Investigation of Compressibility Characteristics of Paracetamol using Compaction Simulator

Yıldız Özalp, Joseph Turemi Chunu, Nailla Jiwa
Department Of Pharmaceutical Technology, Faculty Of Pharmacy, Near East University, Nicosia, TRNC

Abstract

INTRODUCTION: This study was performed to understand the behavior of poorly compressible paracetamol powder using compaction simulator (CS), an equipment which records data during compaction process. The aim of this work was to investigate the compressibility of paracetamol tablet using dry granulation (slugging) process, with different formulation compositions.
METHODS: Formulations were prepared to observe the effect on compressibility with two different lactose-based fillers, Flowlac®100, Granulac®70 and binder Kollidon® K90. In each combination, total of four formulations were prepared with paracetamol to filler ratio as 1: 1 and 0.8: 1. Tablets were produced by single punch (11.28 mm) compaction simulator at six different pressures (152, 210, 263, 316, 400, 452 MPa). During compression, upper punch displacement and force data were produced by CS equipment. Compressed tablets were tested for hardness, thickness and weight variation and compared with each other.
RESULTS: All formulations reached maximum tensile strength at compaction pressures between 263-316 MPa. In formulations without binder, formulations containing Granulac®70 had higher tensile strength than formulations containing Flowlac®100 at both filler ratios. Results obtained, indicated that the addition of binder in formulations (F-45-1, F-45-2, F-50-3 and F-50-4), improved compressibility of paracetamol. Formulation F-45-2, containing Flowlac®100 and binder showed better compressibility at 2.9 MPa tensile strength. Data from compaction simulator, was used to compare Young's Modulus and work of compaction on selected formulations (F-45-1 and F-45-2).
DISCUSSION AND CONCLUSION: Proposed lactose-based filler; Flowlac®100 with low pressure can be successfully applicable for improving compressibility of paracetamol. Optimum formulation can be designed with less amount of materials using compaction simulator.

Keywords: Compaction simulator, Tableting, Compactibility, Paracetamol, Alpha-Lactose

Introduction

In manufacturing pharmaceutical tablets, there are certain problems that may arise, such as poor flowability, poor mixing, compactibility, compressibility, inconsistent die filling etc. The need to avert such problems in manufacturing may include the use of different tableting method such as granulation [1, 2].

Slugging, an old conventional method is chosen for research purposes in respect to the Roller Compactor (RC) which is a more modern and efficient method used for dry granulation.

The effect of dry granulation (DG) process often shows results of decreased tensile strength in tablets in comparison to other processes. This outcome is due to the loss of binding potential which is affected after the first compression [3-5].

The ability to transform powder into tablets includes certain factors, these factors such as, compactiblity (tensile strength vs. pressure) and other tableting measures, gives a perspective of powder tableting characteristics [1,6].

In tableting process, three important stages are paramount in understanding the characteristics of powders. The stages are, die filling; powder blends are filled into the die under gravity which applies to powder flowability, compaction; where compression is made in between two punches, ejection; when the tablet is ejected from the die. These three stages determine the powder behavior and tableting parameters [7].

The compaction behavior can be assessed using stress strain graphs to obtain Young's modulus which gives insight into plastic, elastic or brittle nature of powders. Data obtained from measurements of macroscopic dimensional variations during compaction cycle gives information about compressibility and compactibility of powder material [8].

In formulating a poorly compressible active ingredient, the choice of excipient is important to the outcome. Therefore, finding the best tableting parameters is essential for further production and can also be used as an outline in fixing production problems.

To understand and characterize the compaction behavior and tableting parameters, instrumented single station and multi-stations have been widely used. As observed, powders with good performance in laboratory tablet press sometimes perform differently, with problems during scale up. However, with compaction simulator these problems can be predicted with data which are used to analyze compaction behavior of pharmaceutical materials. Compaction simulator gives advantages, limitations and modifications by using methods such as F-D curve, tensile strength, hardness

measurement and other techniques to improve design and development of solid dosage forms [9,10].

The use of compaction simulator as a mimicking machine which emulates a scale-up production, gives real time data on every tablet pressed. These data can be analyzed, powder behavior and characteristics can be observed [11].

In this study, data obtained from compaction simulator are used from industrial perspective to determine and evaluate the tableting parameters to obtain improved compactibiltiy of poorly compressible paracetamol.

Materials and Methods

Materials

Paracetamol is used as the model drug in this study, USP grade (Kimetsan), two types of lactose-based fillers from Meggle; milled alpha-lactose monohydrate (Granulac®70) and spray dried lactose (Flowlac®100) were used in the formulation at different concentrations, to understand the effect of fillers on tableting parameters using slugging process. Stearic acid (Kimetsan) was used as lubricant, which was kept at a constant concentration of 2% in every formulation.

The idea to have an addition of binder from BASF (Kollidon® K90) to specific formulations, is to further understand certain variables that may influence tablet behavior during compaction.

Methods

Slugging

Tablets (slugs) were made containing API, filler and lubricant mixture, with ratios 1:1 and 0.8:1 (paracetamol to filler loading) [4,11]. The slugs were made with the mixture of paracetamol powder and filler (both Flowlac®100 and Granulac®70, at different ratios) with the addition of 1% of the lubricants in the mixture [12,13].

The slugs were produced using 18mm single punch (Korsch XP1), milled using Erweka oscillating mill granulator and passed through a sieve with sieve size of 0.68mm.

Mixing

The granules obtained from the dry granulation slugging process were mixed with the binder and the remaining 1% lubricant (w/w) (according to each concentration variation in different formulation composition and ratio).

Tableting

Formulations were compressed at different compaction pressure; 152, 210, 263, 316, 400, 452 MPa. Tablets were produced with flat faced Euro B punch of 11.28mm diameter, using compaction simulator (Stylcam 200R). Tablets of eight different formulation mixture were pressed to understand and characterize formulations of each compaction force.

For die filling, each powder was weighed individually using Mettler Toledo AB 104-S/PH analytic balance and hand-filled in the die for compaction. From tablets pressed, tablets from each formulation and batch were selected randomly and immediately characterized for weight variation and thickness.

Tensile Strength

Tensile strength was calculated from crushing force (TBH 225; Erweka), and thickness.

Tensile strength was calculated using the following equation:

$$TS = \frac{2F}{\pi Dt} \quad (1)$$

where F is the crushing force in *N*, D the diameter, and t the thickness of tablet, both in mm.

Stress-strain graph

Graph was obtained using both upper and lower punch displacement data derived from compaction simulator. Young's modulus is obtained from slope of line of stress-strain graph.

F-D Curve

Compression force vs punch displacement profiles (F-D Curve) can be obtained in other to assess the compaction behavior of materials and to calculate the work involved during tablet compaction.

Results

Figure 1 shows the tensile strength for the set of formulations with different filler type at different ratios (1:1 and 0.8:1). The formulations containing Granulac®70 (F-45-3 and F-50-1) gave higher tensile strength in comparison to formulations containing Flowlac®100. The effect of the filler ratio is seen in figure 1, with formulations F-45-3 and F-45-4 showing better compressibility than formulations F-50-1 and F-50-2 respectively. Granulac®70 containing formulations improved the compressibility of paracetamol more than Flowlac®100 at both ratios.

Figure 2 shows the effect of binder on tensile strength of the formulations. There was an increase in the tensile strength of all different formulation composition. Formulation F-45-2 containing Flowlac®100 had a higher tensile strength at lower compaction pressure than F-45-1 containing Granulac®70, at similar filler ratio (0.8:1). Flowlac®100 had more improved tensile strength with addition of binder in comparison to figure 1.

In figure 3, both tablets results are derived from similar compaction conditions, having been selected from tensile strength resulting data to be the optimum tablets from different filler type formulation compositions. Figure 3 shows the variation of stress-strain for F-45-1 and F-45-2. It was seen that, there is a linear increase in F-45-2, a different result was observed in F-45-1, which takes more loading capacity to see a significant change in the strain of formulation F-45-1. The Young's Modulus results were given at 60 for F-45-1 and 98 for F-45-2. As calculated from figure 3, Young's Modulus for F-45-1 is lower than F-45-2, indicating that F-45-1 has greater elastic recovery.

Figure 4 shows the total of work compaction for the selected formulations. Area under the curve shows the energy required during compaction process. F-45-2 is seen to require more energy in comparison to F-45-1.

Discussion

As seen in the results in figure 1, Granulac®70 displayed better loading capacity than Flowlac®100. In both filler ratio, Granulac®70 containing formulations performed better under higher compaction pressure. However, Flowlac®100 had better tensile strength at lesser pressures. Particle structure and size difference of filler affects the bonding and may show different results at identical compaction conditions [14-16]. All formulations had a significant decline in tensile strength as compaction pressures increased above (316 MPa).

Figure 2 gives a description of change in formulation composition, with the addition of binder. From the tensile strength results, both filler types at ratios 1:1 and 0.8:1, improved in compressibility when compared with results from figure 1. It is seen that binder effect has more impact significant change in Flowlac®100 than Granulac®70. Formulations F-50-3 containing Granulac®70, maintained a slightly better higher tensile strength than formulation F-50-4 containing Flowlac®100. This indicates the need for higher filler loading ratio for Flowlac®100 to exhibit proper bonding, increasing the tensile strength. Granulac®70 however, has more compactibility at different loading ratio. It was observed that with the addition of binder and tensile strength increase, the tableting behavior of all formulations at different filler ratio and formulation compositions, had a distinctive pattern in respect to compaction pressure. These results suggest that lactose-based fillers may have unpredictable compression behavior, which gives more deviations when lubricated [16,17].

As seen in stress-strain curve, the variation in deformation of both formulations at similar tableting parameters may have many reasons and explanation. Factors that may give rise to these variations are density distribution in the tablets as a result of stress transmission, which is dependent on internal friction, contact powder and lubrication [18,19,20]. The relationship between Young's Modulus and tablet strength is that, the higher the elastic recovery, the lower the tablet strength [21,22]. This can be further supported from the results that F-45-1 has lower tensile strength than F-45-2 because of its greater elastic recovery, shown by higher Young's Modulus. Flowlac®100 containing formulations showed lower elastic recovery because of its spray-dried property, which gives it harder tablets [23].

Results from F-D curve show that the work of compaction gives detailed assessment of the characteristics of tableting parameters due to differences in packing characteristics of individual formulation powder [10,24]. Powders with different plastic and elastic deformational properties and different packing characteristics will absorb varying amounts of energy; [25] as seen by differences in compaction energy between formulations F-45-1 and F-45-2.

Conclusion

With compaction simulator it's possible to define;

- the mechanical properties of powders
- optimum tabletability profile for designed formulations.
- compaction data such as, stress strain and FD curves can help in optimizing a formulation.

Granulac®70 is seen to have better loading capacity than Flowlac®100. However, it needs more pressure during compaction process. The addition of binder has more effect on Flowlac®100 in improving the compressibility of paracetamol, at lower compaction pressure.

The most robust formulation F-45-2, is selected from the set of formulations due to its superior compaction characteristics. Based on the information obtained from compaction simulator, large-scale manufacturing can be reproduced.

References

[1] Sun CC, Kleinebudde P. Mini review: Mechanisms to the loss of tabletability by dry granulation. European Journal of Pharmaceutics and Biopharmaceutics. 2016 Sep 1; 106:9-14.

[2] Mosig J, Kleinebudde P. Critical evaluation of root causes of the reduced compactability after roll compaction/dry granulation. Journal of pharmaceutical sciences. 2015 Mar 1;104(3):1108-18.

[3] Herting MG, Kleinebudde P. Roll compaction/dry granulation: effect of raw material particle size on granule and tablet properties, Int. J. Pharm. 2007; 338: 110-118.

[4] Kochhar SK, Rubinstein MH, Barnes D. The effects of slugging and recompression on pharmaceutical excipients. International journal of pharmaceutics. 1995 Feb 28;115(1):35-43.

[5] Herting MG, Kleinebudde P. Studies on the reduction of tensile strength of tablets after roll compaction/dry granulation. European Journal of Pharmaceutics and Biopharmaceutics. 2008 Sep 1;70(1):372-9.

[6] Bozic DZ, Vrecer F. Influence of dry granulation on compactibility and capping tendency of macrolide antibiotic formulation. International journal of pharmaceutics. 2008 Jun 5;357(1-2):44-54.

[7] Wu CY, Ruddy OM, Bentham AC, Hancock BC, Best SM, Elliott JA. Modelling the mechanical behaviour of pharmaceutical powders during compaction. Powder Technology. 2005 Apr 29;152(1-3):107-17.

[8] Freitag F, Kleinebudde P. How do roll compaction/dry granulation affect the tableting behaviour of inorganic materials? Comparison of four magnesium carbonates. European journal of pharmaceutical sciences. 2003 Jul 1;19(4):281-9.

[9] Sun CC. Dependence of ejection force on tableting speed—A compaction simulation study. Powder Technology. 2015 Jul 1; 279:123-6.

[10] Çelik M. Overview of compaction data analysis techniques. Drug development and industrial pharmacy. 1992 Jan 1;18(6-7):767-810.

[11] Çelik M, Marshall K. Use of a compaction simulator system in tabletting research. Drug Development and Industrial Pharmacy. 1989 Jan 1;15(5):759-800.

[12] Kawashima Y, Takeuchi H, Hino T, Niwa T, Lin TL, Sekigawa F. Preparation of a sustained-release matrix tablet of acetaminophen with pulverized low-substituted hydroxypropylcellulose via dry granulation. Chemical and pharmaceutical bulletin. 1993 Oct 15;41(10):1827-31.

[13] Khan KA, Musikabhumma P. Effect of slugging pressure on the properties of granules and tablets prepared from potassium phenethicillin. Journal of Pharmacy and Pharmacology. 1981 Sep;33(1):627-31.

[14] Jain S. Mechanical properties of powders for compaction and tableting: an overview. Pharmaceutical Science & Technology Today. 1999 Jan 1;2(1):20-31.

[15] Sun C, Himmelspach MW. Reduced tabletability of roller compacted granules as a result of granule size enlargement. Journal of pharmaceutical sciences. 2006 Jan;95(1):200-6.

[16] Haware RV, Tho I, Bauer-Brandl A. Multivariate analysis of relationships between material properties, process parameters and tablet tensile strength for α-lactose monohydrates. European Journal of Pharmaceutics and Biopharmaceutics. 2009 Nov 1;73(3):424-31.

[17] Boschini F, Delaval V, Traina K, Vandewalle N, Lumay G. Linking flowability and granulometry of lactose powders. International journal of pharmaceutics. 2015 Oct 15;494(1):312-20.

[18] Kadiri MS, Michrafy A. The effect of punch's shape on die compaction of pharmaceutical powders. Powder technology. 2013 May 1;239:467-77.

[19] Michrafy A, Ringenbacher D, Tchoreloff P. Modelling the compaction behaviour of powders: application to pharmaceutical powders. Powder Technology. 2002 Nov 5;127(3):257-66.

[20] Michrafy A, Dodds JA, Kadiri MS. Wall friction in the compaction of pharmaceutical powders: measurement and effect on the density distribution. Powder Technology. 2004 Oct 20;148(1):53-5.

[21] Han LH, Elliott JA, Bentham AC, Mills A, Amidon GE, Hancock BC. A modified Drucker-Prager Cap model for die compaction simulation of pharmaceutical powders. International Journal of Solids and Structures. 2008 May 15;45(10):3088-106.

[22] Malamataris S, Hatjichristos T, Rees JE. Apparent compressive elastic modulus and strength isotropy of compacts formed from binary powder mixes. International journal of pharmaceutics. 1996; 141(1-2): 101-8.

[23] Vromans H, Bolhuis GK, Lerk CF, Van de Biggelaar H, Bosch H. Studies on tableting properties of lactose. VII. The effect of variations in primary particle size and percentage of amorphous lactose in spray dried lactose products. International journal of pharmaceutics. 1987;35(1-2): 29-37.

[24] Krycer I, Pope DG, Hersey JA. An evaluation of the techniques employed to investigate powder compaction behaviour. International Journal of Pharmaceutics. 1982 Oct 1;12(2-3):113-34.

[25] Fell JT, Newton JM. Assessment of compression characteristics of powders. Journal of pharmaceutical sciences. 1971 Sep;60(9):1428-9.

Table 1a. Formulation composition with paracetamol to filler (ratio 0.8:1).

Formulation	Paracetamol	Flowlac®100	Granulac®70	Kollidon® K90	Stearic Acid
F-45-1	45%	-	51%	2%	2%
F-45-2	45%	51%	-	2%	2%
F-45-3	45%	-	53%	-	2%
F-45-4	45%	53%	-	-	2%

Table 1b. Formulation composition with paracetamol to filler (ratio 1:1).

Formulation	Paracetamol	Flowlac®100	Granulac®70	Kollidon® K90	Stearic Acid
F-50-1	50%	-	48%	-	2%
F-50-2	50%	48%	-	-	2%
F-50-3	50%	-	46%	2%	2%
F-50-4	50%	46%	-	2%	2%

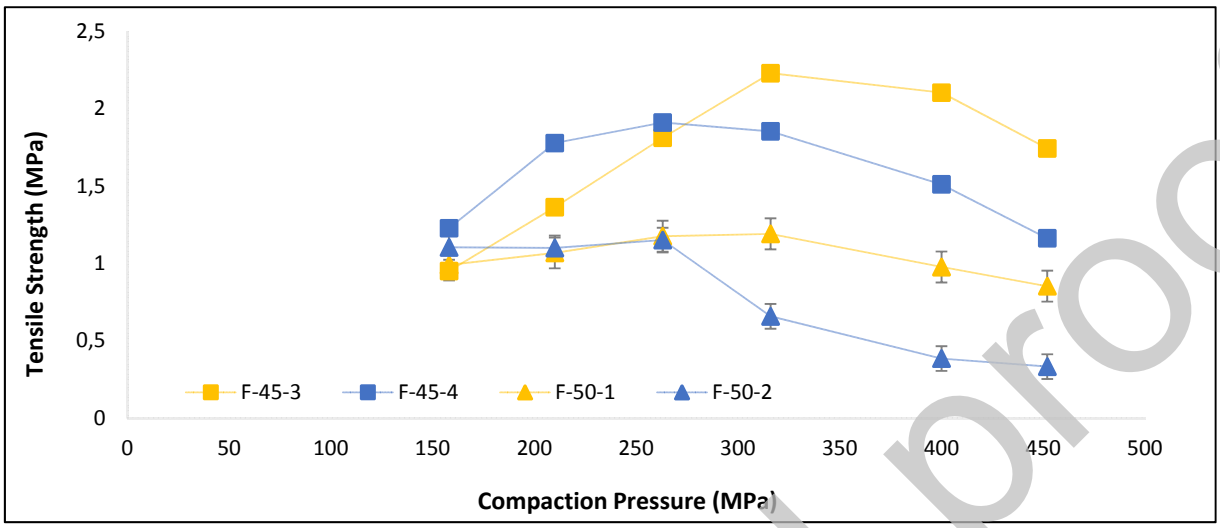

Figure 1. Flowlac®100 and Granulac®70 effect with different ratio on tensile strength.

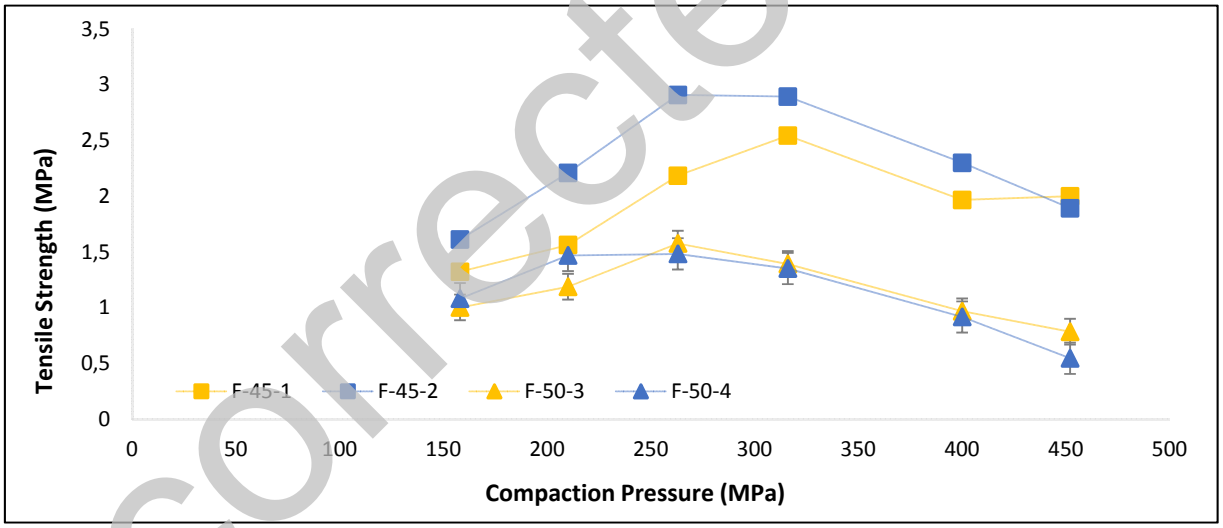

Figure 2. Flowlac®100 and Granulac®70 composition with binder (Kollidon® K90) effect on tensile strength.

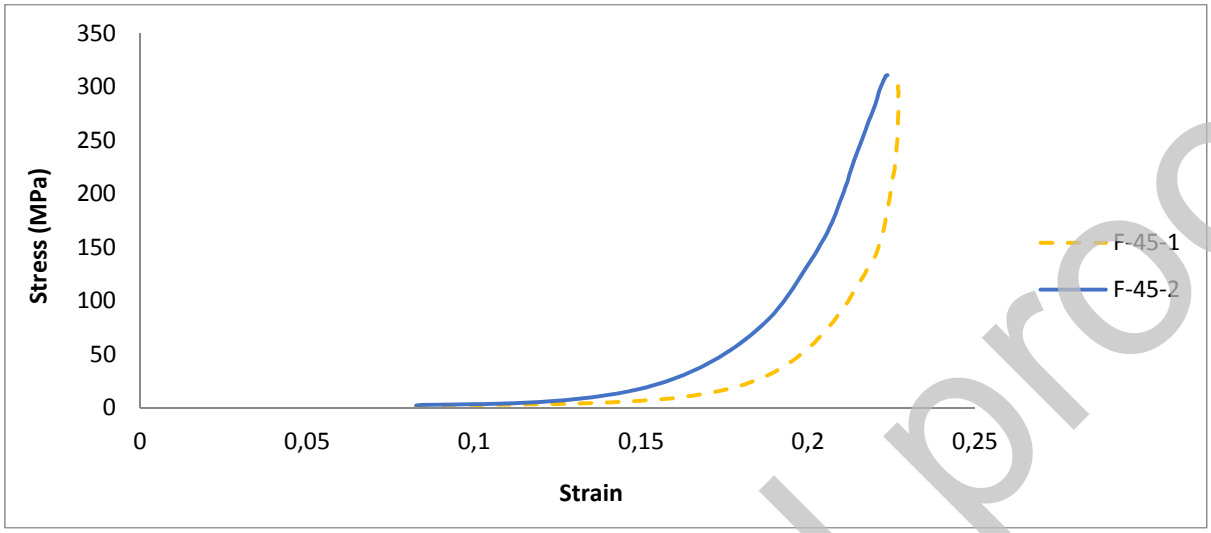

Figure 3. Stress vs strain for selected formulations (F-45-1 and F-45-2).

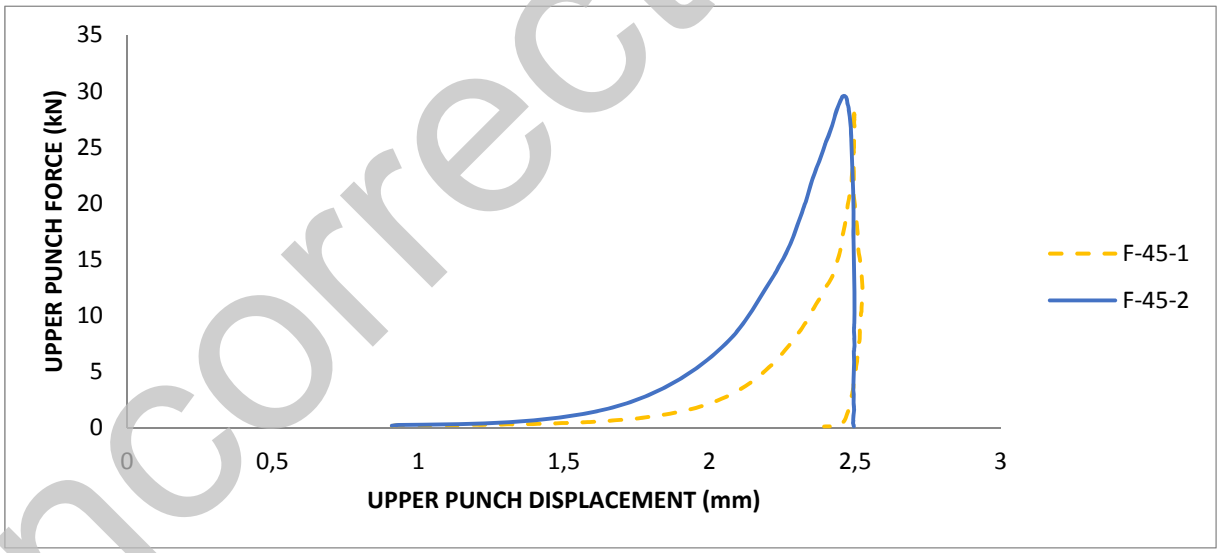

Figure 4. Determination of energy for selected formulations (F-45-1 and F-45-2).