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Accelerated Physical Stability Testing of Tolmetin Sodium Fast Dissolving Tablets Prepared by Direct Compression Method

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ABSTRACT

This work aims to evaluate the effect of environmental factors, including temperature, humidity, and light, on the quality of a drug substance or a formulated product which is utilized for prediction of its shelf life, to determine proper storage conditions and to suggest labeling instructions. Moreover, the data generated during the stability testing is an important requirement for regulatory approval of any new drug or formulation. In this work, stability studies were performed on two formulations (F1 and F2) which were developed for studying the effect of different storage conditions such as physical properties, drug content and release profile of the drug from TS-FDTs. The tablets were stored for three months at 30^{o}C and 75±5% Relative Humidity (RH) and 40^{o}C and 75±5% RH in thermostatically-controlled cabinet. The stored tablets showed accepted properties (thickness, hardness, weight variation, drug content, wetting time, *in-vitro* disintegration time, and percentage friability). Regarding the release profile of TS-FDTs, the obtained results indicated that the storage of the chosen formulae for three months at stress conditions has a minimum effect on the rate of drug release.

INTRODUCTION:

United States Food and Drug Administration (FDA) define orally disintegrating tablets as "a solid dosage form which contains a medicinal substance or active ingredient which disintegrates rapidly within a matter of seconds when placed upon a tongue" **[1]**. According to the European Pharmacopoeia, the fast dissolving tablets (FDTs) should dissolve/disintegrate with the aid of saliva in the mouth in less than three minutes **[2, 3]**. The quality of a drug product changes with time under the influence of environmental factors such as temperature, humidity and light**[4].** Stability of a pharmaceutical product may be defined as the ability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, toxicological, protective and informational specifications**[5]**. Stability studies aimed to evaluate the effect of environmental factors, including temperature, humidity, and light on the quality of the drug substance or formulated product which is utilized for prediction of its shelf life and to determine proper storage conditions and to suggest labeling instructions. Moreover, the data generated during the stability testing is an important requirement for regulatory approval of any drug or formulation**[6]**.

Tolmetin sodium (TS) is one of the non-steroidal anti-inflammatory drugs (NSAIDs) that are widely used as analgesics and anti-rheumatic agents. It was introduced into clinical practice in the United States in 1976**[7]**. Tolmetin sodium is currently used for the treatment of adult and juvenile rheumatoid arthritis and osteoarthritis. In addition, it exhibits antipyretic properties and is used for the treatment of inflammation and pain that results from musculoskeletal and bone related diseases**[8]**.

In the current work, stability studies were performed on two formulations of TS-FDTs (F1 and F2) that were prepared by direct compression methods. These two formulations were designed for studying the effect of different storage conditions on the change in the physical properties and drug content as well as in the release profile of the active drug from TS-FDTs.

MATERIALS AND METHODS

Tablet formulations

Two direct compression tablet formulations were tested for moisture sensitivity. The composition of the two formulations is illustrated in detail in **Table 1.**

Methods:

The tablets were stored for three months at 30ºC and 75±5% relative humidity (RH) and 40ºC and 75±5% RH in thermostatically-controlled cabinet. The degradation reactions of TS-FDTs at the investigated temperatures and relative humidity conditions were studied. The designed tablets were stored in tightly closed light protected bottles and wrapped in aluminum foil and stored at 30ºC and 75% RH and at 40 ºC and 75% RH for three months in thermostatically-controlled cabinets containing saturated solution of sodium chloride to attain the required RH at 75%. Samples of each formula from each temperature were taken at 7, 15, 30, 45, 60, 75 and 90 days of storage and evaluated for: thickness, hardness, weight variation, drug content, wetting time, *in-vitro* disintegration time, percentage friability and amount of TS released after 10 minutes then compared to the properties of the tablets at zero time of storage (pre-storage)**[9]**.

Accelerated stability testing of the designed formulae

The stability of TS-FDTs was studied using accelerated stability testing at 30 ºC and 40 ºC for three months· The kinetic parameters were calculated in order to obtain the suitable kinetic order for TS-FDTs stability· The expiry date (t_{90}) was estimated for two designed formulations (F1 and F2). In accelerated stability testing, a product is stressed at several high (warmer than ambient) temperatures and the amount of heat input required to cause product failure is determined. This is done to subject the product to a condition that accelerates degradation. This information is then projected to predict shelf life**[10]**. The shelf life of a product may be defined as the time that essential performance characteristics are maintained under specific handling conditions**[11].** The kinetics of drug decomposition at elevated temperatures were studied by plotting some functions of remaining amounts of drug against time according to different models (zero- and first-order) and the model giving the highest values of correlation coefficient (r) assigned the decomposition mechanism. It was possible from the calculated experimental accelerated stability testing to calculate the specific reaction rate constants corresponding to the two elevated temperature using some form of Arrhenius equation and by substituting the experimentally established specific rate constants at the two elevated temperatures, the energy of activation was determined using following equation:**[12]**.

$$\log\left(\frac{K2}{k1}\right)=\left(\frac{Ea}{2.303R}\right)\left(\frac{1}{T2}-\frac{1}{T1}\right)$$

Where, K_1 is the specific decomposition reaction rate constant at temperature t_1. K_2 is the specific reaction rate constant at temperature t_2. Ea is the energy of activation (Cal. /mole). R is the gas constant (1.987cal./mole.degree). T_1 is the absolute temperature in Kelvin (t_1 +273 ^oC). T_2 is the absolute temperature in Kelvin (t_2 +273 ^oC).

This equation describes the relationship between storage temperature and degradation rate. Use of the Arrhenius equation permits a projection of stability from the degradation rates observed at high temperatures. Activation energy, the independent variable in the equation, is equal to the energy barrier that must be exceeded for the degradation reaction to occur. When the activation energy is known (or assumed), the degradation rate at low temperatures may be projected from those observed at "stress" temperatures **[12]**. Activation energy (Ea) was determined from the slope and the Arrhenius factor (A) was determined from the intercept of the straight lines. By substituting the values of (Ea) and (A) in Arrhenius equation, the specific rate constant at room temperature (K_{25}) was calculated. The expiration date (t_{90}) was calculated by applying the kinetics equations using K_{25} value **[13]**.

Table 1: Composition of different formulations of TS-FDTs

Formula	TS	CP	CCS	Camphor	Lactose	Aspartame	Saccharin	Mg-stearate	Total
F1	50	16	20	10	46.5	4.5	1.5	1.5	150
F2	50	20	16	10	46.5	4.5	1.5	1.5	150

All the above mentioned amounts are presented as mg of each component. TS, Tolmetin sodium; CP, Crospovidone; CCS, Croscarmellose sodium; Mg-stearate, Magnesium stearate.

RESULTS AND DISCUSSION:

Results of storage of TS-FDTs (F1 and F2) at 30 ^oC +75% RH and 40 ^oC +75% RH are listed in **Table 2**. The results showed that no significant changes were observed in properties of stored tablets at the selected conditions during the storage period of three months. The stored tablets showed accepted properties such as thickness, hardness, weight variation, drug content, wetting time, *in-vitro* disintegration time, and percentage friability. Regarding the

drug release profile, the obtained results indicated that the storage of the designed formulae for three months at stress conditions have a minimum effect on the rate of TS release from TS-FDTs as graphically represented in **Figures 1 and 2**.

Table 2: Physicochemical properties of TS-FDTs (F1 and F2) after storage at 30 °C and 40°C+RH 75% for three months compared to corresponding pre-stored tablets

Parameters	Pre-stored tablets		Stored tablets	
	Formula	Zero time	30°C+RH 75%	40°C+RH 75%
Thickness (mm)	F1	3.00±0.07	3.00±0.21	2.95±0.11
	F2	3.20±0.70	3.15±0.36	3.11±0.25
Hardness (Kg/Cm^2)	F1	4.50±0.30	4.02±0.15	3.98±0.21
	F2	4.34±0.18	4.28±0.21	4.17±0.31
Weight Variation (mg)	F1	150.50±0.58	150.00±0.69	149.10±1.20
	F2	152.30±0.75	150.00±0.69	149.10±1.20
% Drug Content	F1	95.20±1.74	94.65±1.15	93.92±2.03
	F2	96.80±1.79	95.92±1.66	95.20±3.08
Wetting Time (sec)	F1	22.00±2.85	21.00±3.54	20.00±2.11
	F2	19.00±2.54	18.00±2.88	18.00±3.25
Disintegration Time (sec)	F1	19.00±4.21	19.00±3.25	18.00±2.36
	F2	20.00±3.65	19.00±2.15	19.00±1.58
% Friability	F1	0.46±2.24	0.53±1.89	0.70±2.00
	F2	0.56±2.63	0.60±2.30	0.65±1.78
% TS released at 10 min.	F1	76.22±1.58	75.03±2.54	74.36±4.36
	F2	74.86±2.19	73.65±3.69	72.69±2.25

All data are expressed as mean ± SD (n = 10)

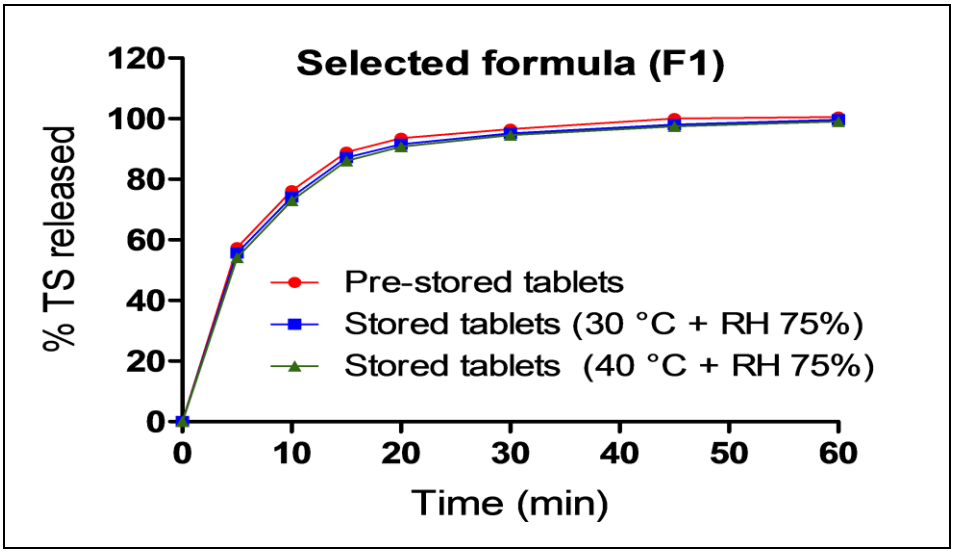
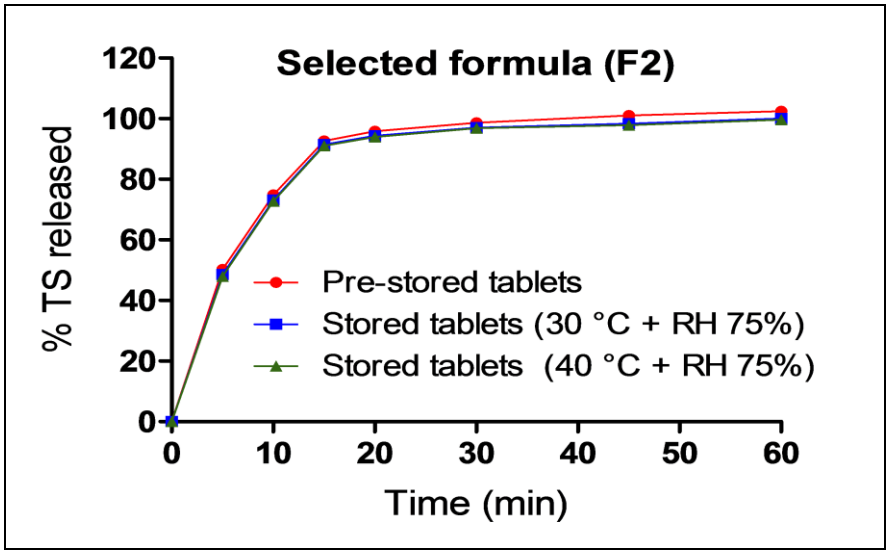


Figure 1: Release profiles of TS from TS-FDTs (F1) after storage at 30 and 40°C+RH 75% for three months compared with the corresponding recently prepared tablets.



Figures 2: Release profiles of TS from TS-FDTs (F2) after storage at 30 °C and 40°C+RH 75% for three months compared with the corresponding recently prepared tablets.

Kinetic treatment of the accelerated stability testings of TS-FDTs at different storage conditions were represented in **Tables 3** and **4** as well as in **Figures 3** and **4**. Kinetic parameters (intercept, slope, r, k and $t_{1/2}$) for the accelerated stability testing of TS-FDTs were illustrated in **Tables 5.**

Table 3: Accelerated stability testing of TS-FDTs (F1 and F2) stored at 30°C and 40°C+RH 75%

Time (day)	Percentage of TS remained after (days)			
	F1		F2	
	30°C+RH 75%	40°C+RH 75%	30°C+RH 75%	40°C+RH 75%
0	100	100	100	100
7	99.60	99.35	99.45	99.25
15	99.14	98.25	98.85	98.45
30	98.75	97.52	98.02	97.22
45	97.85	95.61	97.01	95.37
60	97.15	94.01	96.89	92.07
75	96.79	92.14	95.95	90.78
90	95.57	90.72	94.69	90.04

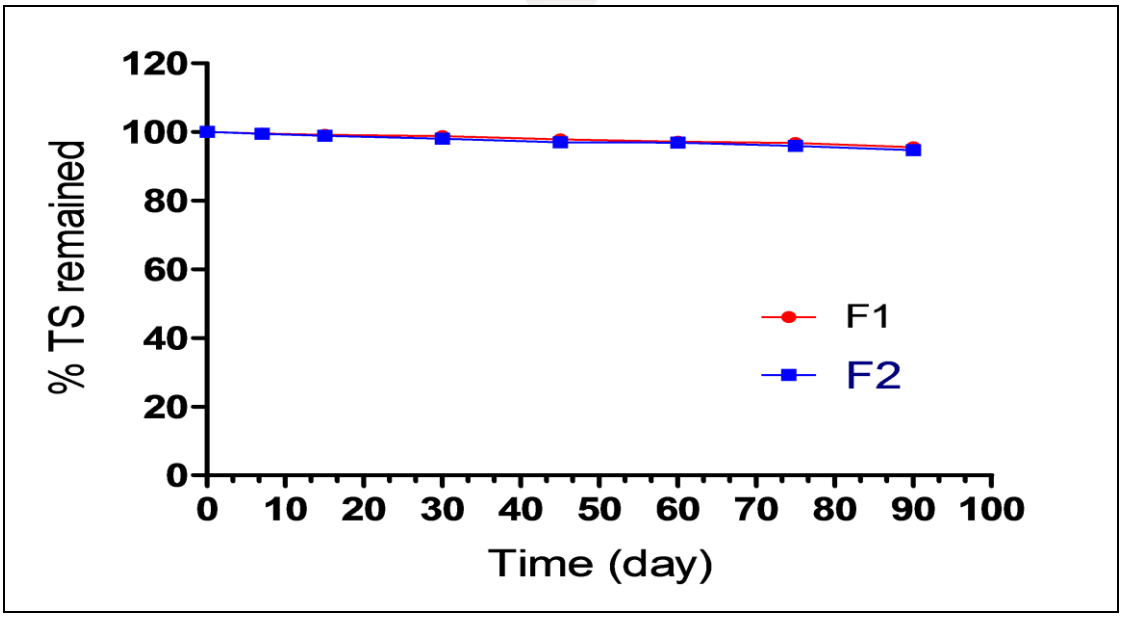


Figure 3: Accelerated stability testing of TS-FDTs (F1 and F2) at 30°C+75% RH.

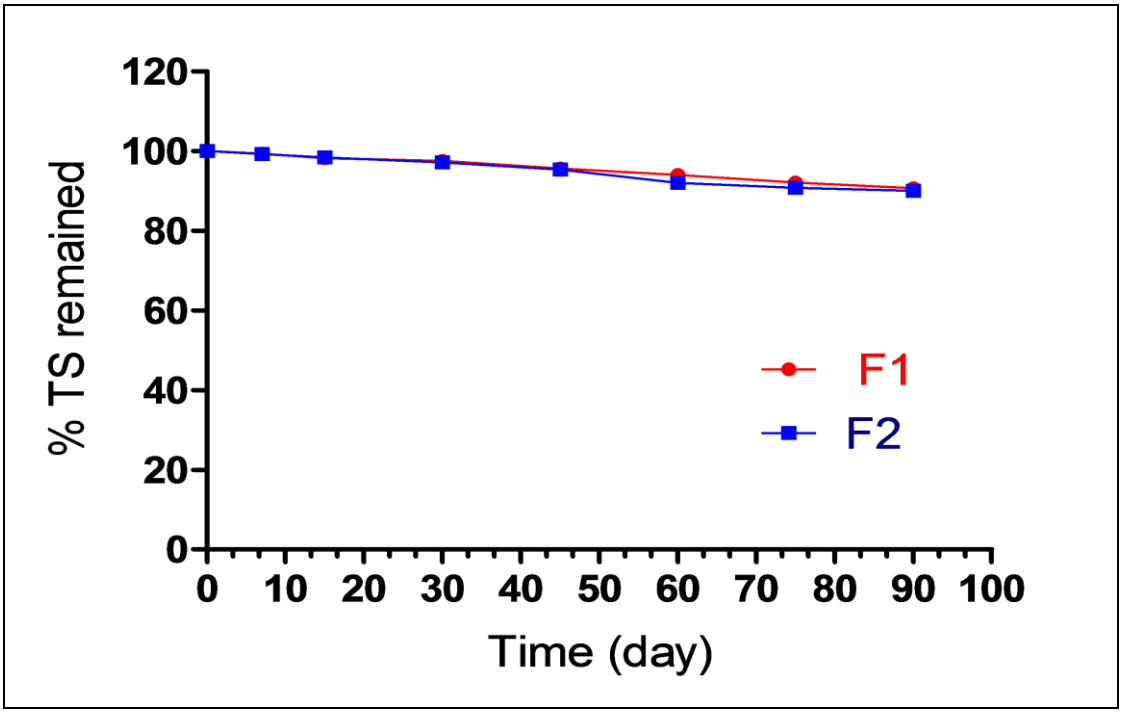


Figure 4: Accelerated stability testing of TS-FDTs (F1 and F2) at 40°C+75% RH.

Table 4: Accelerated stability testing of TS-FDTs (F1 and F2) stored at different conditions (30 °C and 40 °C + RH 75%) for three months according to zero-order and first-order Kinetic

Time (day)	Zero -order Kinetic				First-order Kinetic			
	Percentage of TS decomposed				Log percentage of TS remained			
	F1		F2		F1		F2	
	30°C+RH 75%	40°C+RH 75%	30°C+RH 75%	40°C+RH 75%	30°C+RH 75%	40°C+RH 75%	30°C+RH 75%	40°C+RH 75%
0	0.40	0.65	0.55	0.75	1.9982	1.9971	1.9976	1.9967
7	0.86	1.75	1.15	1.55	1.9962	1.9923	1.9949	1.9932
15	1.25	2.48	1.98	2.78	1.9945	1.9890	1.9913	1.9877
30	2.15	4.39	2.99	4.63	1.9905	1.9805	1.9868	1.9794
45	2.65	5.99	3.11	7.93	1.9883	1.9731	1.9820	1.9641
60	3.21	7.86	4.05	9.32	1.9858	1.9644	1.9763	1.9575
75	4.43	9.28	5.31	9.96	1.9803	1.9577	1.9763	1.9544
90	0.40	0.65	0.55	0.75	1.9982	1.9971	1.9976	1.9967

Table 5: Kinetic parameters of TS-FDTs (F1 and F2) based on accelerated stability testing stored at different conditions (30°C and 40°C + RH 75%) for three months according to zero-order and first-order:

Formula Nr		Intercept		Slope		r		K(mg.hr-1)		$T_{1/2}$ (Days)	
		Zero order	First order	Zero order	First order	Zero order	First order	Zero order	First order	Zero order	First order
F1	**30°C**	0.03623	1.99991	0.04564	0.00020	0.99134	0.99076	0.04564	0.00047	1095.51	1482.95
F2	**40°C**	0.17477	2.00115	0.10442	0.00047	0.99650	0.99600	0.10442	0.00110	478.83	630.64
F1	**30°C**	0.29528	1.99881	0.05302	0.00024	0.98886	0.98859	0.05302	0.00055	943.01	1296.31
F2	**40°C**	0.30764	2.00181	0.12134	0.00056	0.98692	0.98680	0.12134	0.00128	412.04	539.65

Table 5 showed the degradation of TS in the estimated FDTs was found to obey zero-order kinetic model based on the highest values of correlation coefficient (r).

Estimation of shelf life of the selected TS-FDTs:

The shelf life is determined from the data obtained from the accelerated stability studies. The calculated t_{90} for accelerated stability testing was found to be 1.4941 and 1.2865 years for TS-FDTs formulae F1 and F2 respectively as seen in **Table 6**.

Table 6: Kinetic data for the accelerated stability testing of TS-FDTs

Formula Nr.	(k_{30}) Day^{-1}	(k_{40}) Day^{-1}	E_a Cal/mole	Calculated (k_{20}) Day^{-1}	$t_{1/2}$ (Day)	(t_{90}) (Day)	(t_{90}) (Year)
F1	0.0461	0.1044	15599.22	0.018852	2652.146	530.4292	1.4941
F2	0.0530	0.1216	15604.7	0.021894	2283.695	456.7391	1.2865

CONCLUSION:

Accelerated stability studies showed that the differences in physical and chemical properties between the stored and freshly prepared tablets were non-significant. The accelerated stability testing of TS-FDTs (F1 and F2) at 30°C and 40°C+ 75% RH obey USP specifications. Shelf-

lives (t90) of the tested formulae were found to be 1.4941 and 1.2865 years for F1 and F2, respectively. It was obvious that the degradation of TS-FDTs (F1 and F2) was found to follow a zero-order reaction at based on the highest values of correlation coefficient.

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Conflict of interest: The authors declare that there is no conflict of interests.

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