DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(3), 529-546 (1987)

AGING EFFECT ON STABILITY AND BIOAVAILABILITY OF GLIBENCLAMIDE IN SOLID DOSAGE FORMS

S.P.Jayaswal and H.S.Srivastava

Department of Pharmaceutics
Institute of Technology
Banaras Hindu University
Varanasi 221 005, India

ABSTRACT

Aging effect of some solid dosage forms of glibenclamide, after storage at various storage conditions and accelerated temperatures for certain length of time, affected percentage degradation, physical properties, in-vitro dissolution and in-vivo performances, has been investigated and compared with the marketed tablets of Dionil®. The percentage degradation responding to accelerated conditions has been extrapolated by formal Arrhenius treatment. However, maximum stability and highest shelf-life of direct compression lactose tablets, followed by

Dionil^{R} and then suppositories have been observed. The aging and elevation of temperature, adversely affected dissolution rate and indicated a decrease in bioavailability of glibenclamide based on C_{max}, T_{max} and AUC.

INTRODUCTION

In solid dosage form the aging effect is of critical importance to certify the pharmaceutical stability where the drug and pharmaceutical necessities considerably affects, the bioavailability of the drug in formulations. Glibenclamide[1] is a synthetic potent hypoglycemic drug having maximum efficacy in minimum dose and is administered through gastrointestinal tract in solid dosage forms. The positive role of the pharmaceutical necessities in adjusting dose and in shaping the physical form is over as soon as the formulation is prepared. However, it is increasingly recognised that the physical and mechanical properties of the tablets may undergo change on aging or an exposure to environmental stresses, thus having a stability profile that affects bioavailability and other fundamental properties of solid dosage forms.[2]

Allen et al.[3] reported that a corticosteroid-sugar glass dispersion sample after storage at 25°C

for 30 days showed no decrease in the dissolution rate, but this storage term is rather shorter. Fromming et al[4] studied the dissolution rate of salicylic acid in PEG 6000, and reported that dissolution rates of solidified melts with amorphous salicylic acid were stable during storage for one year. However, they did not study the effect of temperature or humidity during storage on the dissolution rate. Barret et al[5] studied the effect of aging on the physical properties and dissolution behaviour of phenylbutazone tablets. Physical aging of compressed tablets causes complex changes of hardness over a relatively short period.[6]

Therefore, the present study was undertaken to evaluate the physico-chemical stability and the dissolution rate of glibenclamide on storage, especially in its solid dosage forms. The relationship between the in-vitro dissolution behaviour and in-vivo bioavailability parameters in healthy rabbits were also studied to confirm the aging effect on storage of the solid dosage form formulations on its bioavailability.

EXPERIMENTAL

Materials - Glibenclamide B.P. was obtained from Hoechst Pharmaceuticals Ltd., Bombay. The tablet batches DCPE, ADCPE, LDC, DCP and DTC were prepared by

incorporating dicalcium phosphate engranule (Enar Chemi Ltd., Bombay; Avicel pH 101 (FMC Corporation, USA) + dicalcium phosphate engranule (1:1); Lactose DC (DMV, Holland); Dicalcium phosphate (Albright and Wilson Mfg., Ltd., England)and Dionil^{R} (marketed tablets) respectively, while suppository batches SPF, SPS and SPT were prepared by incorporating polyethelene glycol (Ferrichem India Ltd., Bombay) bases listed in USP in different compositions respectively. Other chemicals were of reagent grade.

Methods - Preparation of Tablets: Each tablet of 100 mg contained 5 mg glibenclamide B.P., 85 mg diluent (directly compressible vehicle 87 mg), starch paste 10% equivalent to 4 mg (excluded in direct compression) along with 5% potato starch, 2% talc and 1% magnesium stearate of total weight of granulations and compressed in Manesty E-2 type single punch tabletting machine, using 7/32" die and punch set at an appropriate compression pressure.

Preparation of Suppository: Each suppository was prepared by moulding method, incorporating the PEG bases I, II and III listed in U.S.P. and then each suppository weight was adjusted to 1.26 gm that contained 5 mg glibenclamide.

Storage Conditions - Following storage conditions were selected for stability studies:

1. Room temp.,Dry condition, protected from light (RDP)
2. Room temp.,Dry condition,unprotected from light (RDU)
3. Room temp.,Humid condition,protected from light (RHP)
4. Room temp.,Humid condition,unprotected from light (RHU)
5. Cold condition (4-8°C) in Amber coloured glass bottle (FDP)

Accelerated Conditions of Temperature - Accelerated stability study was performed at following temperatures:

40°C, 50°C, 60°C & Room temperature (20-30°C)

The products from all batches were assayed at 0, 8th, 16th and 24th week on storage and at accelerated conditions of temperature.

Physico-chemical Stability Study - Properties of solid dosage forms i.e. drug content, hardness, friability, disintegration time/liquidification time and melting range, have been determined, after storage for 16 weeks at ordinary temperature and 4 weeks at 40°, 50° and 60°C in thermostatic electric ovens. The products were stored in sealed screw capped bottles with rubber washers.

Dissolution Study - After storage at different temperatures, the in-vitro release rate of glibenclamide from the tablets and suppositories were determined by dissolution apparatus USP XIX, using 900 ml (0.007M phosphate buffer at pH 7.4) of dissolution fluid.

Glibenclamide was estimated spectrophotometrically at 199 nm using Beckman Spectrophotometer Model 24 (USA). The assay, tests and dissolution study protocol were performed as stated by Srivastava H.S. et al.[8]

Bioavailability Study Protocol - The oral administration of the tablets and rectal administration of the suppositories were performed after storage and then the BSL in the whole blood were estimated by means of Dextrometer Reflectance Colorimeter.[7] The entire in-vivo methodology has been followed as adopted by Srivastava H.S. et al.[8] The mean values of the percentage reduction in BSL after storage are plotted.

RESULTS AND DISCUSSION

1. Chemical Stability of Glibenclamide in Tablets and Suppositories -

The degradation of glibenclamide solid dosage forms at different storage, accelerated conditions of temperature and their shelf-life ($t_{10\%}$) have been determined in order to judge the most stable product among batches under-taken for stability testing. Data revealed that the light and humidity affected stability of the drug (Tables 1 and 2). Least degradation of the drug was found in cold conditions protected from light and humidity. Batch DCPE showed highest degradation in all storage conditions. However, the shelf-life of

Table 1. Chemical stability of glibenclamide in solid dosage forms at different storage conditions in tablets batches DCPE, LDC, ADCPE, DCP and DTC with average initial drug contents (mg) 3.54, 3.35, 3.47, 3.45 and 4.15 respectively and suppository batches SPF, SPS and SPT with average initial drug contents (mg) 4.63, 4.60 and 5.00 respectively

Batch	Storage condition	Residual drug (mg) Time in weeks 8	16	24	Shelf life in weeks
DCPE	1 RDP	3.50	3.46	3.42	51.13
	2 RDU	3.47	3.42	3.36	57.39
	3 RHP	3.45	3.40	3.30	24.89
	4 RHU	3.41	3.36	3.25	20.12
	5 FDP	3.49	3.46	3.42	50.63
LDC	1 RDP	3.33	3.30	3.27	75.76
	2 RDU	3.30	3.25	3.22	44.17
	3 RHP	3.29	3.22	3.23	38.16
	4 RHU	3.27	3.23	3.16	29.91
	5 FDP	3.34	3.32	3.30	116.60
ADCPE	1 RDP	3.45	3.41	3.38	90.26
	2 RDU	2.41	3.34	3.28	30.80
	3 RHP	3.38	3.32	3.24	25.05
	4 RHU	3.36	3.29	3.21	22.32
	5 FDP	3.46	3.45	3.44	200.60
DCP	1 RDP	3.42	3.38	3.35	64.40
	2 RDU	3.39	3.31	3.26	30.26
	3 RHP	3.35	3.26	3.20	22.51
	4 RHU	3.33	3.22	3.10	14.31
	5 FDP	3.43	3.41	3.40	159.69
DTC	1 RDP	4.12	4.08	4.05	72.08
	2 RDU	4.09	4.02	3.98	41.68
	3 RHP	4.07	3.99	3.92	30.71
	4 RHU	4.04	3.94	3.85	23.32
	5 FDP	4.14	4.11	4.10	148.20
SPF	1 RDP	4.45	4.42	4.38	92.03
	2 RDU	4.48	4.38	4.34	68.84
	3 RHP	4.43	4.33	4.27	47.70
	4 RHU	4.41	4.32	4.20	36.23
	5 FDP	4.46	4.44	4.42	139.00

contd....

Table 1

SPS	1 RDP	4.45	4.41	4.39	100.90
	2 RDU	4.41	4.34	4.27	47.00
	3 RHP	4.40	4.32	4.22	38.95
	4 RHU	4.36	4.27	4.16	31.80
	5 FDP	4.47	4.41	4.40	110.70
SPT	1 RDP	4.85	4.81	4.72	93.69
	2 RDU	4.84	4.79	4.74	75.30
	3 RHP	4.82	4.77	4.65	47.92
	4 RHU	4.80	4.73	4.58	37.14
	5 FDP	4.88	4.85	4.83	176.00

Mean of three determinations.

Table 2. Accelerated stability testing

Batch	Temp. °C	Residual drug (mg) 8	16	24	Rate constt. $K+10^{-5}$	1/T x10 3	T 10% (weeks)
DCPE	40	3.41	3.26	3.12	749	3.19	17.23
	50	3.40	3.24	3.11	770	3.09	
	60	3.38	3.20	3.02	949	3.00	
LDC	40	3.31	3.24	3.19	288	3.19	73.46
	50	3.26	3.18	3.10	463	3.09	
	60	3.24	3.19	3.00	660	3.00	
ADCPE	40	3.38	3.29	3.19	502	3.19	32.83
	50	3.34	3.20	3.09	688	3.09	
	60	3.30	3.17	3.01	848	3.00	
DCP	40	3.35	3.25	3.15	536	3.19	30.64
	50	3.32	3.17	3.02	736	3.09	
	60	3.28	3.12	2.95	934	3.00	
DTC	40	4.07	3.98	3.90	367	3.19	45.33
	50	4.05	3.96	3.85	433	3.09	
	60	4.02	3.90	3.78	565	3.00	
SPF	40	4.41	4.34	4.23	375	3.19	27.73
	50	4.38	4.32	4.18	425	3.09	
	60	4.36	4.27	4.16	446	3.00	
SPS	40	4.43	4.36	4.32	261	3.19	39.84
	50	4.39	4.32	4.20	378	3.09	
	60	4.36	4.27	4.16	419	3.00	
SPT	40	4.80	4.77	4.65	302	3.19	34.40
	50	4.77	4.67	4.56	383	3.09	
	60	4.75	4.60	4.49	447	3.00	

batch DTC, ADCPE and LDC were found to be maximum. The rate constants were calculated by using first order kinetics and utilizing plots of the log of the concentration remaining against time (weeks). The residual drug percentage were calculated by using the Arrhenius equation and plotting the log of each rate constant versus the reciprocal of absolute temperature. The parallel lines obtained in Arrhenius type plots explain that the mechanism of degradation is similar in all cases. There existed a linear relationship between drug degradation and the duration of the study in accelerated conditions of temperature. It has been shown by correlation coefficient for various products percentage degradation with duration.

Lesser stability was found in tablets made with dicalcium phosphate prepared by wet granulation method, while more in tablets prepared by direct compression method incorporating direct compression grade lactose, Avicel + Dical. phosphate Engranule (1:1) mixture followed by Dionil^{R}. However, suppositories showed greater stability at storage condition but medium on accelerated conditions of temperature due to the drug and the bases melts solidified on cooling during preparation.

2. Aging Effect on Physical Properties of the Tablet and Suppository -

The importance of aging and elevation of temperature on the strength of tablet compacts and other physico-mechanical properties has been recognized (Table 3). Physical aging of compressed tablets causes complex changes of hardness over a relatively short period. Hardness of compacts provides a direct measure of the bonding potential of a given material. The tablet batches DCPE, LDC and DTC showed decrease in hardness from fresh conditions to stored conditions, while batch DCP showed no change of hardness due to aging. The marked increase in disintegration time has been noticed in batch DCP and ADCPE while DCPE and DTC showed decrease in disintegration time. The batch LDC showed increase in disintegration time but at 40°C, value decreased. In case of suppositories only liquification time and melting range have been assessed. There existed a constant decrease of values on storage and at elevated conditions of temperature. Therefore, formulations were recommended to store under dry and light protected containers at lower temperature.

3. Aging Effect on in-vitro Release Rate of Solid Dosage Forms -

The in-vitro release rate of tablets and suppositories after aging in 7.4 pH dissolution fluid (Table 4). The dosage forms showed an overall decrease

Table 3. Physical stability testing parameters of of glibenclamide tablets and suppositories after storage

Parameters	Storage conditions	Tablet batch				
		DCPE	LDC	ADCPE	DCP	DTC
Hardness (Kg/cm^2)	Initial*	6.5	4.0	6.0	7.0	5.5
	RT	6.0	4.0	5.5	7.0	4.5
	40	6.2	3.5	6.5	6.0	5.2
	50	6.0	3.5	6.5	6.6	5.0
	60	5.5	3.0	6.0	7.0	4.8
Disintegration time (sec)	Initial*	330	30	600	900	210
	RT	360	45	650	945	200
	40	310	25	680	915	180
	50	300	34	650	945	176
	60	280	37	640	930	160
Friability (%)	Initial*	0.43	0.14	0.17	0.10	0.10
	RT	0.45	0.13	0.18	0.12	0.10
	40	0.43	0.12	0.16	0.09	0.10
	50	0.44	0.10	0.16	0.09	0.10
	60	0.48	0.08	0.17	0.09	0.09
		Suppository batch				
		SPF		SPS		SPT
Liquification time (sec)	Initial*	975		1080		910
	RT	980		1095		930
	40	968		1070		900
	50	965		1020		890
	60	960		1000		855
Melting range (°C)	Initial*	39		42		46
	RT	39		42		46
	40	38		41		45
	50	38		41		44
	60	37		40		44

*Reading in fresh condition. Each value is average of three determinations.

Table 4. USP XIX *in-vitro* dissolution test and T_{50} values of glibenclamide tablets and suppositories in 7.4 pH dissolution fluid after storage

Batch	Initial dose of drug (mg)	Storage condition °C	Cumulative percentage release@(mts.)*** Progressive dissolution time interval 10	20	30	40	50	60	Dissolution time@ T_{50} values (mts.) Initial*	Final***
DCPE	3.54	RT	33.53	35.62	37.49	44.56	45.32	47.91	60^{+}	60^{+}
		40	30.21	33.43	35.51	41.62	43.98	45.42		60^{+}
		50	35.21	37.32	47.42	49.55	50.98	52.32		50
		60	37.36	42.19	49.92	52.24	55.55	57.51		33
LDC	3.35	RT	66.21	72.34	82.45	86.49	93.42	98.56	8	7
		40	60.48	70.83	79.91	82.84	86.56	94.12		8
		50	68.51	74.62	86.84	95.42	97.61	99.12		7
		60	70.89	79.69	88.58	96.12	98.45	99.56		7
ADCPE	3.47	RT	22.55	30.34	34.21	37.18	39.42	41.51	60^{+}	60^{+}
		40	22.48	25.51	30.52	33.61	36.92	38.48		60^{+}
		50	26.21	32.42	36.56	39.87	44.92	46.42		60^{+}
		60	26.43	33.31	35.42	40.55	48.64	51.46		55
DCP	3.45	RT	30.98	35.18	42.92	47.63	52.41	54.32	58	46
		40	29.41	31.21	40.22	43.21	49.52	50.62		56
		50	31.42	37.61	44.46	49.12	53.22	56.32		42.50
		60	33.42	29.12	46.51	53.42	56.21	58.42		35
DTC	4.15	RT	40.81	50.95	56.56	70.71	75.32	82.62	20.25	19
		40	39.98	48.56	52.12	68.31	73.25	80.24		24
		50	44.21	56.35	70.66	76.56	81.12	83.62		15
		60	48.48	58.58	72.27	80.10	82.51	84.98		11.50

Table 4 contd...

SPF	4.63	RT	55.24	77.34	78.40	80.25	81.42	81.42	9	9
		40	48.98	70.43	78.42	78.55	79.28	79.10		10
		50	50.43	75.25	78.41	78.84	79.35	79.90		9
		60	52.24	75.25	78.40	79.14	80.10	80.85		9
SPS	4.60	RT	55.55	79.56	85.62	90.43	92.21	92.84	8	8
		40	50.55	81.23	83.49	83.45	83.81	83.42		10
		50	53.32	78.75	84.65	86.66	87.62	87.85		9
		60	54.24	78.95	85.10	87.25	88.29	88.35		9
SPT	5.00	RT	66.62	82.43	94.21	96.34	96.34	96.79	7	6
		40	62.24	85.45	86.12	86.44	86.80	86.80		7
		50	59.80	81.25	87.24	92.35	93.40	93.54		8
		60	67.20	85.50	91.20	94.74	95.50	95.62		6

@ Mean of three runs; RT Room temperature; + T_{50} not determined within 60 mts.;
* Initial reading in fresh condition; *** Final reading after storage

in their dissolution time T_{50} values at elevated temperature on storage. T_{50} values of batch LDC & DTC were found less than 30 minutes but others showed higher T_{50} values. However, T_{50} values of suppositories reached within 10 minutes, a faster in-vitro release of drug has been observed due to predominant solubility effect of the polyglycol bases. The inferior dissolution behaviour in solid dosage forms after storage was due to drug diluent interaction, degradation due to elevation of storage temperature and also due to physico-mechanical stability.

4. Relationship Between Dissolution Behaviour and Bioavailability -

Stability based on biopharmaceutical exercise, besides conditional requirements over an appropriate period of time has been well recognized. It has been observed that on storage and on aging the batch DCPE, DTC and SPF, degraded considerably as regard to their shelf-life and in-vitro performances. Therefore, they have been selected for their bioavailability evaluations. The in-vivo change in blood sugar level after administration of the respective dosage forms through oral and rectal routes in healthy rabbits were performed. The bioavailability parameters C_{max} and AUC revealed a good relationship between in-vitro dissolution behaviour and percentage bioavailability in

Table 5. Summary of comparative bioavailability parameters ± S.E. obtained from percentage reduction in blood sugar level (BSL) profiles of glibenclamide solid dosage forms on storage

Batch	Storage condition (°C)	C_{max} highest % reduction in BSL	T_{max} time to reach highest % BSL (hrs.)	AUC (0-24 hrs.)	Percentage bioavailability
DCPE	RT	60±1.5	5±0.50	432±10.23	97.95
	40	60±1.20	5±0.23	428±9.28	97.05
	50	36±1.15	7±0.55	385±5.40	87.30
	60	50±1.10	7±0.62	405±8.50	91.83
DTC	RT	54±1.20	5±0.05	441±11.24	100.00
	40	48±1.11	5±0.08	425±10.60	96.37
	50	47±1.22	5±0.15	410±5.56	92.97
	60	38±0.95	7±0.09	375±7.85	85.03
SPF	RT	60±0.75	15±0.98	542±3.21	123.00
	40	60±0.50	15±1.25	533±15.12	121.00
	50	56±1.56	15±0.80	520±12.25	118.50
	60	55±2.21	15±1.48	516±4.51	117.00

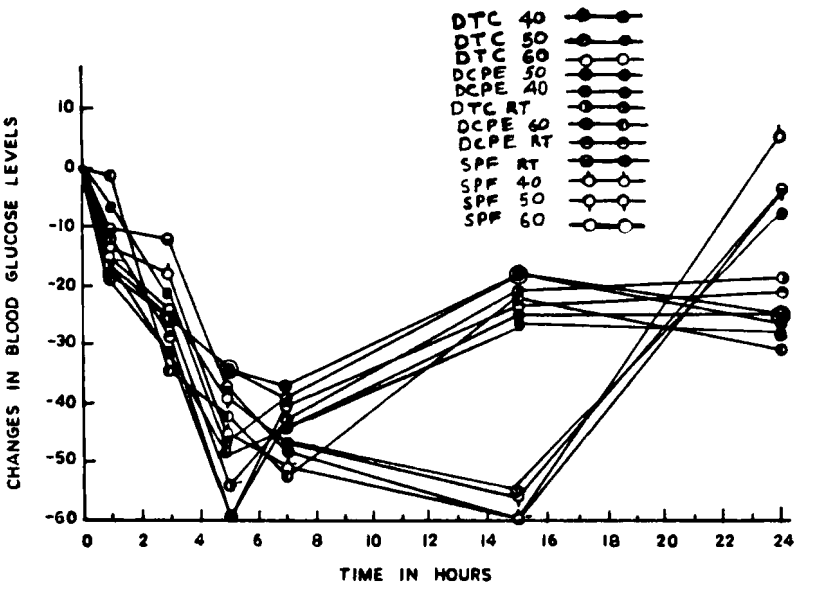

FIG. I. CHANGE IN BLOOD SUGAR LEVELS (BSL) PROFILES AFTER ORAL AND RECTAL ADMINISTRATION OF GLIBENCLAMIDE IN SOLID DOSAGE FORMS (TABLETS AND SUPPOSITORIES) ON AGING.

tablets and suppositories on storage under elevated conditions of temperature. Tablets showed decrease in their extent C_{max} and AUC, but increase in their rate T_{max} in production of hypoglycemia, while suppositories showed decrease in their extent but more or less same rate. C_{max} of batch DCPE and SPF were found to be similar after aging at room temperature and at 40°C but at higher temperature inferior bioavailability have been observed (Table 5). Batch DTC showed constant decrease in all the parameters on aging. Based on C_{max}

and AUC values the solid dosage forms showed the stability order as RT > 40° > 50° > 60°C. Thus, it has been found that on aging and elevation of temperature of storage conditions affected the bioavailability of solid dosage forms (Fig.1).

CONCLUSION

The present investigation revealed that dosage forms prepared with direct compression incorporating direct compressible vehicles and polyglycol bases are superior in production of pharmaceutical stable solid dosage forms. It is also concluded that glibenclamide tablets with directly compressible vehicles should be protected from temperature and humidity so as to avoid decrease in the stability and bioavailability.

ACKNOWLEDGEMENTS

The authors are grateful to Dr.R.Rosha, Works Manager, Hoechst Pharmaceuticals Ltd., Bombay for generously supplying glibenclamide B.P. as gift. Financial assistance from the C.S.I.R., New Delhi, is gratefully acknowledged.

REFERENCES

1. British Pharmacopoeia, 1973, Addendum, General Medical Council, London, 22, (1975).
2. Lieberman H.A. and Lachman L., Pharmaceutical Dosage Forms: Tablets, Vol.3, Marcel Dakker INC New York and Basel (1981).

3. Allen,L.V. et al, J.Pharm.Sci., 66, 494 (1977).
4. Fromming,K.H. et al, Pharm.Ind., 40, 967 (1978).
5. Barret,D. and Fell,J.T., J.Pharm.Sci., 64, 335 (1975).
6. Nicholas Lordi and Prafull Shiroman, Drug Dev. Ind.Pharm., 10(5), 729 (1984).
7. West et al, Diabete et Metabolisme (Paris), 3, 165, 238, 147 (1977); Through Acta Endocrinol., 94, Suppl., 238, 147 (1980).
8. Srivastava,H.S. et al, Indian Drugs, 20(9), 373-375 (1983).