULTS AND DISCUSSION

Results of physical characteristics of glibenclamide tablets are given in table 2. The weight variation of tablets of all the batches was found well within the pharmacopoeial limit but the maximum drug content as well as weight variation were found in the batch GT-4. No correlation could be established between hardness and friability. But, the disintegration time was found to increase in the batch GSLS-1 to GSLS-4 on increasing the concentration of sodium lauryl sulphate. Tablets containing tween^{R}80 exhibited lesser hardness as the concentration of the surfactant was increased in the batch GT-1 to GT-4 but no appreciable change in the disintegration time was observed.

TABLE 2

Physical Properties of Glibenclamide Tablets

Batch	Drug content mean (mg) ± S.D.	Tablet weight mean (gm) ± S.D.	Tablet thickness mean (cm) ± S.D.	C.R. mean (gm/cm)	Hardness mean (kg/cm^2) ± S.D.	Friability mean(%) ± S.D.	D.T. mean(sec) ± S.D.
Plain	5.90 ±0.36	0.1209 ±0.0020	0.23 ±0.004	0.53	5.2 ±0.27	0.67 ±0.09	66.00 ±8.21
GSLS-1	5.32 ±0.32	0.1101 ±0.001	0.23 ±0.003	0.48	7.4 ±0.42	0.61 ±0.01	41.00 ± 3.60
GSLS-2	5.24 ±0.29	0.1172 ±0.0029	0.25 ±0.005	0.47	5.6 ±0.42	0.58 ±0.02	82.00 ± 3.61
GSLS-3	5.21 ±0.35	0.1167 ±0.0018	0.24 ±0.005	0.49	5.1 ±0.65	0.74 ±0.07	87.33 ±2.51
GSLS-4	5.66 ±0.36	0.1104 ±0.0024	0.23 ±0.003	0.48	6.2 ±0.45	0.62 ±0.09	108.33 ± 2.88
GT-1	5.04 ±0.41	0.1185 ±0.0058	0.26 ±0.021	0.46	7.9 ±0.22	0.42 ±0.03	61.66 ± 2.88
GT-2	4.63 ±0.23	0.1045 ±0.0019	0.20 ±0.004	0.52	4.6 ±0.55	0.53 ±0.03	66.33 ± 1.15
GT-3	5.17 ±0.33	0.1104 ±0.0057	0.23 ±0.009	0.49	4.2 ±0.45	0.68 ±0.04	66.66 ± 2.88
GT-4	4.57 ±0.40	0.1106 ±0.0093	0.23 ±0.012	0.48	4.0 ±0.50	0.58 ±0.03	65.33 ± 2.31

The bioavailability in terms of therapeutic effect of the drug from the tablets containing surfactants was studied in rabbits by measuring the lowering in BSL. The results are given in table 3 and 4. It was found that the increase in the concentration of sodium lauryl sulphate in tablets of the batches GSLS-1 to GSLS-4 enhanced the lowering in BSL. Tablets of the batch GSLS-1 exhibited the lesser rate and extent of lowering in BSL than the solution. Both the rate and extent of lowering could not differ significantly ($P > 0.05$) from tablets of the batches GSLS-2 and GSLS-3 than the solution. However tablets of the batch GSLS-4 significantly ($P < 0.01$) enhanced the rate and extent of lowering in BSL than the solution. Tablets of the batch GT-3 exhibited a significantly higher ($P < 0.05$) rate and extent of lowering in BSL but the maximum significant ($P < 0.01$) lowering was achieved in the batch GT-4 when compared to that of solution. Thus, sodium lauryl sulphate and tween^{R}80 are found to increase the lowering of BSL on increasing their concentration in tablet formulations. This might be due to more permeation and absorption of the drug[13] and greater stimulation of pancreatic β-cells to release more of insulin followed by larger reduction in the BSL in rabbits.

The in-vivo studies of all the Glibenclamide tablet formulations showed that the maximum lowering

TABLE 3

Mg % Lowering in BSL from Glibenclamide Tablets in Rabbits

Batch	mg % lowering BSL (Mean ± S.D.)							
	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	8 hr	24 hr
Solution	16.35 ± 1.60	28.45 ± 2.61	45.90 ± 3.70	45.15 ± 3.10	42.00 ± 4.05	38.67 ± 2.80	35.70 ± 2.71	30.50 ± 2.67
Plain	15.35 ± 2.61	25.25 ± 3.45	30.00 ± 3.85	37.65 ± 4.95	35.85 ± 4.10	34.16 ± 3.27	31.11 ± 2.69	28.85 ± 2.07
GSLS-1	8.91 ± 3.25	18.81 ± 2.85	28.91 ± 3.75	38.50 ± 5.85	35.00 ± 2.16	32.35 ± 2.16	30.41 ± 2.80	28.66 ± 3.35
GSLS-2	9.75 ± 2.16	21.65 ± 2.33	32.00 ± 5.38	42.25 ± 7.35	41.00 ± 5.60	40.15 ± 5.25	38.35 ± 4.11	35.25 ± 3.85
GSLS-3	20.50 ± 5.75	25.35 ± 5.11	50.45 ± 6.85	49.11 ± 5.55	47.35 ± 4.35	45.95 ± 4.85	40.25 ± 3.25	37.85 ± 3.15
GSLS-4	35.51 ± 1.23	53.00 ± 3.61	69.75 ± 6.75	66.34 ± 5.04	64.66 ± 5.06	62.68 ± 4.67	56.67 ± 5.38	50.83 ± 3.45
GT-1	10.35 ± 2.85	20.50 ± 4.35	30.75 ± 4.85	40.50 ± 5.31	39.25 ± 5.75	38.50 ± 3.75	35.25 ± 3.25	29.85 ± 2.15
GT-2	15.25 ± 3.37	25.50 ± 3.86	38.85 ± 4.57	50.50 ± 5.90	48.15 ± 5.25	45.35 ± 4.70	42.50 ± 4.75	38.50 ± 3.15
GT-3	27.75 ± 2.85	40.25 ± 2.75	55.25 ± 5.35	54.50 ± 5.80	53.85 ± 5.26	51.15 ± 4.38	45.25 ± 3.75	40.50 ± 3.25
GT-4	36.15 ± 4.35	71.00 ±10.75	69.85 ±10.15	68.90 ± 9.45	66.85 ± 8.55	66.75 ± 8.25	62.60 ± 7.65	56.69 ± 6.16

TABLE 4

Bioavailability in Terms of Therapeutic Effect of Glibenclamide Tablets in Rabbits

Batch	AUC mg % - hr	C_{maxl} mg %	t_{maxl} hr	% Frel
Solution	797.42 ± 63.33	45.90 ± 3.69	3.0 ± 0.001	100.0 ± 7.94
Plain	670.36 ± 67.61	37.65 ± 4.34	4.0 ± 0.001	71.20 ± 9.30
		P > 0.05		P < 0.01
GSLS-1	703.92 ± 74.44	38.50 ± 5.85	4.0 ± 0.001	77.91 ± 13.84
		P < 0.05		P < 0.05
GSLS-2	852.06 ± 89.67	42.25 ± 7.35	4.0 ± 0.001	101.96 ± 10.73
		P > 0.05		P > 0.05
GSLS-3	918.65 ± 84.93	50.45 ± 6.85	3.0 ± 0.001	110.53 ± 10.22
		P > 0.05		P > 0.05
GSLS-4	1296.46 ± 87.05	69.75 ± 6.75	3.0 ± 0.001	143.49 ± 9.63
		P < 0.01		P < 0.01
GT-1	764.20 ± 68.20	40.50 ± 5.31	4.0 ± 0.002	95.14 ± 8.49
		P > 0.05		P > 0.05
GT-2	954.09 ± 90.37	50.50 ± 5.90	4.0 ± 0.002	129.19 ± 12.24
		P > 0.05		P < 0.01
GT-3	1039.05 ± 81.15	55.25 ± 11.35	3.0 ± 0.001	125.91 ± 9.82
		P > 0.05		P < 0.05
GT-4	1145.54 ± 66.76	71.00 ± 10.75	2.0 ± 0.001	198.40 ± 22.69
		P < 0.01		P < 0.01

in BSL was achieved within 2-4 hours after ingestion of the tablets to the rabbits. The lowering in BSL appeared slightly lesser between 8th and 24th hours.

Based on the in-vivo BSL lowering in rabbits the tablets of batches GSLS-4, GT-4 and solution of the drug were subjected to clinical trials to see their therapeutic effect in terms of rate and extent of BSL lowering in recently diagnosed and previously untreated patients of maturity onset diabetes mellitus. The results are given in figure 1 and table 5.

The tablets of batch GSLS-4 exhibited significantly higher rate ($P < 0.01$) and greater extent ($P < 0.05$) of

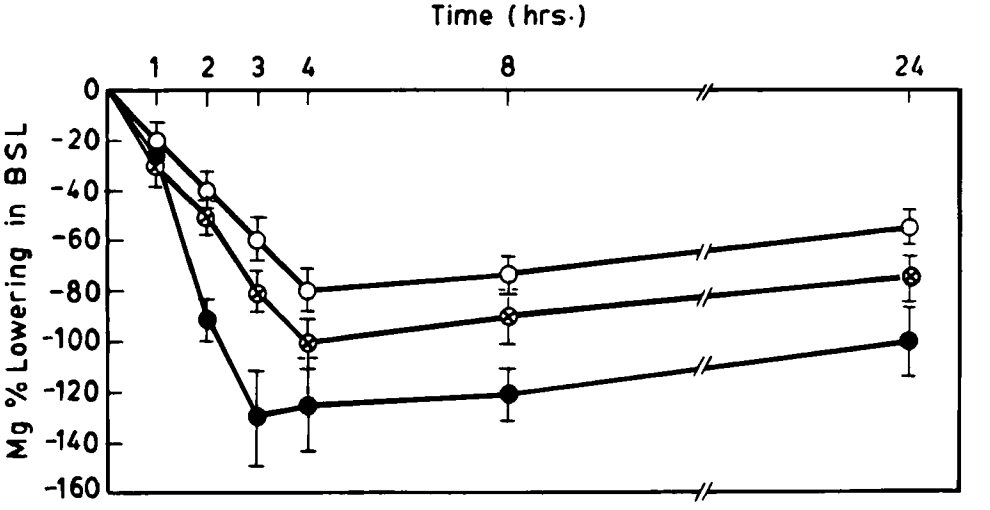

FIGURE 1

Mg % Lowering in BSL in maturity onset diabetes mellitus patients from Glibenclamide Tablets.

Key: -O- solution; -Θ- GSLS-4; -●- GT-4;
Each of the data points represents the mean ± S.D.

TABLE 5

Clinical Trials in Terms of Therapeutic Effect of Glibenclamide Tablets in Maturity onset Diabetes Mellitus Patients

Batch	AUC mg % - hr	C_{maxl} mg %	t_{maxl} hr	% Frel
Solution	1548.45 ± 117.74	80.50 ± 8.54	4.0 ±0.002	100.00 ± 7.50
GSLS-4	1947.96 ± 213.71	100.50 ±10.73 P < 0.01	4.0 ±0.002	111.03 ±12.17 P > 0.05
GT-4	2540.82 ±324.85	130.05 ±20.45 P < 0.01	3.0 ± 0.02	179.59 ±22.96 P < 0.01

BSL lowering than the solution. However both the rate and extent of BSL lowering were significantly more ($P < 0.01$) in the batch GT-4 than the solution.

O' sullivan et al[9] have found the drug to be more effective in recently diagnosed and previously untreated diabetics than in those the other hypoglycaemic agents had been previously tried unsuccessfully. Further, the workers also noted a definite dose-effect relationship which was found in all the patients who responded to the drug. Therefore, based on the dose-effect relationship, the tablets of the batch GT-4 exhibited the maximum absorption of the drug at a faster rate to give the highest therapeutic effect. This might be due to greater stimulation of pancreatic beta-cells to release larger amounts of insulin[14], hence the greater therapeutic effect.

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