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Effect of Polymer Blend on Diltiazem HCl Matrix Tablets Prepared by Direct Compression

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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 Deltiazem (DZ) directly compressed tablets namely Kollidon ® 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 (DZ1) 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 DZ 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 DZ from formulae DZ 2 and DZ 4 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 (DZ), the release rate was greatly retarded.

Key words: Diltiazem HCl, 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, intermolecular bonding takes place, and a coherent mass is formed. Three types of bond applicable to tablets include solid bridges, intermolecular forces and mechanical interlocking [1], but they never act independently [2]. Intermolecular forces constitute the dominating bond mechanism for pharmaceutical materials [3]. Solid bridges have been defined as areas of physical contact between adjacent surfaces. They can occur due to melting followed by resolidification or by dissolution of solid materials followed by recrystallization [4]. The nature of solid bridges is dependent on the chemical structure of the material [5, 6]. 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 [7, 8].

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 [9, 10]. Van der Waals forces are considered to be the most important distance attraction forces holding particles together [11].

Study by Olsson and Nystrom 2000 [12], 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 [13]. 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 [13]. The mechanism of compaction not only depends on the powder properties [14] but also affected by particle size (Roberts et al., 1989; Sun et al., 2001), shape [15], moister content [16, 17] and experimental conditions, e.g. applied pressure [18] and velocity of compaction [19]. In addition, the properties of the resulting compact can be influenced by the presence of a lubricant and binder [20], since pharmaceutical materials normally consolidate by more than one of the mechanisms [21], adequate characterization techniques are needed. Various techniques have been utilized to determine the extent of consolidation and bonding mechanisms in pharmaceutical powders [22, 23], such as stress relief under pressure [24], X-ray diffraction [25] and multi-compression cycle [26].

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 [2, 27]. 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 [23].

The frequency of defects in crystalline solids can be related to deformation during compression [28]. 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 [29].

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 [30]. 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 [31-33]. 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 release 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 obtained [34-35].

Diltiazem HCl (DZ) has a therapeutic concentration range of 50-200 $ng.mL^{-1}$. The bioavailability of sustained release formulation (120 mg two times daily) was 93%compared to the regular tablet (60 mg four times daily) and 92% compared to solution, while the time to reach maximal plasma DZ concentration was 6.4 h [36, 37].

The objective of this study was to formulate sustained release DZ tablets by directly 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 DZ from the formulated tablets were studied over the sustained release period.

Experimental:

Materials

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

Method

Formulation of directly compressed tablets

The compositions of the prepared direct compressed tablets containing DZ 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 through a sieve of 250μm opening size and the powders were then thoroughly mixed using turbula mixer for 15 min. The powder then compresses into tablets by using Flexitap single punch manesty machine at 5,10, 15 and 20 Kn or using Korsch single punch tablet press by fixing tablet weight and measuring the maximum compression forces.

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 for 20 min at room temperature. Five mL aliquot was filter through 0.45 μm filter, suitably diluted and analyzed spectrophotometrically at λ_{max} of 273 nm.

Tablet thickness

The thickness of DZ 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.

Table 1: Amount of ingredient in each formulation in mg for Diltiazem HCl tablets, total weight of one tablet = 201mg containing 50 mg drug.

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

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:

$$\% \text{ Friability} = [(\text{Initial weight} - \text{Final weight}) / \text{Initial weight}] \times 100$$

Tablet hardness

The hardness of DZ 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 [38], 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 σ_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 tablets were conducted for a period of 8 h using a six station USP 28 type II apparatus (paddle) at 37± 0.5°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 tribasicsodium 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.

3.4. 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:

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

Where C_o 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 [39].

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

Korsmeyer-Peppas equation

$$Mt / M \infty = K. t^n$$

Where $Mt/M \infty$ 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 ± standard 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:

Physical evaluation of tablets

The effect of compression force on the physical properties of DZ tablets of different compositions has been evaluated and the results are tabulated in Table 2A and 2B at a compression force 5Kn, tablets physical properties (weight uniformity, diameter, thickness, friability and die filling) were almost the same for all DZ tablet formulations and are complying with the required guidelines. However, tablet hardness was highly affected by the type of matrix forming polymer used. Matrix tablets formulated with KL SR only exhibited the highest value of hardness [40]. It is also clear that the addition of EC and CW exhibited a reducing action on tablet hardness, especially when EC and CW were used without KL SR as matrix forming polymers. Considering the effect of the other compression forces (10, 15 and 20Kn), one can see that all tablet formulations exhibited hardness values higher than 5 Kn except those formulated with high concentrations of CW or in absence of KL SR. 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 [40, 41]. The relation between compression force and each of hardness, friability and tensile strength is illustrated in Figure 1. 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 [42], that the higher the porosity and dissolution rate, the smaller the tensile strength.

Machine mechanical behavior

The aim of any tabletting 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

Table 2A: Physical characterization of matrix tablets of diltiazem compressed at 5 and 10 kN.

	Weight (mg) n=10	Diameter (cm) n=10	Thickness (cm) n=10	Hardness (N) n=10	Friability (%) n=10	Tensile strength (N/cm^2) n=10	Die filling
A. Compression force 5 kN							
DZ 1	198 ±0.4	0.87	0.45	241.3 ± 5.6	0.002±0.001	391.6±5.3	7.7
DZ 2	199± 1.4	0.87	0.45	160.0 ± 2.0	0.01±0.02	260.3±3.6	7.4
DZ 3	192 ±1.54	0.87	0.45	153.0 ± 4.3	0.00±0.00	249.2±4.3	8.1
DZ 4	201 ± 0.21	0.87	0.45	92.70 ± 3. 5	0.02±0.052	150.4±5.8	7.5
DZ 5	189± 1.12	0.87	0.45	85.00 ± 2.5	0.025±0.024	138.3±3.4	8.6
DZ 6	196 ±1.00	0.87	0.45	70.00 ± 2.7	0.035±0.01	114.2±3.6	8.0
B. Compression force 10 kN							
DZ 1	198 ±0.5	0.87	0.45	349.6 ± 4.3	0.0±0.00	568.7±4.4	7.7
DZ 2	198 ± 0.8	0.87	0.45	250.3± 3	0.0±0.00	407.2±3.5	7.4
DZ 3	194 ± 1.25	0.87	0.45	199.4 ± 3.6	0.0±0.00	324.4±4.2	8.1
DZ 4	193±1.25	0.87	0.45	153.4 ± 3.2	0.0±0.00	249.6±2.6	7.5
DZ 5	190 ±1.2	0.87	0.45	107.0 ± 1.4	0.0±0.00	174.3±2.3	8.6
DZ 6	193 ±1.1	0.87	0.45	89.70 ± 2.2	0.03±0.01	145.9±2.2	8.0

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

Table 2B: Physical characterization of matrix tablets of diltiazem compressed at 15 and 20 kN.

	Weight (mg) n=10	Diameter (cm) n=10	Thick-ness (cm) n=10	Hardness (N) N=10	Friability (%) n=10	Tensile strength (N/cm^2) n=10	Die filling
C. Compression force 15 kN							
DZ 1	198 ±1.2	0.87	0.45	356.4 ± 5.3	0.00 ± 0.0	579.8 ± 7.4	7.7
DZ 2	199 ± 0.25	0.87	0.45	291.5 ± 2.1	0.00 ± 0.0	474.2 ± 2.3	7.4
DZ 3	194 ± 1.5	0.87	0.45	204.8 ± 3.4	0.00 ± 0.0	333.1 ± 4.3	8.1
DZ 4	203 ± 0.21	0.87	0.45	179.4 ± 2.8	0.00 ± 0.0	291.8 ± 2.8	7.5
DZ 5	187 ± 1.15	0.87	0.45	113.0 ± 2.2	0.00 ± 0.0	185.1 ± 2.9	8.6
DZ 6	191 ± 1.25	0.87	0.45	93.60 ± 2.2	0.01±0.02	152.2 ± 3.7	8.0
D. Compression force 20 kN							
DZ 1	200 ±1.3	0.87	0.45	411.2 ± 5.4	0.002±0.00	668.9 ± 4.6	7.7
DZ 2	199 ± 1.2	0.87	0.45	301.4 ± 2.5	0.004±0.00	490.4 ± 2.9	7.4
DZ 3	192 ±1.5	0.87	0.45	213.0 ± 13.6	0.002±0.01	346.6 ±10	8.1
DZ 4	202 ±1.4	0.87	0.45	186.4 ± 2.2	0.001±0.0	303.3 ± 3.4	7.5
DZ 5	195 ±1.3	0.87	0.45	117.0 ± 1.9	0.001±0.04	190.3 ± 1.2	6.8
DZ 6	198 ±1.2	0.87	0.45	90.50 ± 3.0	0.01±0.02	147.2 ± 3.6	8.0

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 DZ formulations based on the deformation mechanism. When the polymer used was mainly plastically deformed KL SR, The upper detected force for formulae DZ1 was 5.63 Kn where the lower punch force was 5.04 and the difference between the upper and lower forces (U-L) was 0.59 Kn and the ejection force was 0.24 N.

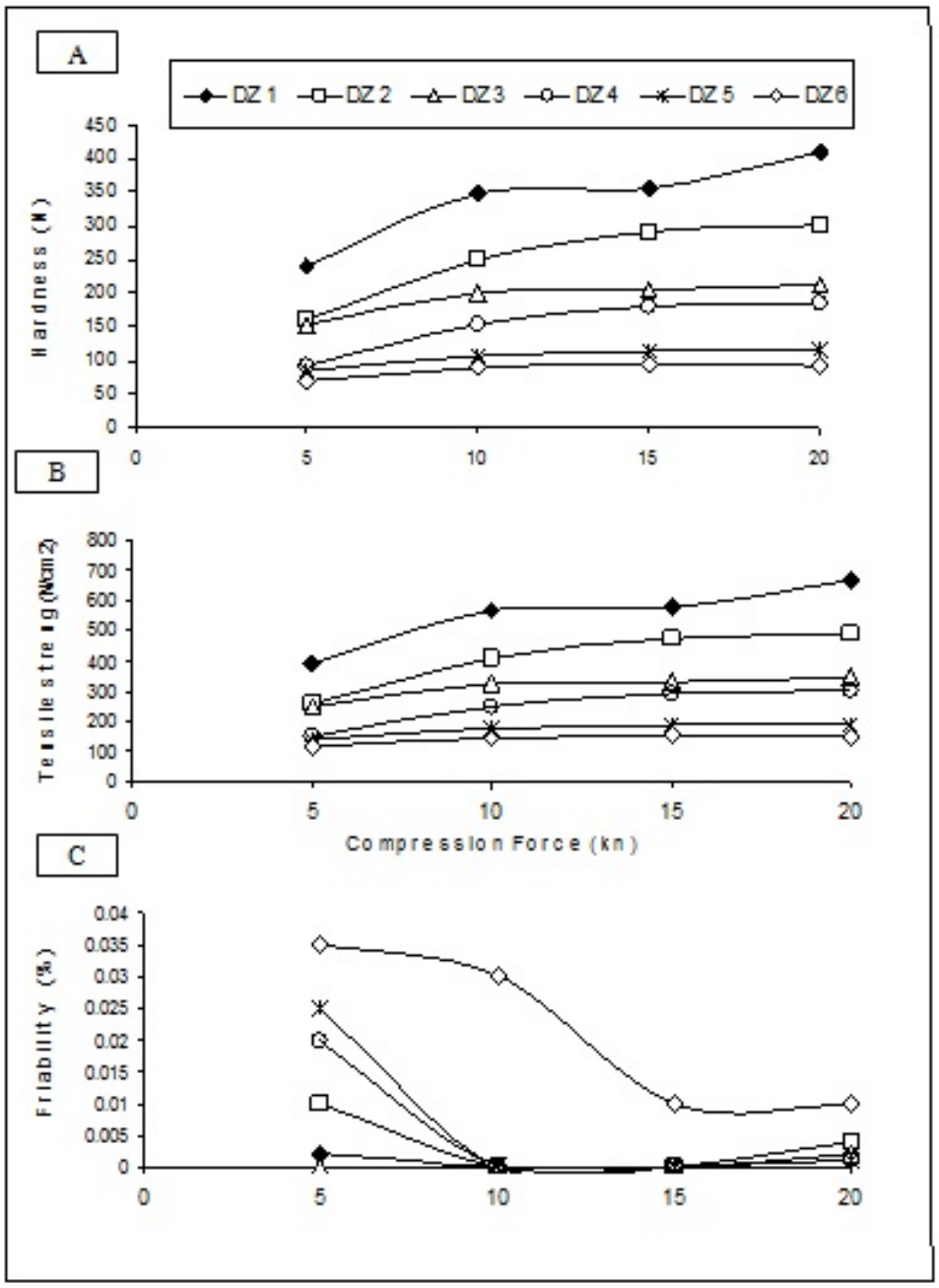

Figure 1: Relation between compression force and each of A- Hardness, B- Friability, and C- Tensile strength for diltiazem formulation compressed at 5, 10, 15 and 20 kN.

While changing the deformation type from a mainly plastic deformation mechanism to a blend composed of (2KL SR: 1EC) plastic: elastic (DZ2), the detected upper punch force was 5.93 Kn and the lower force was 5.16 Kn and the U-L was 0.77 and the ejection force was 6.28N. This difference is attributed to the work done during the compression phase as well as the work lost during the decompression phase. That difference remarkably affected the release rate constant of the drug, where in the formulae DZ1, the k was 12.45 % h^{-1} while it was 15.03 % h^{-1} in the case of formulae DZ2 as will be discussed later.

Content uniformity

The content uniformity of DZ matrix tablets formulations manufactured at different polymer weight ratios and at different compression forces has been evaluated results are depicted in Table 4 diltiazem HCl content in all of the tested

Table 3: Direct compression mechanical parameters released from diltiazem formulations.

Formulae	Compressibility index (CI)	Upper Punch Compression Force (U) (kN)	Lower Punch Compression Force (L) (kN)	*U – L (kN)	In-vitro Release Rate Constant k (%.h^{-1})	Ejection Force (N)	Deformation Mechanism
DZ1	18.56	5.63	5.04	0.59	12.45	0.24	Plastic
DZ 2	27.90	5.93	5.16	0.77	15.03	6.28	Plastic : Elastic (2:1)
DZ 3	29.50	5.66	5.06	0.60	14.69	0.04	Plastic : Brittle (2:1)
DZ 4	29.90	5.77	4.96	0.81	18.89	5.89	Plastic: Elastic (1:2)
DZ 5	26.00	5.36	4.77	0.59	20.17	0.09	Plastic : Brittle (1:2)
DZ 6	27.55	5.56	4.99	0.57	21.94	0.09	Elastic : Brittle (1: 1)

*Upper punch- Lower punch

Table 4: Content uniformity of diltiazem powder and tablets (n=3)

Formulation	Content uniformity for tablets (%) n=3			
	5 kN	10 kN	15 kN	20 kN
DZ 1	97.0 ± 1.20	97.0 ±1.10	97.9 ± 1.20	99.0 ± 1.25
DZ 2	98.0 ± 1.00	99.0 ±1.25	99.0 ± 0.50	98.6 ± 1.80
DZ 3	97.0 ± 1.40	97.1 ±1.60	96.0 ± 1.45	97.9 ± 1.52
DZ 4	99.5 ± 1.10	97.5 ±1.00	100 ± 0.44	99.5 ± 0.98
DZ 5	96.5 ± 1.75	97.2 ±1.10	95.4 ± 1.00	95.5 ± 1.10
DZ 6	97.0 ± 1.25	96.0 ±1.20	95.8 ± 1.5	95.0 ± 0.95

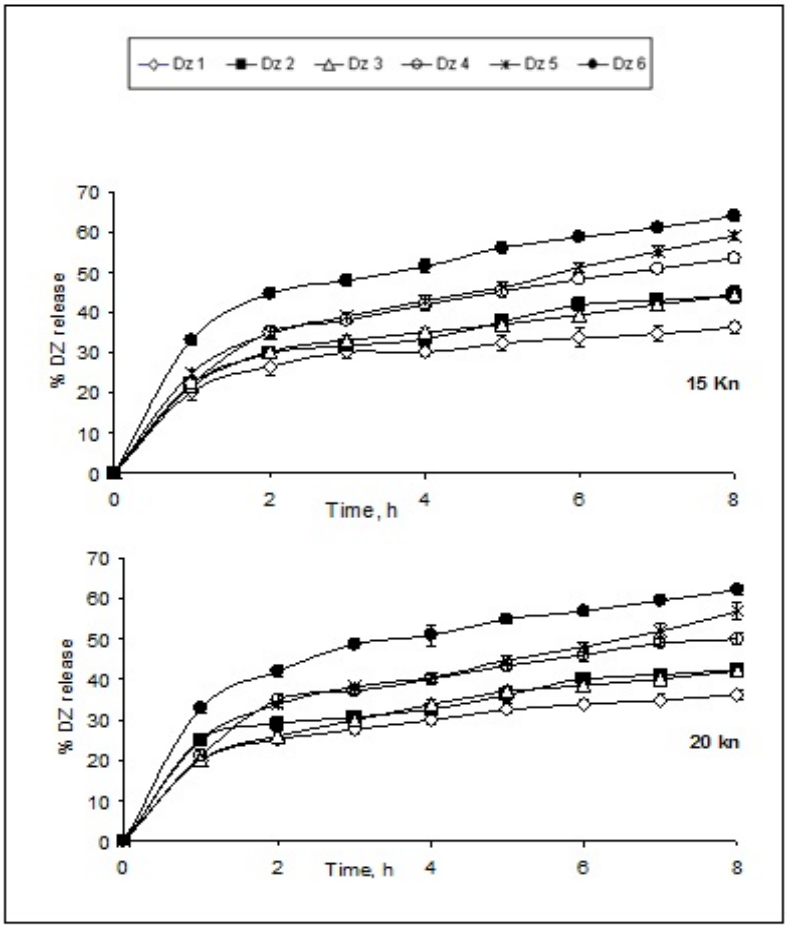

Figure 3: Release profile of diltiazem from tablet compressed at 15Kn and 20Kn

tablet formulations meets the USP guidelines (96.5-99.5% with SD values less than 1.5) even when different compression forces were applied. In addition, it could be seen also that the type and ratio of the matrix forming polymers as well as the compression force did not influence the drug content.

In-vitro release profiles

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 [43]. 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 [44]. 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 tabletting 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.

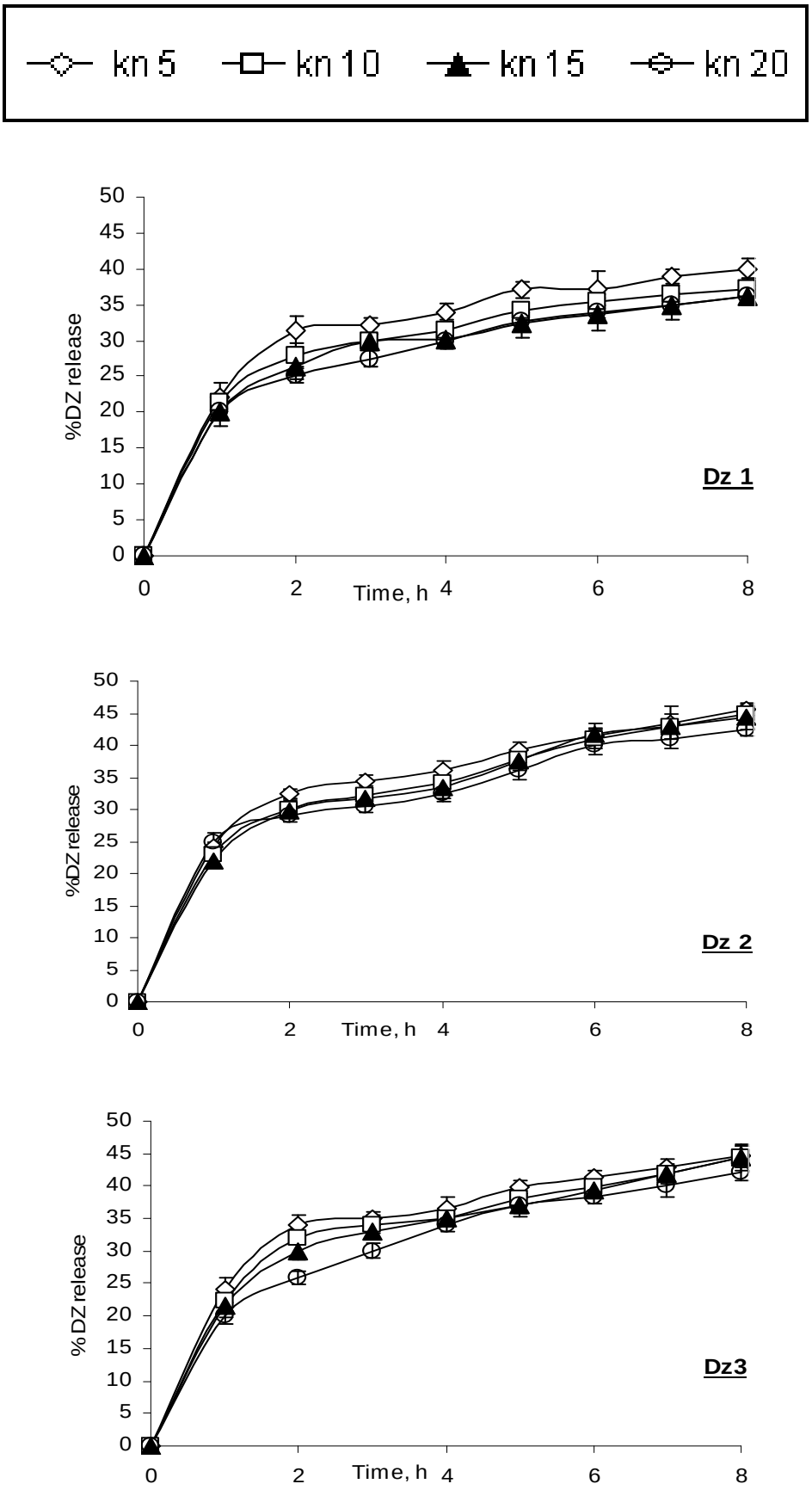

Figure 4: Release profile of diltiazem from formulations DZ 1, DZ 2 and DZ 3.

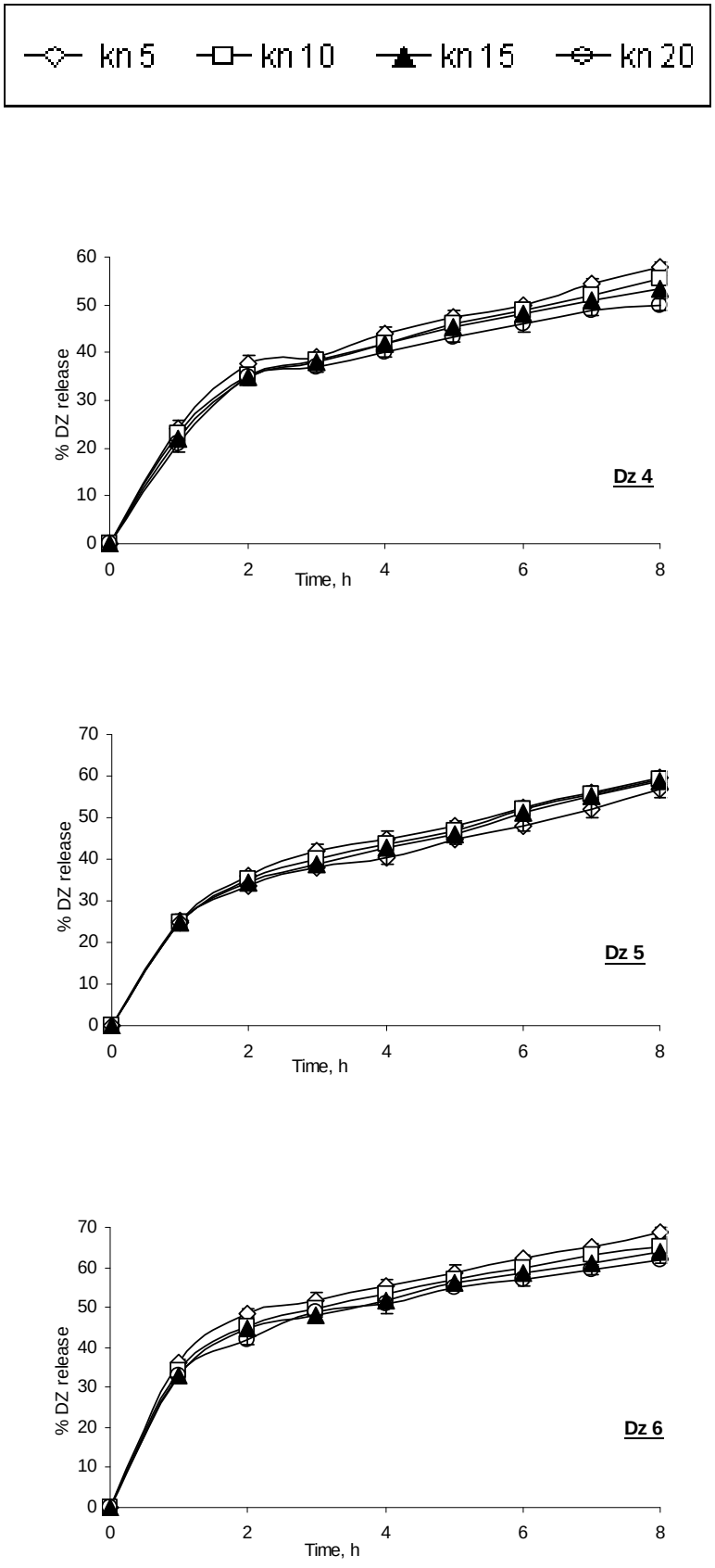

Figure 5: Release profile of diltiazem from formulations DZ 4, DZ 5, and DZ 6.

Table 5A: Mathematical modeling and diltiazem release kinetic from tablets compressed at 5Kn and 10Kn.

A. Compression force 5 kN

Formulation	Zero Order		First Order		Higuchi model		Korsmeyer-Peppas		
	r*	$k_o(\%h^{-1})$	r	$k(h^{-1})$	R	$k(\%h^{-1/2})$	r	$k(h^{-n})$	n#
DZ 1	0.825	3.79	0.861	0.050	0.952	13.34	0.968	23.7	0.263
DZ 2	0.86	4.39	0.904	0.061	0.969	15.06	0.989	24.99	0.285
DZ 3	0.838	4.24	0.880	0.0589	0.958	14.79	0.972	25.44	0.273
DZ 4	0.907	5.91	0.954	0.0927	0.987	19.61	0.982	25.6	0.388
DZ 5	0.914	6.15	0.961	0.0984	0.991	20.33	0.993	26.14	0.393
DZ 6	0.860	6.59	0.936	0.120	0.969	22.65	0.990	37.43	0.288

B. Compression force 10 kN

Formulation	Zero Order		First Order		Higuchi model		Korsmeyer-Peppas		
	r*	$k_o(\%h^{-1})$	r	$k(h^{-1})$	R	$k(\%h^{-1/2})$	r	k (h^{-n})	n#
DZ 1	0.833	3.55	0.867	0.0464	0.957	12.45	0.989	22.2	0.258
DZ 2	0.885	4.45	0.925	0.062	0.980	15.03	0.993	23.19	0.312
DZ 3	0.859	4.28	0.900	0.059	0.968	14.69	0.977	23.72	0.299
DZ 4	0.909	5.72	0.953	0.087	0.989	18.98	0.987	24.48	0.394
DZ 5	0.922	6.14	0.966	0.097	0.993	20.17	0.9959	25.6	0.396
DZ 6	0.867	6.41	0.963	0.112	0.974	21.94	0.9950	35.06	0.302

Table 5B: Mathematical modeling and diltiazem release kinetic from tablets compressed at 15Kn and 20Kn.

A. Compression force 15 kN

Formu-lation	Zero Order		First Order		Higuchi model		Korsmeyer-Peppas model		
	r*	k_o ($\%h^{-1}$)	r	k (h^{-1})	R	k ($\%h^{-1/2}$)	r	k (h^{-n})	n#
DZ 1	0.834	3.43	0.866	0.044	0.957	12.02	0.983	21.05	0.267
DZ 2	0.893	4.51	0.930	0.0626	0.982	15.12	0.9890	22.29	0.331
DZ 3	0.877	4.34	0.916	0.0596	0.977	14.73	0.9894	22.57	0.319
DZ 4	0.903	5.56	0.946	0.0836	0.987	18.53	0.982	23.82	0.398
DZ 5	0.927	6.13	0.969	0.0972	0.994	20.03	0.996	25.12	0.399
DZ 6	0.868	6.27	0.934	0.1078	0.973	21.46	0.992	34.15	0.304

B. Compression force 20 kN

Formu-lation	Zero Order		First Order		Higuchi		Korsmeyer-Peppas		
	r*	k_o ($\%h^{-1}$)	r	k (h^{-1})	r	k ($\%h^{-1/2}$)	r	k (h^{-n})	n#
DZ 1	0.859	3.53	0.891	0.0456	0.97	12.17	0.997	20.24	0.285
DZ 2	0.864	4.08	0.905	0.0557	0.967	13.92	0.978	24.08	0.26
DZ 3	0.898	4.33	0.931	0.0587	0.987	14.52	0.998	20.02	0.359
DZ 4	0.888	5.2	0.929	0.0759	0.980	17.49	0.969	23.3	0.386
DZ 5	0.918	5.73	0.961	0.0885	0.990	18.84	0.993	25.14	0.371
DZ 6	0.862	6.07	0.926	0.1019	0.972	20.85	0.995	33.7	0.298

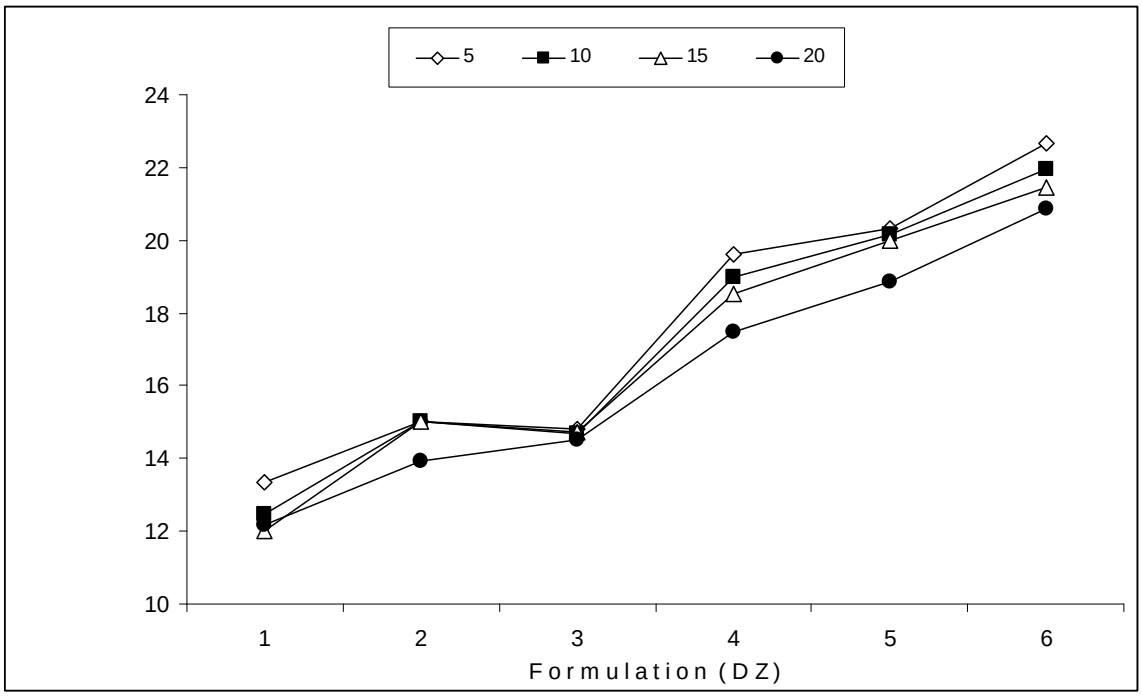

Figure 6: Effect of (k) release constant on Higuchi diffusion model for diltiazem formulations compressed at different compression force 5, 10, 15 and 20 kN

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 tabletted products is a function of the tablets residual micro-porosity, variability in the initial voidage level may be the root cause of inconsistent dissolution profiles [45]. 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 I 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 DZ release constant (k), of fitting the release data to zero, first, Higuchi diffusion and Peppas model for spheres are listed in Table 5-6 and Figure 6. Higher correlation coefficient (r) values were recorded for Higuchi diffusion model obtained in most formulae demonstrating a diffusion mechanism for DZ release. The kinetic data proved that the Higuchi diffusion model is the prominent mechanism that controls the release of drug from the tested matrix tablet formulations even at different compression forces (due to higher correlation coefficient values).

The results showed the presence of a high correlation between the tablet composition and the k values at all the studied compression forces. Higher k values were observed in formulae DZ4-DZ6, in which lower or no concentration of KL SR was incorporated in the formulae. For example, at a compression force 10Kn, the value of k for DZ4, DZ5 and DZ6 were 18.98, 20.17 and 21.94% $h^{-1/2}$, respectively. On the other hand, the formulations based on pure or higher concentrations of KL SR (DZ1-DZ3) showed k values of 12.45, 15.03 and 14.69 %$h^{-1/2}$, respectively, at the same compression force.

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 tabletting 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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