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## Formulation and *in vitro* evaluation of theophylline matrix tablets prepared by direct compression: Effect of polymer blends

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### ABSTRACT

The deformation mechanism of pharmaceutical powders, used in formulating directly compressed matrix tablets, affects the characteristics of the formed tablets. Three polymers of different deformation mechanisms were tested for their impact on theophylline directly compressed tablets namely Kollidon<sup>®</sup> SR (KL SR, plastic deformation), Ethylcellulose (EC, elastic deformation) and Carnauba wax (CW, brittle deformation) at different compression forces. However, tablets based mainly on KL SR, the plastically deformed polymer (TN1) exhibited the highest hardness values compared to the other formulae which based on either blends of KL SR with CW, the very brittle deformed polymer. The upper detected force for TN formulae and the lower punch force were found to dependent mainly on the powder deformation. This difference is attributed to the work done during the compression phase as well as the work lost during the decompression phase. Furthermore, the release profiles of TN from formulae TN2 and TN4 that based on the composition (2KL SR: 1EC) and (1KL SR: 2EC), respectively, were consistent with different deformation mechanisms of KL SR and EC and on the physicochemical properties like the water absorptive capacity of EC. Upon increasing the weight ratio of KL SR (TN2), the release rate was greatly retarded (39.4, 37.1, 35.0 and 33.6 % released after 8 h at 5, 10, 15 and 20 kN. © 2011 Trade Science Inc. - INDIA

### KEYWORDS

Theophylline;  
Matrix tablets;  
Deformation mechanism;  
*In vitro* release.

### INTRODUCTION

The consolidation of powder into a tablet can be divided into initial packing of the particles and elimination of void spaces in the powder bed. As the applied forces rise, elastic deformation, plastic deformation and brittle fracture of the particles occur. At this stage, in-

termolecular bonding takes place, and a coherent mass is formed. Three types of bond applicable to tablets include solid bridges, intermolecular forces and mechanical interlocking<sup>[1]</sup>, but they never act independently<sup>[2]</sup>. Intermolecular forces constitute the dominating bond mechanism for pharmaceutical materials<sup>[3]</sup>. Solid bridges have been defined as areas of physical

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contact between adjacent surfaces. They can occur due to melting followed by resolidification or by dissolution of solid materials followed by recrystallization<sup>[4]</sup>. The nature of solid bridges is dependent on the chemical structure of the material<sup>[5,6]</sup>. Compression force is spread into the mass by particle to particle contacts. Presence of moisture is also reported to be important in the formation of solid bridges<sup>[7,8]</sup>.

If two surfaces are sufficiently close to each other, they will exhibit mutual attraction. Intermolecular forces include three types of forces: van der Waal's forces, hydrogen bonding and electrostatic forces. The strength of these forces is affected by the type of material, the distance between the molecules or particles and the surrounding medium<sup>[9,10]</sup>. Van der Waals forces are considered to be the most important distance attraction forces holding particles together<sup>[11]</sup>.

Study by Olsson and Nystrom 2000<sup>[12]</sup>, considered features of the internal tablet structure that were important for tablet strength and assessed bond types by establishing interaction factor that reflected the dominating bond type. The incidence and importance of mechanical interlocking obviously depends on the size and shape of the particles. Smooth spherical particles will have little tendency to interlock, where as irregular shaped particles might be expected to do so<sup>[13]</sup>. Bonding with mechanical interlocking is a bonding mechanism of minor importance for most of the investigated materials with the possible exception of Avicel PH 101<sup>[3]</sup>. The mechanism of compaction not only depends on the powder properties<sup>[14]</sup> but also affected by particle size, shape<sup>[15]</sup>, moisture content<sup>[16,17]</sup> and experimental conditions, e.g. applied pressure<sup>[18]</sup> and velocity of compaction<sup>[19]</sup>. In addition, the properties of the resulting compact can be influenced by the presence of a lubricant and binder<sup>[20]</sup>, since pharmaceutical materials normally consolidate by more than one of the mechanisms<sup>[21]</sup>, adequate characterization techniques are needed. Various techniques have been utilized to determine the extent of consolidation and bonding mechanisms in pharmaceutical powders<sup>[22,23]</sup>, such as stress relief under pressure<sup>[24]</sup>, X-ray diffraction<sup>[25]</sup> and multi-compression cycle<sup>[26]</sup>.

There exists no pharmaceutical powder that exhibits only one of the above mentioned deformation mechanisms, although there is a spectrum of ranges

from highly elastically deforming to highly plastically deforming or highly brittle materials. Even for materials that are known to be brittle, smaller particles may deform plastically<sup>[2,27]</sup>. A prerequisite for the formation of a coherent compact is that the surfaces deform to such an extent that the combined effects of bonding with intermolecular forces and solid bridges are greater than the elastic component of the material. This can be expressed as the critical compaction pressure needed to form a compact<sup>[23]</sup>.

The frequency of defects in crystalline solids can be related to deformation during compression<sup>[28]</sup>. The change can take place in crystal structure and shape. Such structural changes are opposed by intermolecular forces which restore the crystal to its original form, as in the case of elastic materials. If the intermolecular forces are exceeded, plastic or permanent deformation will result and, if the stress is continued, plastic flow will continue<sup>[29]</sup>.

The deformation characteristics may be elastic, plastic, brittle fracture or a combination of these deformation mechanisms. Various parameters that characterize the deformation characteristics of powders include Young's modulus, Poisson's ratio, yield stress, and fracture toughness. Elastic deformation is time independent, reversible deformation of a particle, and can create residual stresses within the compact during the decompression phase of the compaction cycle<sup>[30]</sup>. The force applied on a compact or powder divided by the surface area of a compact is called (stress) causes a change in dimensions and the magnitude of dimensional change is called strain, for example, relative volume change. Hook's law denotes the linear portion of the stress-strain plot and the proportionality constant between stress and strain is given by the Young's modulus.

Polymer blending is an alternative approach to obtaining new materials with desirable properties based on commercially available polymers rather than to design and synthesize completely new polymers. Polymer blending is designed to generate materials with optimized chemical, structural, mechanical, morphological and biological properties<sup>[31-33]</sup>. The use of polymers as release rate modifiers has become an important area of drug development work. Over the years, the use of polymers and other materials to prolong the drug re-

lease rate has become more popular. The use of polymer combinations is an approach that may allow formulators to develop sustained release drug dosage forms that may show performance improvements over the individual polymer components. Polymer blending provides a neat and smooth means of combining desirable properties of different polymers. Biodegradable matrices with new combinations of polymer properties and modification of drug release profiles can thus be obtained<sup>[34,35]</sup>.

Theophylline (TN) is structurally classified as methyl xanthine. It is widely used as a bronchodilator in patients with airflow limitation diseases such as bronchial asthma and chronic obstructive pulmonary disease (COPD)<sup>[36]</sup>. Theophylline is rapidly and completely absorbed from liquid preparation, capsules and uncoated tablets. The rate, but not the extent, of absorption is decreased by food. Theophylline is approximately 40% bound to plasma proteins, but in neonates, or adults with liver disease, binding is reduced<sup>[37]</sup>. There are marked variations in TN pharmacokinetics with plasma half-lives ranging from 3 to 9 h.

The objective of this study was to formulate sustained release TN tablets by direct compression of the tablets at four different compression forces using different polymer blends. Tablets were evaluated for their strength, uniformity of thickness, friability, in addition to their mechanical behavior as hardness, upper and lower compression force, ejection force and tensile strength. Moreover, the *in vitro* release patterns of TN from the formulated tablets were studied over the sustained release period.

## MATERIALS

Anhydrous theophylline (TN) and Carnauba wax (CW) were kindly supplied from Tabuk Pharmaceutical Manufacturing CO, KSA. Ethylcellulose (EC) was purchased from BDH Laboratory Supplies Poole, England. Kollidon<sup>®</sup> SR (KL SR) was obtained from BASF Aktiengesellschaft, Germany. Magnesium stearate and Hydrochloric acid were obtained from Riedel-de-Haen, AG, Germany. Tribasic phosphate octahydrate (Scharlau Chemies.A, European). All other materials and solvents used are of reagent or analytical grade and they were used without further purification.

## EXPERIMENTAL

### Formulation of directly compressed tablets

The compositions of the prepared direct compressed tablets containing TN are shown in TABLE 1. Each tablet contains 50 mg drug and use one polymer or blend of the polymer KL SR, EC and CW in different ratios. The powders of all ingredients were passed separately through a sieve of 250 $\mu$ m opening size and the powders were then thoroughly mixed using turbula mixer for 15 min. The powder then compressed into tablets by using Flexitap single punch machine (IWKA Manesty, UK) at different compression forces, namely 5, 10, 15 and 20 kN. In another study, the powder also compressed into tablets using Korsch single punch tablet press (EKO, K3300079, Germany) by fixing tablet weight and measuring the maximum compression forces.

**TABLE 1 : Amount of ingredient in each formulation in mg for theophylline tablet, total weight of one tablet = 201mg containing 50 mg drug.**

Code	Kollidon sr	Carnauba wax	Ethylcellulose	Magnesium Stearate
TN 1	150	-	-	1
TN 2	100	-	50	1
TN 3	100	50	-	1
TN 4	50	-	100	1
TN 5	50	100	-	1
TN 6	-	75	75	1

### Characterization of tablets

#### Tablets weight uniformity

The tablets weight uniformity test was carried out according to USP 29. Ten tablets were weighed individually. The results were expressed as mean value of 10 determinations.

#### Drug content uniformity

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with a negligible variation among tablets within a batch. Ten tablets from each formulation were tested. Each tablet was weighed individually and crushed to a powder. An accurately weighed sample (100 mg) was placed in a 50 mL volumetric flask and the drug was extracted by distilled water. The content of the flask was sonicated

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for 20 min at room temperature. Five mL aliquot was filter through 0.45  $\mu\text{m}$  filter, suitably diluted and analyzed spectrophotometrically at  $\lambda_{\text{max}}$  of 271 nm.

### Tablet thickness

The thickness of theophylline matrix tablets with the tested polymers or polymers blends was determined using a micrometer (Type TB-24, Erweka Apparatebau, Heusenstamm, Germany). and the result was expressed as mean values of 10 determinations.

### Tablet friability

Ten tablets were selected at randomly; their surfaces cleaned with a hair brush to remove any adhering dust, weighed and placed in the friabilator (Type TA3R, Erweka Apparatebau, Heusenstamm, Germany). They were then allowed to fall freely 100 times from a height of 6 inch at a speed of 25 rpm for 4 min. The tablets were then dusted, and weighed. Any loss in weight due to fracture or abrasion was recorded as a percentage weight loss. The replicate determinations of each formulation were averaged. The percent friability was calculated as follow:

$$\% \text{ Friability} = \left[ \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \right] \times 100$$

### Tablet hardness

The hardness of theophylline loaded matrix tablets was determined using Pharmatest Test System (WHT 32.V02.09.00/15, Multicheck, Germany) and the average hardness of 10 determinations in Newton (N) was determined.

### Tensile strength determination

The determination of the tensile strength of the tablet depends on the development of a correct state of stress within the compact<sup>[38]</sup>, but is less dependent on the compact geometry than the crushing strength measurements. The radial tensile strength, which measures the tablet failure as a result of the application of tensile stress only, is given by the relationship:

$$\sigma_x = 2F/\pi DT$$

Where  $\sigma_x$  is the tensile strength, F is the force required to break the tablet, D is the diameter of the tablet, and T is the tablet thickness.

### In-vitro release studies

In vitro drug release studies from the prepare tab-

lets were conducted for a period of 8 h using a six station USP 28 type II apparatus (paddle) at  $37 \pm 0.5^\circ\text{C}$  and 50 rpm speed (Dissolution apparatus (Erweka DT-6, Germany)). The dissolution studies were carried out in triplicate for 8 h (initial 2 h use 750 mL 0.1N HCl, and the rest 6 h add 250 mL 0.2M tribasic sodium phosphate octahydrate PH 7.4) under sink condition, at every 1 h interval samples of 5ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed by UV spectrophotometer. The amounts of drug present in the samples were calculated with help of appropriate calibration curves. Drug dissolved at specified time periods was plotted as percent release versus time curve.

### Mathematical modeling of release kinetics

The kinetic release of drug from different tablets formulations were evaluated by fitting the dissolution data obtained to the following equations.

#### Zero order equation

$$C_t = C_0 - K_0 t$$

Where  $C_t$  is the amount of the drug released at time t,  $C_0$  is the initial amount of drug in the tablet and  $K_0$  is the zero-order release rate constant.

#### First order equation

$$\text{Log } C_t = \text{Log } C_0 - K_1 t/2.303$$

Where  $C_t$  is the amount of drug remaining as a solid state at time t,  $C_0$  is the total amount of drug in the matrix and  $K_1$  is the first-order release rate constant.

#### Higuchi model equation

$$Q = 2 C_0 (Dt/\pi)^{1/2}$$

Where  $C_0$  is the initial drug concentration, t is time of release, Q is amount of drug released/unit area and D is diffusion Coefficient and it was calculated according to the following equation<sup>[39]</sup>.

$$D = (\text{Slope}/2C_0)^2 \pi$$

#### Korsmeyer-Peppas equation

$$Mt/M_8 = K. t^n$$

Where  $Mt/M_8$  is the fraction released by the drug at time t, K is a constant incorporating structural and geometric characteristic and n is the release exponent characteristic for the drug transport mechanism.

### Statistical analysis

All results were expressed as means values  $\pm$  stan-

dard deviation (SD). The determined dissolution data was subjected to statistical analysis using a computer program, Graphpad INSTAT tm Copyright© 1990-1993 (Version 2.04, Ralf Stahlman, Purdue University, USA, 931897S) for a one-way analysis of variance (ANOVA).  $P < 0.05$  was considered as evidence of a significant difference.

## RESULTS AND DISCUSSION

### Tablet evaluation

#### Physical evaluation of tablets

Tablets containing TN manufactured by direct compression at different polymer blends and at different compression forces, viz., 5, 10, 15 and 20 kN, were evaluated and the data are presented in TABLE 2 A&B. It was clear that the manufactured tablets exhibit acceptable properties in term of weight uniformity, diameter, thickness, hardness, friability and die filling at the studied compression forces. For all the compression forces used, the weight variation was under 4%. The variation of diameter and thickness was un-existing as can be seen in the table. Hardness is obviously a parameter which can be related directly to the compression force used. However, tablets based mainly on KL SR, the plastically deformed polymer (TN1) exhibited the highest hardness values compared to the other formulae which based on either blends of KL SR with CW, the very brittle de-

formed polymer as the tablet formulae TN 3 and TN5, or EC, the elastically deformed polymer as the case of TN2 and TN4 formulations or on blend of EC and CW (TN6), which showed lower hardness values. This finding is matched with that reported data that show that direct compression using KL SR resulted in tablets with an extremely high hardness and a low friability<sup>[40]</sup>. According to the chemical composition and the adjusted particle size distribution, the marked dry binding capacity in combination with the good flow properties, are regarded as additional benefits<sup>[40,41]</sup>. Another finding that the increase in hardness upon increasing the compression force was also higher and remarkable in the case of KL SR TN1 compared to the rest of formulae, Figure 1A. The friability of the tablets behaved normally and quite expectedly (Figure 1B). Within the compression force region 5-20 Kn the friability of the tablets was 0.0 in case of the KL SR based tablets TN1, while decreased with increasing the compression force for the other formulae and that was clearly evident in the TN6 formulae, where it decreases from 0.05, 0.03, 0.015 and 0.0075 % at 5, 10, 15 and 20 kN compression forces respectively. In this work, the friability of the tablets behaves as expected at lower compression force. When the compression force increases, the particles deform plastically and the tablets become harder and less friable. However, the recorded friability values for TN formulae were under 1% which can generally be regarded as desirable.

TABLE 2A : Physical characterization of matrix tablets of Theophylline compressed at 5 and 10 kN.

Formulation	Weight (mg) n=10	Diameter (cm) n=10	Thickness (cm) n=10	Hardness (N) n=10	Friability (%) n=10	Tensile strength (N/cm2) N=10	Die filling
<b>A. Compression force 5 kN</b>							
TN 1	1.3±199	0.87	0.45	243.2±12	0.0±0	395.6±10	6.8
TN 2	0.5±201	0.87	0.45	162.9±6	0.0±0	265.1±4.0	6.9
TN 3	1.4±199	0.87	0.45	138.1±2	0.01±0	224.5±2.1	6.8
TN 4	1.1±199	0.87	0.45	102.4±3	0.0±0	165.9±3.0	7.2
TN 5	1.0±200	0.87	0.45	87.1±1.1	0.01±0.03	141.7±2.2	6.6
TN 6	1.0±203	0.87	0.45	57.6±1.05	0.02±0.06	93.79±0.5	6.6
<b>B. Compression force 10 Kn</b>							
TN 1	1.5±196	0.87	0.45	360±12.4	0.00±0	586.7±8.4	6.9
TN 2	0.5±199	0.87	0.45	246.8±4.3	0.00±0	401.5±3	6.9
TN 3	0.25±200	0.87	0.45	180.5±2.5	0.00±0	293.6±2.2	6.8
TN 4	0.45±200	0.87	0.45	170.3±3.4	0.0±0	277±2.6	7.2
TN 5	1.0±201	0.87	0.45	104.6±0.9	0.01±0.02	170.2±1	6.6
TN 6	0.21±203	0.87	0.45	81±0.93	0.01±0.03	133±0.87	6.6

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TABLE 2B : Physical characterization of matrix tablets of Theophylline compressed at 15 and 20 kN.

Formulation	Weight (mg) n=10	Diameter (cm) n=10	Thickness (cm) n=10	Hardness (N) n=10	Friability (%) n=10	Tensile strength (N/cm <sup>2</sup> ) n=5	Die filling
<b>C. Compression force 15 kN</b>							
TN 1	0.2 ± 203	0.87	0.45	362.9 ± 2.3	0.00 ± .000	590.4 ± 2	6.9
TN 2	1.1 ± 194	0.87	0.45	266.1 ± 4	0.0 ± .0010	432.9 ± 1.1	6.9
TN 3	0.42 ± 199	0.87	0.45	189.5 ± 2.2	0.0 ± 0.002	308.3 ± 2.1	6.8
TN 4	0.04 ± 203	0.87	0.45	202.9 ± 3.5	0.00 0 ± 0.0	330 ± 2.6	7.2
TN 5	1.0 ± 200	0.87	0.45	106.7 ± 1.15	0.02 ± 0.01	173.9 ± 1.9	6.6
TN 6	0.03 ± 201	0.87	0.45	88 ± 0.85	0.01 ± 0.015	144.5 ± 1.1	6.6
<b>D. Compression force 20 Kn</b>							
TN 1	1.4 ± 203	0.87	0.45	399.2 ± 10.2	0.00 ± 0.00	649.5 ± 10.1	6.8
TN 2	1.2 ± 198	0.87	0.45	293.1 ± 4.7	0.00 ± 0.001	476.85 ± 3.1	6.9
TN 3	1.3 ± 198	0.87	0.45	1.7 ± 195.6	0.01 ± 0.002	318.2 ± 1.18	6.8
TN 4	1.1 ± 201	0.87	0.45	210.3 ± 2.1	0.0 ± 0.0032	342.1 ± 3.15	7.2
TN 5	1.1 ± 199	0.87	0.45	0.9 ± 109.4	0.04 ± 0.0048	177.98 ± 1.4	6.6
TN 6	1.4 ± 200	0.87	0.45	85.3 ± 1	0.02 ± 0.0075	138.7 ± 2.3	6.6

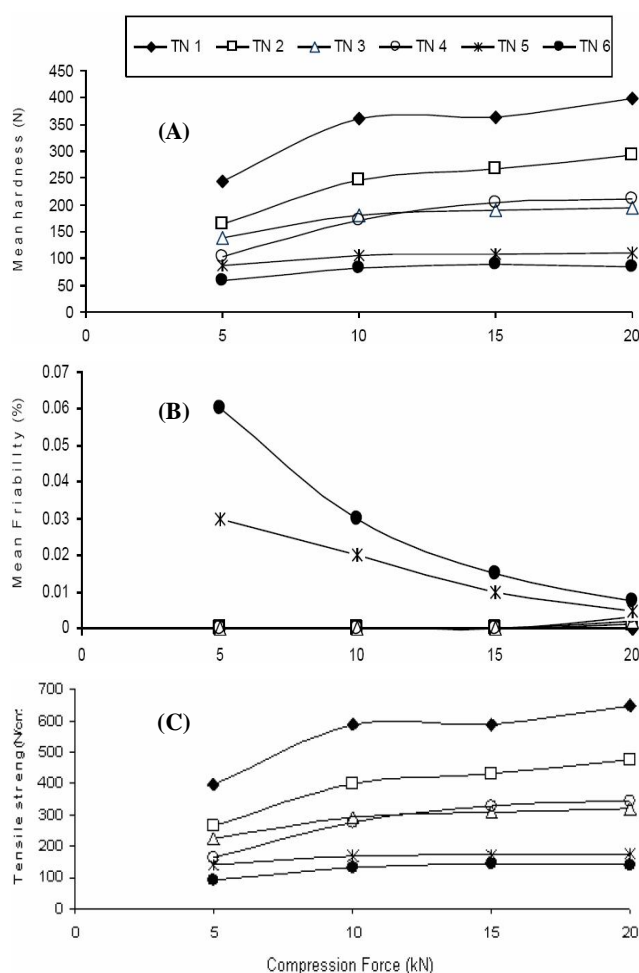


Figure 1 : Relation between compression force and each of A- Hardness, B- Friability, and C- Tensile strength for theophylline formulation compressed at 5, 10, 15 and 20 kN.

The physical strength of a tablet is also dependent on its dimension. In the construction of a force strength profile, all tablets will have the same cross-sectional area as the same tooling will have been used. However, as the compression force is changed, so will the tablet height. Hence, comparison made on the basis of breaking strength will not be truly valid. This problem has been circumvented in part by the calculation of the tensile strength of the tablet. Tensile strength data presented in TABLES 2A and 2B illustrated how the tensile strength is correlated to the tablet hardness and how both the tablet hardness and the tablet tensile strength been affected at the same manner with the compression force (Figure 1C) and deformation mechanism of the used material. Formula TN1, the highest hardness value showed, the highest value of tensile strength and that tensile strength value increases as the compression force. These tensile strength observations are matched with was reported by<sup>[42]</sup>, that the higher the porosity and dissolution rate, the smaller the tensile strength.

### Machine mechanical behavior

The aim of any tableting process is to produce tablets that are of satisfactory quality. Virtually all tablet properties e.g., porosity, physical strength, dissolution time are dependent in some way on the force that is applied by the punches to the particles in the die. As the upper punch enters the die and comes into contact with

the particles, the height of the bed of particles is reduced and hence porosity decreases. Initially porosity reduction is brought about by particle rearrangement. This requires a very low force transducer, the output of which remains zero. The upper punch then encounters a resistance to its motion as further consolidation by rearrangement becomes impossible. Hence, the output of the upper punch force transducer rises, slowly at first then more rapidly. Particles are deformed and/or fragmented during this stage to form a coherent tablet. Force is transmitted to the lower punch, and a similar rise is detected by transducer there. As maximum upper punch penetration is achieved, force maximum are detected on both punches that on the lower punch being less than that on the upper. Once the maximum have occurred, the upper punch begins to rise, and the force detected on both punches falls. That on the upper punch returns to zero as contact is lost between the ascending punch and the top surface of the tablet. That on the lower punch does not fall to zero until ejection is complete. The greater the ejection force, the greater the need for a lubrication in the formulation.

The reason why the lower punch maximum force is less than that of the upper punch is because a fraction of the force applied by the upper punch is transmitted to the die wall and the deformation mechanism. That

the elastic deformation is a spontaneous reversible deformation in which, upon removal of the load, the powder mass reverts back to its original form. After exceeding the elastic limit of the material, the deformation may become plastic, that is, the particles undergo viscous flow. This is the predominant mechanism where the shear strength between the particles is less than the tensile or breaking strength. Upon exceeding the elastic limit of material, the particles undergo brittle fracture if the shear strength between the particles is greater than the tensile or breaking strength. TABLE 3 illustrated the direct compression mechanical parameters released from TN formulations based on the deformation mechanism. When the polymer used was mainly plastically deformed KL SR, the upper detected force for formulae TN1 was 8.18 kN where the lower punch force was 7.45 and the difference between the upper and lower forces (U-L) was 0.73 kN and the ejection force was 33.94 N. While changing the deformation type from a mainly plastic deformation mechanism to a blend composed of (2KL SR: 1EC) plastic: elastic (TN2), the detected upper punch force was 8.46 kN and the lower force was 7.63 kN and the U-L was 0.83 and the ejection force was 29.74 N. This difference is attributed to the work done during the compression phase as well as the work lost during the decompression phase.

**TABLE 3 : Direct compression mechanical parameters released from theophylline formulations using Korsch single punch tablet press.**

Formula	Compressibility index	Upper Punch Compression Force (U) (kN)	Lower Punch Compression Force (L) (kN)	*U -L (kN)	Ejection Force (N)	Deformation Mechanism
TN1	23.42	8.18	7.45	0.73	33.94	Plastic
TN2	20.0	8.46	7.63	0.82	29.74	Plastic : Elastic (2:1)
TN3	24.33	7.28	6.63	0.65	29.56	Plastic : Brittle (2:1)
TN4	33.30	4.94	4.53	0.41	25.86	Plastic: Elastic (1:2)
TN5	25.10	8.85	8.75	0.1	25.84	Plastic : Brittle (1:2)
TN6	31.34	8.85	8.75	0.1	26.38	Elastic : Brittle (1: 1)

\*Upper punch- Lower punch

### Content uniformity

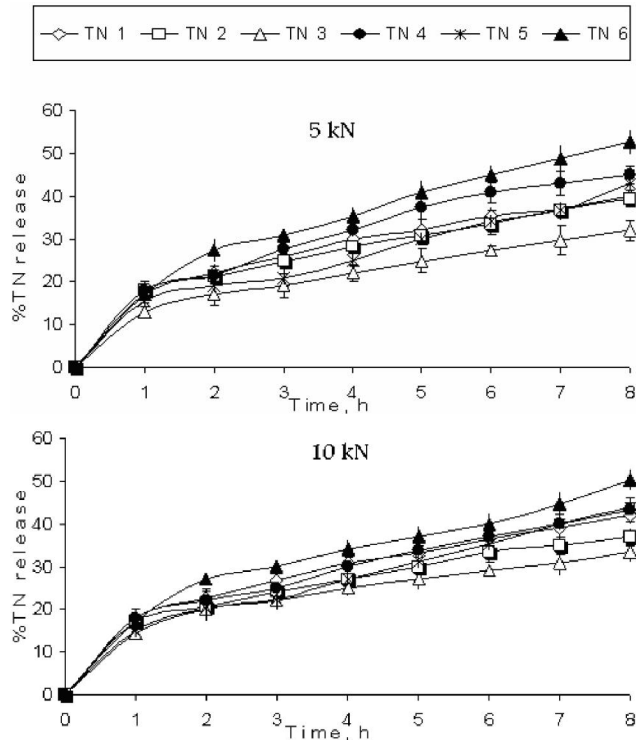
Theophylline content in all of the tested tablet formulations was found to be more than 95% which meets the USP guidelines even when different compression forces were applied. In addition, it is observed that the type and ratio of the matrix forming polymers as well as the compression force have no impact on the TN content.

### In-vitro release profiles

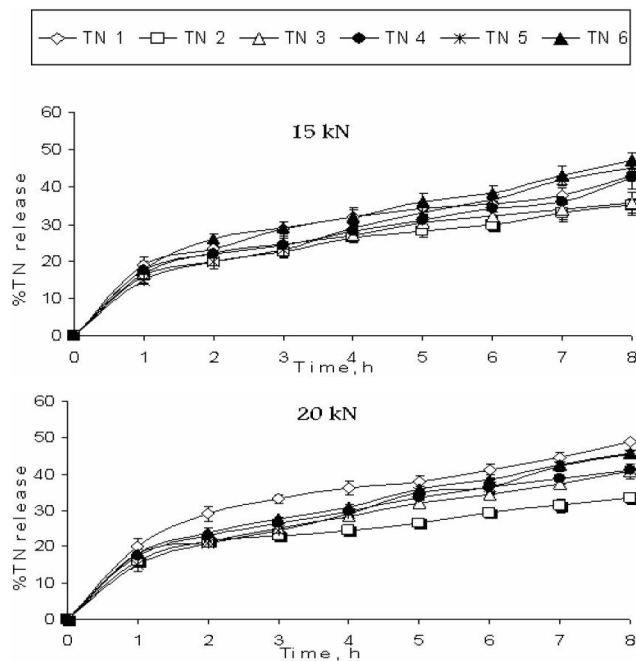
The in vitro release patterns of TN from different matrix tablet formulations compressed at different compression forces (5, 10, 15 and 20 kN) are presented in Figures 2, 3, 4 and 5. For all studied compression forces, the matrix tablet formulation including KL SR, the plastic polymer with reduced repacking during deformation, in

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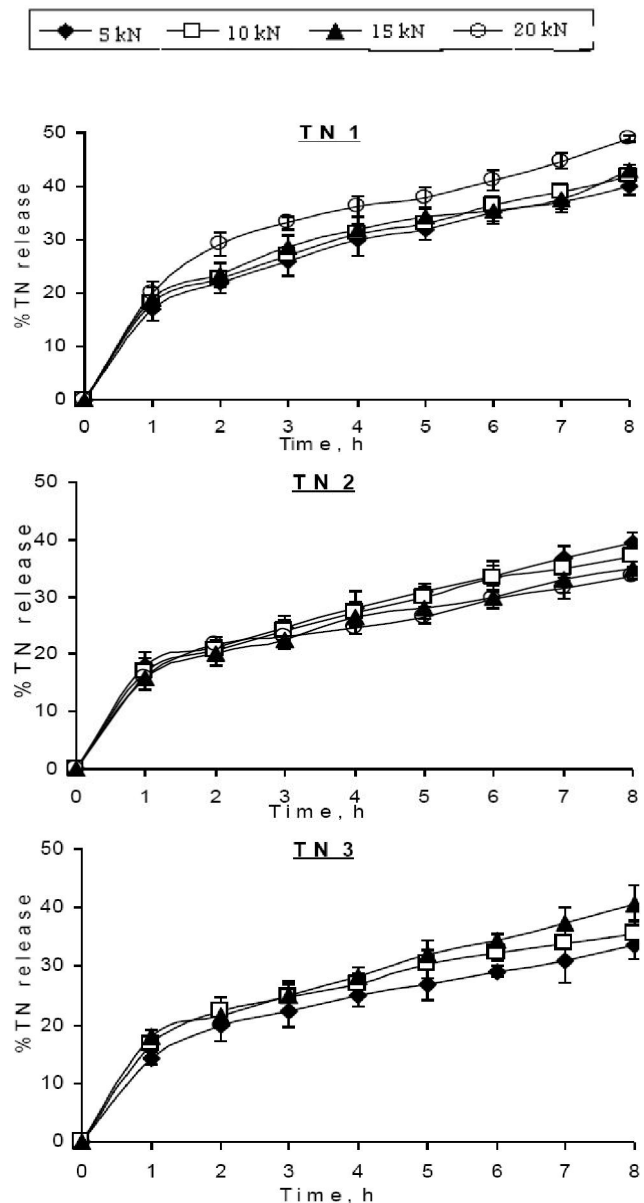
combination with either CW or EC showed very interesting TN release profiles. The release profiles of TN from formulae TN2 and TN4 that based on the composition (2KLSR: 1EC) and (1KLSR: 2EC), respectively, were consistent with different deformation mechanisms



**Figure 2 :** Release profile of theophylline from tablet compressed at 5 kN and 10 kN.



**Figure 3 :** Release profile of theophylline from tablet compressed at 15 kN and 20 kN



**Figure 4 :** Release profile of theophylline from formulations TN 1, TN 2, and TN 3.

of KL SR and EC and on the physicochemical properties like the water absorptive capacity of EC. Upon increasing the weight ratio of KL SR (TN2), the release rate was greatly retarded (39.4, 37.1, 35.0 and 33.6 % released after 8 h at 5, 10, 15 and 20 kN) Figure 4, while formulae TN4 released TN more faster (45, 43.1, 42.3 and 41.2% released after 8 h at 5, 10, 15 and 20 kN). In fact, the water absorptive property of EC has the most prominent impact on the drug release when compared to the reduced repacking of KL SR.

On the other hand, the release profiles of TN from formulae TN3 and TN5 that based on the composition



(2KL SR: 1CW) and (1KL SR: 2CW), respectively, were also consistent with different deformation mechanisms of KLSR and CW. By increasing the weight ratio of KL SR (TN3), the release rate was remarkably enhanced (32, 33.6, 35.6 and 40.7 % released after 8 h at 5, 10, 15 and 20 Kn), while formulae TN5 released TN more retarded (43, 43.8, 45 and 45.5% released after 8 h at 5, 10, 15 and 20 kN) Figure 5. The brittle deformation mechanism of CW plays an important role in increasing TN release<sup>[43]</sup>. This was very clear in formulae TN5, where the weight ratio of CW was double increased. The effect of compression force on the in vitro release rate of TN from each formulae was studied and the results were illustrated in

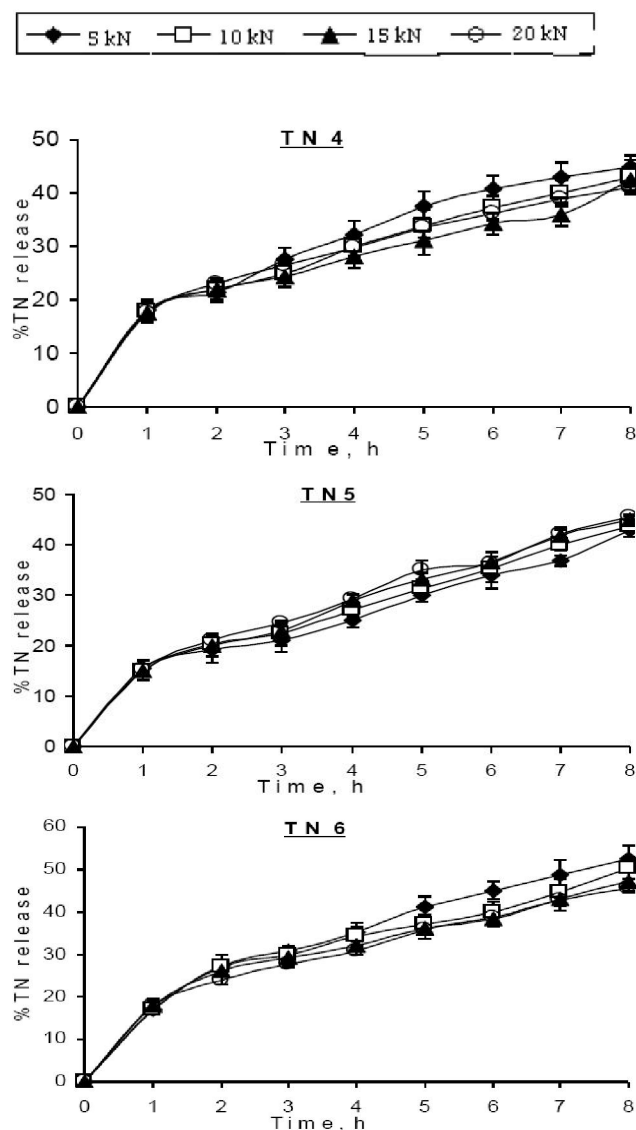


Figure 5 : Release profile of theophylline from formulations TN 4, TN 5, and TN 6.

Figures 4 and 5. The formulae based on Kollidon only or a combination of Kollidon SR 2: 1EC (TN1 and TN3, respectively) showed that a higher release rate was observed at a compression force of 20 Kn. On the other hand, formulae TN2, TN4 and TN6 showed that the release rate of the drug from the matrix tablet formulae is inversely proportional to the applied compression force, Figures 4 and 5. The effect of the compression force on the in vitro release pattern of TN from this matrix tablet formulae was very clear when the comparison was made between the all formulae using the same compression force. On the other hand, when one formula was subjected to different compression forces, the comparison will be of a narrow range, i.e., the in-vitro release curves of different compression forces were superimposing.

During the tablet compression cycle, when the load is first applied, the volume of the mass decreases because some of the air between particles is displaced as the particle move closer together. This is the repacking phase<sup>[44]</sup>. This phase is limited by attainment of the closest possible packing arrangement and/or the friction at the particle contact points. After repacking, most materials then begin (or may have already begun) to undergo elastic deformation and continue to do so until they reach their elastic limit. Beyond this so-called yield stress, various components of the formulation may undergo plastic and/or viscid-elastic deformation. Volume reduction may also cause particles to undergo brittle fracture. The proportion of deformation attributed to one mechanism or another depends on whether the material as a whole is more ductile or more brittle<sup>[45]</sup>. Formulators must determine this during product development and, if elastic recovery is too pronounced, consider adding an adequate quantity of plastic ingredients to compensate. These deformation mechanisms hold great significance when considering the compression and consolidation-related aspects of the tableting process. In most formulations, the repacking phase of compression occurs only at the low end of the applied load, and one or more of the other mechanisms rapidly overtake it. But repacking remains an important factor because, for a given applied peak load, the final porosity (voidage) of the tablet depends to some extent on the porosity of the material at initial loading. Thus, since the dissolution rate of many tableted products is a function of the tablets residual micro-porosity, variability in the initial

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voidage level may be the root cause of inconsistent dissolution profiles<sup>[46]</sup>. In many products, the extent of repacking depends on the compaction rate. Usually, the higher the compaction rate, the less repacking that occurs. Reduced repacking is another possible root cause of inconsistent dissolution profiles. If repacking is reduced, the dissolution rate tends to increase.

### Kinetic assessment of the *in-vitro* release

The correlation coefficient (r), and the release

exponent (n), of fitting the release data to zero, first, Higuchi diffusion and Peppas models for TN matrix tablets are listed in TABLES 4A and 4B in addition to Figure 6. The higher correlation coefficient (r) values for Higuchi diffusion model obtained in most formulae indicate a diffusion mechanism for TN release. The kinetic data provide that the Higuchi diffusion model is the prominent mechanism that controls the release of TN from the tested matrix tablet formulation even

TABLE 4A : Mathematical modeling and theophylline release kinetic from tablets

Korsmeyer-Peppas model			Higuchi model		First Order		Zero Order		Formulation
N#	k (h <sup>-n</sup> )	r	k (%h <sup>-1/2</sup> )	r	k (h <sup>-1</sup> )	r	k <sub>o</sub> (%h <sup>-1</sup> )	r*	
0.41	16.7	0.998	13.71	0.996	0.055	0.957	4.2	0.931	TN 1
0.383	16.94	0.989	13.24	0.994	0.053	0.959	4.08	0.933	TN 2
0.432	12.52	0.993	10.93	0.997	0.042	0.966	3.41	0.948	TN 3
0.476	16.85	0.99	16.14	0.997	0.0699	0.975	5.06	0.952	TN 4
0.483	14.03	0.969	14.17	0.987	0.0607	0.981	4.57	0.969	TN 5
0.522	17.64	0.995	18.53	0.998	0.0858	0.985	5.85	0.960	TN 6

Korsmeyer-Peppas model			Higuchi model		First Order		Zero Order		Formulation
N#	k (h <sup>-n</sup> )	r	k (%h <sup>-1/2</sup> )	r	k (h <sup>-1</sup> )	r	k <sub>o</sub> (%h <sup>-1</sup> )	r*	
0.41	17.47	0.997	14.35	0.996	0.059	0.962	4.42	0.935	TN 1
0.386	16.29	0.994	12.71	0.994	0.05	0.954	3.89	0.929	TN 2
0.39	14.58	0.996	11.34	0.993	0.043	0.943	3.44	0.920	TN 3
0.435	16.79	0.989	14.81	0.997	0.062	0.974	4.63	0.950	TN 4
0.511	14.11	0.985	14.97	0.992	0.0647	0.986	4.81	0.973	TN 5
0.478	17.73	0.990	16.88	0.995	0.075	0.974	5.28	0.949	TN 6

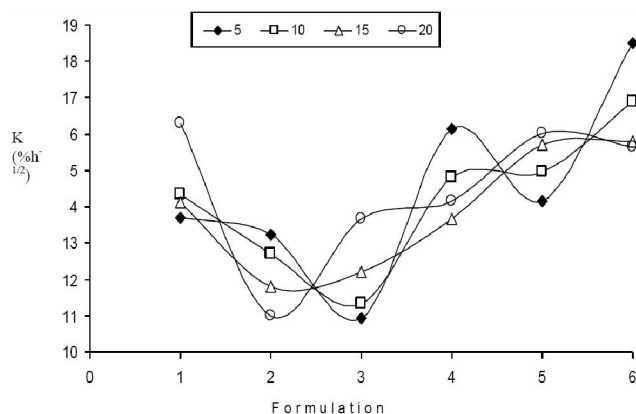
Compressed at 5kN and 10kN.

TABLE 4B : Mathematical modeling and Theophylline release kinetic from tablets compressed at 15 kN and 20 kN.

Korsmeyer-Peppas model			Higuchi model		First Order		Zero Order		Formulation
N#	k (h <sup>-n</sup> )	r	k (%h <sup>-1/2</sup> )	r	k (h <sup>-1</sup> )	R	k <sub>o</sub> (%h <sup>-1</sup> )	r*	
0.376	18.6	0.993	14.14	0.990	0.057	0.946	4.29	0.917	TN 1
0.376	15.5	0.995	11.82	0.993	0.045	0.948	3.6	0.923	TN 2
0.362	16.74	0.997	12.19	0.989	0.046	0.935	3.67	0.908	TN 3
0.398	16.75	0.983	13.66	0.991	0.056	0.963	4.25	0.941	TN 4
0.538	14.03	0.990	15.72	0.994	0.0689	0.989	5.06	0.975	TN 5
0.434	18.22	0.993	15.81	0.995	0.0683	0.969	4.9	0.942	TN 6

Korsmeyer-Peppas model			Higuchi model		First Order		Zero Order		Formulation
N#	k (h <sup>-n</sup> )	r	k (%h <sup>-1/2</sup> )	r	k (h <sup>-1</sup> )	r	k <sub>o</sub> (%h <sup>-1</sup> )	r*	
0.396	20.8	0.99	16.3	0.991	0.07	0.95	4.97	0.918	TN 1
0.334	16.1	0.987	11.08	0.983	0.0417	0.926	3.32	0.9	TN 2
0.397	16.9	0.988	13.66	0.995	0.0559	0.964	4.23	0.939	TN 3
0.408	17.3	0.997	14.16	0.9966	0.058	0.961	4.35	0.934	TN 4
0.534	14.55	0.9951	16.02	0.9965	0.07	0.988	5.13	0.972	TN 5
0.444	17.5	0.9958	15.66	0.9979	0.067	0.975	4.89	0.949	TN 6



**Figure 6 : Effect of (k) release constant on higuchi diffusion model for theophylline formulations compressed at different compression force 5, 10, 15 and 20 kN**

at different compression forces (due to higher correlation coefficient values). In addition, the magnitude of the Higuchi diffusion rate constant (K) was found to be dependent on the formulae composition (i. e. effect of matrix forming polymer nature) and the compression force. For example, increasing concentration of KL SR in the formulae resulted in a reduction of the (K) value in the formulae TN1-TN3 (based on higher weight ratio of KL SR). In contrast, the value of (K) was increased by the presence of higher weight ratios of EC and CW tablet formulations; TN4-TN6. This finding is true for all TN formulations compressed at 5, 10 and 15 kN. However, when these formulae were compressed at 20 Kn, the drug exhibited higher K values from formulae TN1, TN5 and TN6 (16.3, 16.02 and 15.66 %h<sup>-1/2</sup>, respectively).

## CONCLUSION

The design of directly compressed matrix tablets for sustained release properties should take into consideration the deformation mechanism of used polymers. In addition, the critical parameters such as tableting conditions, compression forces, upper and lower punch compression forces, hardness, tensile strength and friability will be affected according to the deformation mechanism such polymers.

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