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INCREASE IN THE RATE OF MOISTURE GAIN BY HYGROSCOPIC DRUGS IN THE PRESENCE OF NON-HYGROSCOPIC WATER-SOLUBLE SUBSTANCES: STUDY OF THE GENERALIZATION OF THIS HITHERTO UNKNOWN PHENOMENON, EXPLANATION TO ITS OCCURRENCE AND IMPLICATIONS IN FORMULATION DEVELOPMENT

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ABSTRACT

The purpose of this study was to explore whether the increase in rate of moisture gain by hygroscopic drugs in the presence of non-hygroscopic water-soluble substances (NHWSS) was a generalized phenomenon. Also, the aims were to provide explanation for the occurrence of this hitherto unknown phenomenon, and to explore its implications in formulation development. An indication to the prevalence of this phenomenon was provided earlier, when moisture gain studies were carried out on ethambutol hydrochloride (E) in the presence of isoniazid (H). Specific ratios of E (a known hygroscopic drug) and H (a NHWSS) were found to gain moisture at a higher rate than the former alone. In the present investigation, E and benzyl penicillin (BP) (both hygroscopic drugs) were separately combined with a variety of NHWSS, viz., gabapentin, ascorbic acid, pyrazinamide and glycine, apart from H. The compounds were mixed in the ratios from 100:0 w/w to 0:100 w/w. The mixtures were exposed to accelerated conditions of temperature and humidity (40 ^{0}C/75% RH) and moisture gain was determined with time. The rate of moisture gain was higher for several mixtures than pure hygroscopic substances, although total moisture gain was more for the pure drugs than any ratio of mixture of hygroscopic drug and NHWSS. This provided confirmation that the phenomenon was of general occurrence. To gain further insight, rate of moisture gain was correlated to structural descriptors of NHWSS calculated using CODESSA, DRAGON and Hyperchem. The results indicated that increased rate of moisture gain by the combination of hygroscopic compounds and NHWSS was perhaps due to removal of water by NHWSS molecules for the purpose of hydration, forcing the hygroscopic substance to withdraw more moisture from the environment. The study suggests that formulations containing hygroscopic material and NHWSS together should be given critical consideration during formulation development, packaging selection and stability testing, as they can gain moisture at a faster rate than normal products.

Keywords: Drugs, formulations, rate, moisture gain, hygroscopic, structural descriptors, correlations

INTRODUCTION

Hygroscopicity is an inherent property of any substance, which is shown due to the presence of polar groups in the structure, and is reflected by the adsorption/absorption of moisture from the environment (1). It is well known that combining two hygroscopic drugs results in increase in total moisture gain, due to additive effect (2). However, we found a previously hitherto unknown phenomenon in one of our earlier studies (3), wherein the rate of moisture gain by a hygroscopic substance was increased even in the presence of a non-hygroscopic water-soluble substance (NHWSS). This was observed with ethambutol hydrochloride (E), a hygroscopic drug, in the presence of isoniazid (H), a NHWSS. The combination gained moisture at a higher rate than pure E on storage at 40 °C and 75% RH for 8 h (3).

The present study was carried out to investigate whether the above was a generalized phenomenon. For this, E and another hygroscopic drug, benzyl penicillin (BP), were mixed with several NHWSS, viz. H, gabapentin (G), ascorbic acid (AA), pyrazinamide (Z) and glycine (GL). These NHWSS were selected based on their good aqueous solubility and non-hygroscopic nature. The obtained moisture gain data were correlated to structural descriptors (generated using CODESSA, DRAGON and Hyperchem) to understand the reason for the occurrence of the phenomenon. The findings and their implications with respect to formulation development are discussed in this paper.

MATERIALS AND METHODS

Materials

E, H and Z were gift samples from M/S Panacea Biotec Ltd., Lalru, India. The other compounds, BP (Alembic limited, Vadodra, India), G (Ranbaxy Laboratories Limited, Gurgaon, India); and tramadol (T) (Alkem Laboratories, Mumbai, India) were also obtained as gift samples. GL and AA of analytical grade were purchased from s.d. fine chemicals, Mumbai, India. All materials were used as received, without purification or size reduction.

Instruments

A stability chamber (KBF 720, WTB Binder, Tuttlingen, Germany) set at 40 ± 1°C and 75 ± 2% RH was used for storage of the samples. Weighings were done on a precision analytical balance (AG 135, Mettler Toledo, Greifensee, Switzerland).

Software

ChemDraw Ultra, v 6.0.1. (CambridgeSoft Corporation, MA, USA) was used to draw the structures of various substances used in the study. CODESSA (COmprehensive Descriptor for Structural and Statistical Analysis), v 2.4 (Semichem, KS, USA), DRAGON, v 3.6 (Braco Imaging, S. P. A., Milan, Italy) and Hyperchem, v 7.0 (Hypercube, Inc., FL, USA) were used for the calculation of structural descriptors and development of correlations.

Methods

Weight gain studies

E and BP were mixed with NHWSS to yield the following combinations: E:H, E:G, E:AA, E:Z, E:GL, BP:H, BP:G, BP:AA, BP:Z and BP:GL. The drug to NHWSS ratio was varied between 0:100 w/w and 100:0 w/w in each case. The materials were weighed to a total quantity of 100 mg and transferred to 10 ml glass beakers. The beakers were charged in an open state to the stability chamber, set at 40 ± 1°C and 75 ± 2% RH. All the studies were done in triplicate. The gain of weight was recorded till there was no further change. Studies were conducted in a similar manner on E:T and BP:T.

Calculation of rate of moisture gain (k)

The moisture gain data till 4h of the combinations containing drug: NHWSS in the ratio of 90:10 were subjected to linear regression and the rate of moisture gain (k) values were calculated from the slopes.

Correlation of k with structural properties of NHWSS

The structures of NHWSS were drawn using ChemDraw Ultra, these were cleaned and their energy was minimized using MM2 subroutine of the program. The minimized structures were saved in molfile format. The molfiles were used further for calculations of structural descriptors using CODESSA, DRAGON and HyperChem. Those descriptors, for which the values were not available for every NHWSS or the values were common, were discarded from the data sets. Descriptors with values constant for all the structures were also excluded. The data for the remaining were loaded into CODESSA for heuristic analysis. For the set of five NHWSS, only one-descriptor correlations were considered, keeping in line with the recommended compound to descriptor ratio of 4:1 (4,5). The significance of obtained correlations was judged by four statistical criteria: multiple correlation coefficient (r), Fisher's F value, t-value, and standard deviation (SD). Descriptors were eliminated from the list when i) F-value for the one-parameter correlation with the descriptor was below 1.0, ii) the coefficient of determination (R^2) of the one parameter equation was less than the minimum acceptable R2 for correlation, iii) the t-test value was less than minimum t-value acceptable for correlation (t_1), or iv) the descriptor was highly inter-correlated with another descriptor and this descriptor had a higher squared correlation coefficient in the one-parameter equations. Further short listing was done based on values of cross-validated correlation coefficient (Q^2), which measured the predictive power of an equation by leave-one-out (LOO) analysis. Although the minimum value of Q^2 for a significant correlation is 0.3 (6), correlations with a Q^2 value of <0.75 were disregarded in our studies.

Selected correlations in the final list were used for prediction of moisture gain for combinations of E:T and BP:T in the validation set.

RESULTS AND DISCUSSION

Moisture gain behaviour of ethambutol hydrochloride and benzyl penicillin in the presence of various NHWSS

Figures 1a-e show the profiles of moisture gain by E in the presence of various ratios of NHWSS. It is evident from the graphs that in each case pure E gained higher total moisture than mixtures of drug: NHWSS. The total moisture gain by E was not affected by the presence of particular NHWSS, as the profile remained the same in all cases. Oppositely, the rate of moisture gain of the combinations containing NHWSS and E was higher than pure E for the mixtures containing drug content between 70%-90% w/w. This behaviour of E:H combinations (Fig. 1 a) was in line with the observation made by us earlier (3,7). Figures 1b-e shows that moisture gain behaviour was almost similar even with other NHWSS, apart from H.

The moisture gain profiles of BP in the presence of same NHWSS are depicted in Figures 2a-e. Evidently, the behaviour is exactly parallel to E, with pure BP showing higher total moisture gain than the drug: NHWSS mixtures, and the rate of moisture gain being higher for drug: NHWSS mixtures (containing 70%-90% w/w drug) than pure BP.

Comparison of Figs. 1a-e with Figs. 2a-e shows that differences exist among the profiles of the two drugs with respect to the extent of total moisture gain, and the time taken for reaching the plateau. These conform to the inherent differences in equilibrium moisture contents of the two drugs (8)

Values of rate of moisture gain (k)

The rate of moisture gain (k) and coefficient of determination (R2) values are listed in Table I. The ratio of 90:10 was selected, as the rate of increase was maximum at this ratio in all the combinations, whether of E or BP. The reason for considering points till only 4 h was to limit to linear portion of the plots. The values in Table I show that R2 were >0.95 in all the cases, thus confirming that the plots were almost linear till the time selected.

Correlations of rate of moisture gain (k) with structural descriptors

Table II gives the correlations of k values with structural descriptors of NHWSS in case of both E and BP. The correlations were obtained as output upon heuristic analysis of the data using CODESSA. The table includes data of regression and predictive parameters (R^2, F-value, S^2 and Q^2). The table lists only those single-descriptor correlations, which were highly significant ($P < 0.001$). As evident, in all the cases, R2 values were = 0.85 and Q^2 were = 0.75, indicating that the equations were well correlated and even had high predictive power.

Results of the validation set

The experimental and predicted results for combinations of E:T and BP:T in the validation set are given in Table III. The structure of T is included in the table. It is shown that predicted and experimental k values were almost similar for the two drugs, with the deviation being only 4.74% and 3.30% for E and BP, respectively. This confirmed the predictive nature of correlations obtained on heuristic analysis.

The probable reason for the phenomenon

A careful look into the types of descriptors involved in the correlations (Table II) shows that there are four descriptors, which were common in case of both the drugs. These are hydration energy (HE), polarizability (Pol), XY Shadow/XY Rectangle and log P. Evidently, the slope of the correlations between rate of moisture gain and log P (Table II) was negative for both the drugs, indicating that the rate of gain of moisture was correlated to log P in an inverse manner. This means instead of hydrophobicity, the correlation was positive with hydrophilicity of the molecule. The involvement of three common and related descriptors, viz., HE, Pol and log P, highlights on the role of hydration potential, polarity and/or hydrophilicity of NHWSS in the observed phenomenon of higher rate of moisture gain by hygroscopic drugs in the presence of NHWSS. This puts forth an understanding that the water gained from environment by hygroscopic drug is taken away by the polar water-soluble molecules (NHWSS) for their hydration. The withdrawal of water forces the hygroscopic component to gain more moisture till the equilibrium is reached (Figs. 1 and 2). While the rate of moisture gain is influenced, total moisture gain remains unaffected because the basic hygroscopic property of the drug, and nature of the mixture are not affected during the moisture gain process.

Implication of the study in formulation development

The study suggests that any formulation containing a hygroscopic component along with NHWSS may gain moisture rapidly and might show stronger stability problems, if the drug or any other component of interest in the formulation was labile to moisture. It means such products need to be subjected to critical evaluation during formulation, packaging development and stability testing.

CONCLUSION

The results from moisture gain studies on combinations containing E and BP with variety of NHWSS and employment of validation set during the studies suggest that the hitherto unknown phenomenon of increase in rate of moisture gain by the combination of hygroscopic material and NHWSS is of general nature. It may apply across other hygroscopic substances in the presence of various NHWSS. The phenomenon is a result of withdrawal of water by polar NHWSS molecules for their hydration, forcing moisture to be gained rapidly by the hygroscopic component, resulting in increase of the rate of moisture gain. It means formulations containing hygroscopic materials with NHWSS stand a chance to deteriorate quickly, thus requiring critical attention during formulation development, packaging selection and stability testing.

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Table 1: Structure of NHWSS and rate of moisture gain (k) and R2 values of moisture gain curves till 4 h in case of both ethambutol hydrochloride (E) and benzyl penicillin (BP)

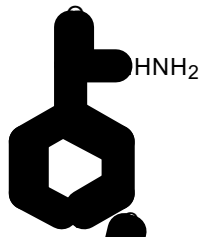
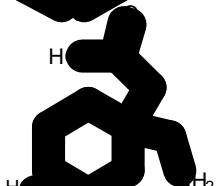
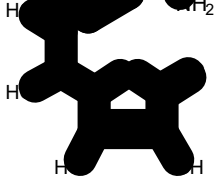
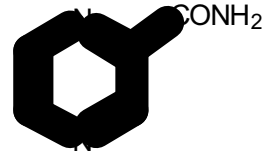
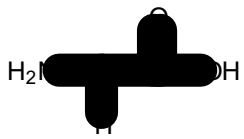
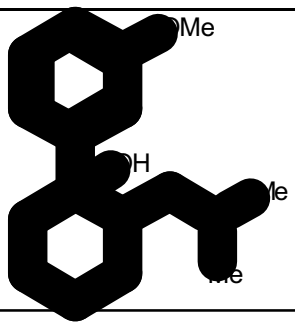
		k and R^2 values	
NHWSS	Structure	kE (R^2)	k¬BP (R^2)
Isoniazid		7.67 (0.9872)	6.01 (0.9756)
Gabapentin		8.38 (0.9958)	5.28 (0.9967)
Ascorbic acid		8.22 (0.953)	7.15 (0.9565)
Pyrazinamide		7.13 (0.9869)	7.06 (0.9793)
Glycine		12.65 (0.95)	7.06 (0.9792)

Table 2: Correlations between k and structural descriptors of NHWSS obtained after heuristic analysis

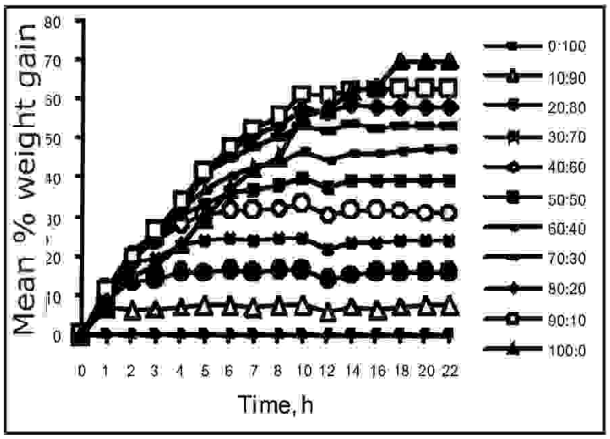
Correlation	R^2	F-value	S^2	Q^2
Ethambutol hydrochloride kE = -2.4576 + 1.360e-02*HE	0.8457	74.94	0.078	0.7933
kE = -9.1533 + 1.4543e+01* XY Shadow/XY Rectangle	0.8531	32.51	0.2738	0.8275
kE = -0.6124 + 0.2184*HyF	0.8945	34.97	0.0974	0.8511
kE = -3.2947 + 0.3115*Pol	0.9187	21.54	2.2413	0.8754
kE = 4.8427 – 0.6162*log P	0.9244	25.94	0.3158	0.9071
kE = -8.3842 + 15.41e-02*HACA2	0.9678	42.38	0.2975	0.9185
kE = 8.3451 – 0.21*log (PNSA2)	0.9683	189.74	0.0094	0.9257
Benzyl penicillin				
kBP = 1.3046e+01 + 4.5405e-01*Pol	0.9572	33.25	0.1241	0.9284
kBP = 5.7595 – 2.3205e-02*DPSA2	0.9514	17.18	0.2228	0.9174
kBP = 4.7022 + 3.831e-01*HE	0.9473	53.96	0.0468	0.9106
kBP = 7.1641e-01 + 8.4347*RNCG	0.9380	45.41	0.551	0.9124
kBP= 4.5497 – 0.06427*log P	0.9329	41.69	0.0597	0.9210
kBP = 2.4576 + 1.316e-02*HASA-1 [Zefirov's PC]	0.9493	56.13	0.0282	0.9318
kBP = 3.2152 + 0.08412* XY Shadow/ XY Rectangle	0.9741	59.41	0.0183	0.9627

Key: DPSA, difference in charged partial surface areas (viz. PPSA-PNSA, where PPSA is partial positive surface area and PNSA is partial negative surface area); HACA2, H-acceptors charged surface area-2; HASA-1, H-acceptors surface area-1; HE, hydration energy; HyF, Hydrophobicity index; log P, partition coefficient; PNSA2, total charge weighted partial negative surface area; Pol, polarizability; RNCG, relative negative charge; and XY Shadow/ XY Rectangle, Jurs XY shadow/ XY rectangle index.

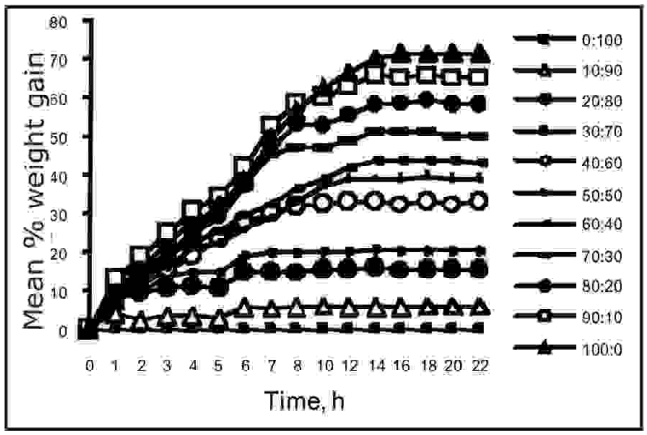
Table 3: Structure of tramadol and comparison of experimental and predicted k values

Structure of tramadol	k					
	Experimental		Predicted*		% Deviation	
	kE	kBP	kE	kBP	kE	kBP
	13.604	5.206	12.958	5.034	4.74	3.30

*** The predicted k values for E and BP are mean of the values predicted using correlations in Table II for the four common descriptors (HE, Pol, log P and XY Shadow/ XY Rectangle).**



a



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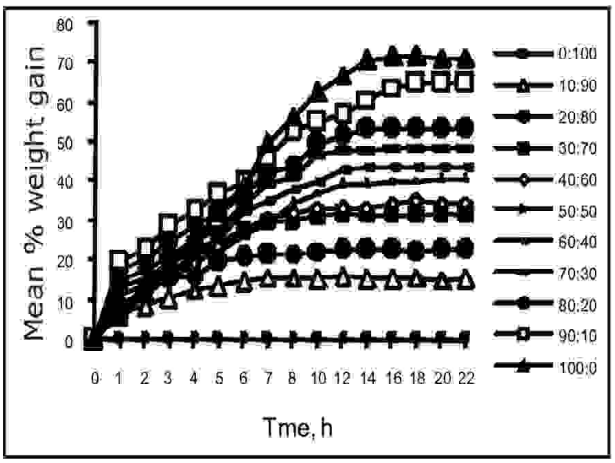
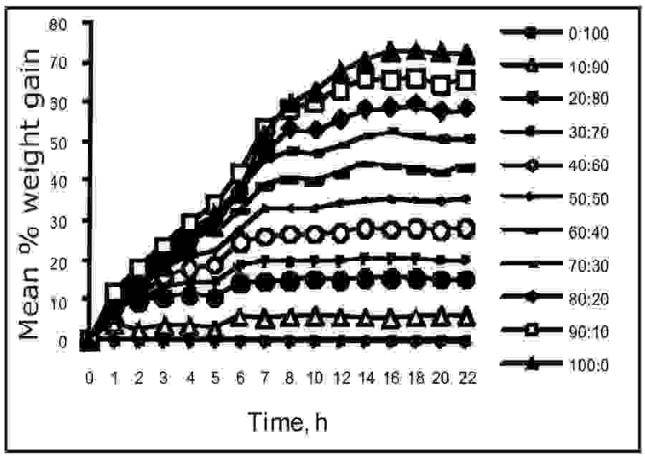


c



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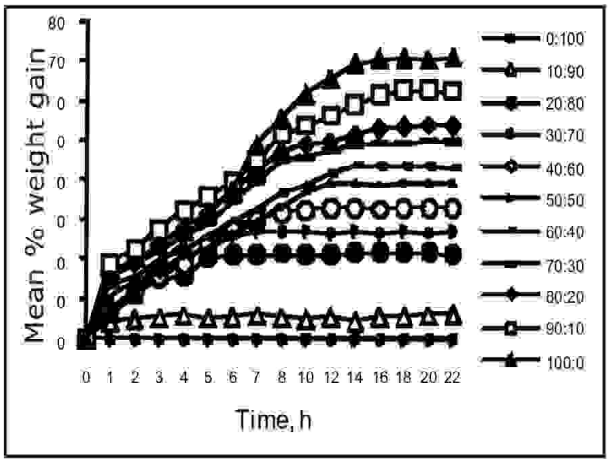
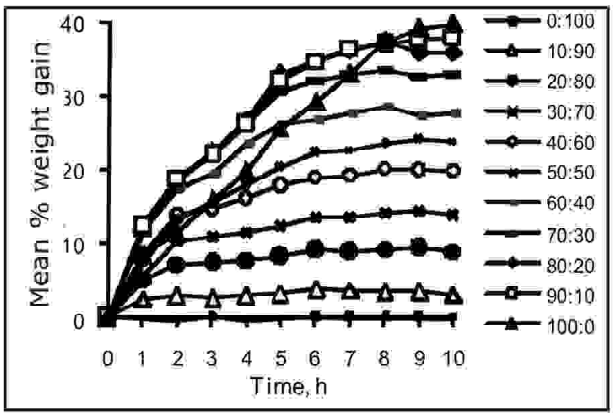


e

Figure 1



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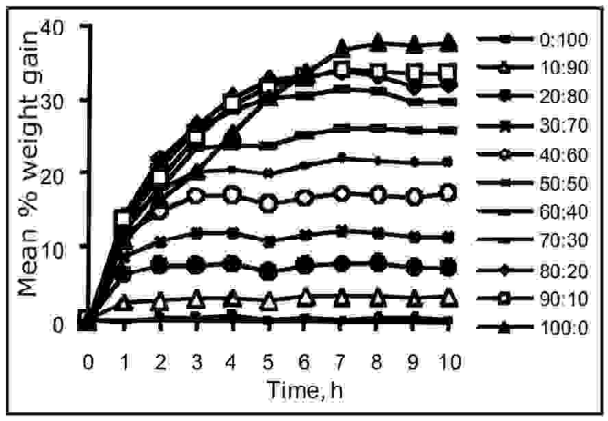

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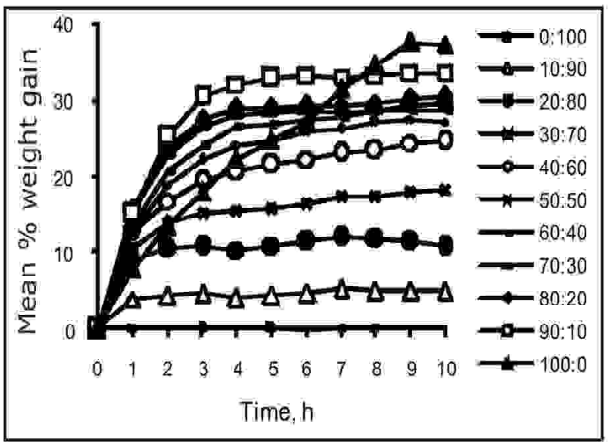

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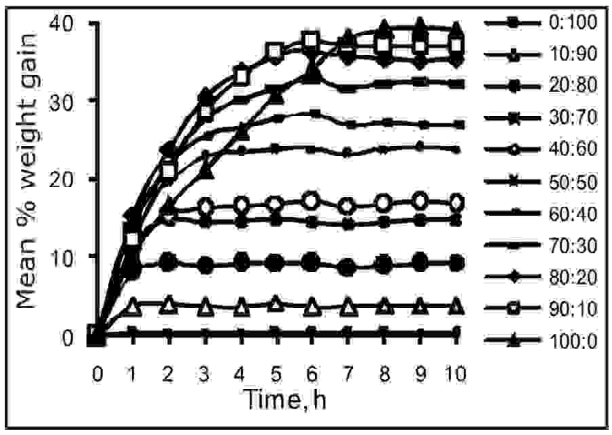

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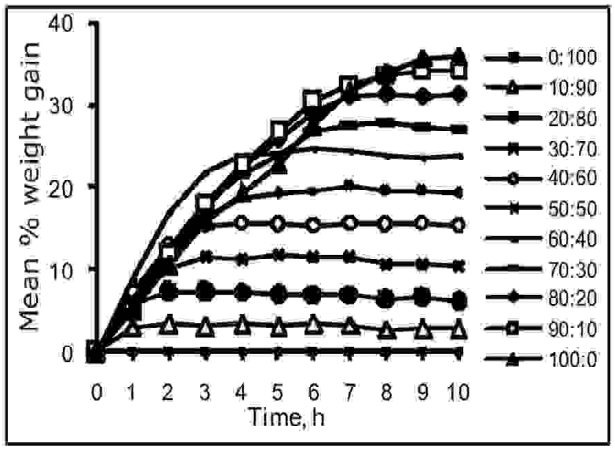

e

FIGURE LEGENDS

FIGURE 1. Moisture Gain Behaviour Of Differential Compositions (0:100 To 100:0 W/W) Of Ethambutol Hydrochloride With Isoniazid (A), Gabapentin (B), Ascorbic Acid (C), Pyrazinamide (D), And Glycine (E) At Accelerated Conditions Of Temperature And Humidity (40 ?C/75% RH).

FIGURE 2. Moisture Gain Behaviour Of Differential Compositions (0:100 To 100:0 W/W) Of Benzyl Penicillin With Isoniazid (A), Gabapentin (B), Ascorbic Acid (C), Pyrazinamide (D) And Glycine (E) At Accelerated Conditions Of Temperature And Humidity (40 ?C/ 75% RH).

Figure2

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