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A STUDY OF THE COMPACTIBILITY CHARACTERISTICS OF A DIRECT COMPRESSION AND A WET GRANULATED FORMULATION OF NORFLOXACIN

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ABSTRACT

Compaction characteristics of norfloxacin tablets manufactured by both wet granulation and direct compression procedures were studied with the aid of an instrumented single punch tablet press interfaced with a digital computer. Under comparable tabletting conditions, the direct compression formulation required less compressional force than the wet granulated formulation to produce tablets of similar breaking strengths, which indicates superior compactibility. The directly compressed tablets were found to disintegrate faster and release their active component more rapidly during the critical early stages of dissolu-tion. Dissolution and disintegration of the directly compressed tablets generally were less affected by changes in breaking strengths than those compressed from granulated systems.

INTRODUCTION

The instrumentation of a single punch press was first described by Brake[1] in his thesis at Purdue. He attached strain gauges to the upper punch of a Colton 4B press to measure the compression force exerted during tabletting. Later Higuchi and his coworkers published a series of papers[2-8] on "Physics of Tablet Compression". These workers instrumented an isolated punch and die set to determine compressional forces and distance of punch travel (displacement). They plotted various compressional parameters against compressional force or against each other. This pioneering concept was utilized by many workers to assist in formulation development. In recent years technological progress and advent of computers has facilitated numerous modifications in the basic machine design, and a variety of methods have been developed for monitoring machine performance[9,10].

The work of Brake was further expanded by Gagnon[11] to measure lower punch compressional force. Shotton and Ganderton[12] bonded strain gauges directly to the upper punch of a single punch machine and to the lower punch holder. The advantage of this system was to obtain better linearity between the distortion occurring and the applied force. Leigh et.al.[13] reported on the compression characteristics of several pharmaceutical materials using foil strain gauges to monitor upper and lower punch force on a Manesty E-2 single punch machine and semiconductor (silicone) gauges to monitor the die wall pressure. They followed radial pressures vs. axial pressure

over the entire compression and decompression cycle and related their findings to capping and laminating phenomena. Marshall[14] reported on the details of the use of the piezo-electric transducers in instrumentation. Miller and Schierstedt[15] developed a method by which the deformation of upper and lower punches could be eliminated simultaneously. In most studies involving reciprocating instrumented tablet presses, the maximum upper punch force is regarded as the tabletting force. The lower punch force has been claimed to be independent of the die wall friction and, therefore, has been suggested to be a more useful measure of the tabletting force[16]. However, Ragnarsson and Sjogren[17] have indicated that the mean force gives a good estimate of the force applied to the compact and offers a simple and practically friction independent measure of compaction load that is more relevant. Ragnarsson and Sjogren[18] have showed that the force needed on the upper punch to maintain the tablet dimensions constant increased with the die wall friction while the lower punch force decreased. The change in punch forces due to differences in die wall friction had no effect on the tablet strength. They suggested that the equation proposed by Jarvinen and Juslin[19] to calculate frictional work gives a more accurate estimation and, thus, can be used to calculate net work. Holzer and Sjogren[20,21] have used instrumented single punch tablet press for measurement of the radial force during tabletting and friction coefficients of lubricated and nonlubricated tablet masses. Jetzer, Leuenberger

and Sucker[22] have proposed a mathematical relationship consisting of a compactibility parameter and compression susceptibility measurement to investigate the additivity of compression parameters.

Alderborn and Nystrom[23] have proposed measurement of axial tensile strength values as a more sensitive measure for detecting capping tendencies of granulations. Lammens, et. al.[24] studied the influence of diameter of punches and die on upper and lower punch pressure. They showed that the upper punch pressure necessary to effect a certain state of density decreased with increasing diameter, whereas the lower punch pressure was independent of it. They proposed a mathematical model for the pressure distribution on the upper punch. Also, a method reported for correction of die wall friction in work measurements was critically evaluated. Based on the evaluation, they proposed that the method is generally valid for the process of densification only. In a later publication[25] they proved that this dependence of upper punch pressure on the die diameter can be exclusively attributed to the process of densification and it could not be accounted for by differences in the real speed of densification, play between punches or by differences in the state of die wall lubrication.

Ragnarsson and Sjogren[26] utilized an instrumented single punch press to study the effect of particle interactions, inter-lot variations on net work due to its high sensitivity to both inter- and intra-particle properties, good reproducibility and low dependence upon die wall conditions.

The instrumented single punch press in our laboratories is interfaced with a digital computer and has been used (a) to determine whether changes in drug properties, excipients or manufacturing process affect compression properties of existing formulations and (b) to generate compression pressure profiles ('fingerprints') of new formulations which then serve as baseline data in subsequent trouble shooting functions. In this investigation two different formulations of norfloxacin were compared for their machinability, compactibility profiles and the effect of processing on physicochemical properties of resulting tablets.

MATERIALS AND METHODS

The instrumented press used to study and compare the two formulations involved in this investigation generates applied and transmitted curves which are essentially force vs. time relationships. The maximum upper and lower punch pressures were obtained from these curves.

The granulated system is obtained by treating a mixture of norfloxacin, a nalidixic acid analog possessing antimicrobial activity, and three excipients with a hydroalcoholic solution of Povidone. This system is dried and milled by conventional procedures but then undergoes a complex rehydration step before the lubricant is added and it is compressed. The direct compression formulation, in comparison, is a simple mixture of the drug, two excipients and a lubricant. Therefore, only the drug and the lubricant are common to both formulations and, in this

study, both ingredients were from the same source and of the same lot number. Since the differences in formulations are extensive, dissimilar tooling sizes were found necessary to accommodate the significant differences in tablet weights and volumes.

Tablet Potency	Punch Size Wet Granulation	Final Tablet Weight in Mg	Punch Size Direct Compression	Final Tablet Weight
200 mg	10/32 X 19/32 in	425	9/32 X 16/32 in	250
400 mg	12/32 X 21/32 in	850	10/32 X 19/32 in	500

Resulting tablets are oval and biconvex.

In addition to computer generated compression parameter values (N usually 50 or more), the compressed tablets were evaluated as to breaking strengths, disintegration times and dissolution rates. Breaking strengths were determined (end to end orientation) using a Schleuniger 2E tester (N=8). Disintegration tests were performed with the USP apparatus in 0.05M sodium acetate buffer (pH 4.0) at 37°C without discs (N=6). Dissolution rates were determined in 900 mls of 0.05M sodium acetate buffer at 37°C using USP dissolution apparatus II at 50 RPM (N=3).

RESULTS AND DISCUSSION

The compaction force parameters for the 200 mg potency tablets made from direct compression and wet granulated formulations are in Table-1. The direct compression formulation required considerably less applied force (expressed in Kilonewtons, KN) than the wet granulated system to produce tablets of comparable breaking strengths, which indicates superior compactibility. The

TABLE 1

Compression Curve Parameters for 200 mg Potency Norfloxacin Tablets

Formulation Type					
Direct Compression			Wet Granulated		
Breaking Strength kps ±SD	Applied Force (AF) KN	Transmitted Force (TF) KN	Breaking Strength kps ±SD	Applied Force (AF) KN	Transmitted Force (TF) KN
9.57 ±0.54	6.38 ± 0.15	4.09 ± 0.06	10.23 ±0.35	9.05 ± 0.34	8.10 ± 0.13
9.94 ±0.26	6.64 ± 0.14	4.20 ± 0.08	11.23 ±0.18	10.63 ± 0.30	9.55 ± 0.16
11.03 ±0.32	7.86 ± 0.26	4.88 ± 0.10	12.95 ±0.26	14.85 ± 0.51	13.95 ±0.42
14.25 0.33	10.35 ± 0.42	6.95 ± 0.13			

forces transmitted to the lower punch were considerably less for direct compression formulation compared to the wet granulated formulation.

The physical properties of the tablets from both formulations are given in Table-2.

The most noticeable difference between these formulations is that both disintegration and dissolution rates of the directly compressed tablets are faster, especially with respect to dissolution during the critical initial 15 minutes. This is attributed to the differences in the tablet matrices and is explained as follows: Since wet granulation results in consolidation of the powder mix into granules, these granules must

TABLE 2

Comparison of Physical Properties of 200 mg Tablets Obtained from Direct Compression and Wet Granulated Formulations

Formulation Type					
Direct Compression			Wet Granulated		
Breaking Strength Kps ±SD	Disint. Time min' sec"	Diss. % Label Claim in Mins. 10, 20, 30	Breaking Strength Kps ±SD	Disint. Time min' sec"	Diss. % Label Claim in Mins. 10,20,30
9.57 ±0.54	2' 24" to 3' 08"	104,101,101			
9.94 ±0.26	2' 35" to 3' 28"	101,100,101	10.23 ±0.35	4' 5" to 4' 56"	99,114, 113
11.03 ±0.32	3' 52" to 4' 25"	103,103,108	11.23 ±0.18	5' 38" to 6' 35"	72,110, 112
14.25 ±0.33	8' 36" to 10' 13"	109,111,110	12.95 ±0.26	10' 10" to 10' 58"	78,111, 114

rupture before the drug starts dissolving. This rupturing/deagglomeration delays the initial dissolution.

The compaction force parameters of 400 mg potency norfloxacin tablets made from both formulations are in Table-3. The force requirements for obtaining tablets of comparable breaking strengths are, again, considerably smaller for the direct compression formulation. The physical properties of the 400 mg potency tablets listed in Table-4 match those trends seen in the 200 mg potency tablets.

TABLE 3

Compression Curve Parameters for 400 mg Potency Tablets

Formulation Type					
Direct Compression			Wet Granulated		
Breaking Strength kps ±SD	Applied Force (AF) KN	Transmitted Force (TF) KN	Breaking Strength kps ±SD	Applied Force (AF) KN	Transmitted Force (TF) KN
11.88 ±0.33	5.29 ± 0.10	3.69 ± 0.07	11.8 ±0.57	11.03 ± 0.47	7.63 ± 0.28
12.45 ±0.31	6.02 ± 0.12	4.05 ± 0.05	13.28 ±0.30	12.20 ± 0.65	7.76 ± 0.20
14.28 ±0.35	6.96 ± 0.12	4.91 ± 0.05	16.18 ±0.35	14.29 ± 0.40	9.55 ± 0.25
17.28 ±0.78	8.67 ± 0.20	6.47 ± 0.10	17.2 ±0.20	14.13 ± 0.46	11.09 ±0.24
18.6 ±0.39	9.08 ± 0.15	6.97 ± 0.12	19.15 ±0.44	17.13 ± 1.35	12.68 ±0.43

The differences in formulations made it necessary that different tooling sizes be used to obtain tablets from different granulations, although they contained the same amount of drug. Thus, the comparisons are based primarily on the amount of drug in the tablets and secondarily on comparable breaking strength. The differences in tablet weights and volumes are not taken into consideration. Incidentally, a very rough comparison based on tooling size can also be done. The same size tooling (10/32 X 19/32) was used for 200 mg potency wet granulated formulation and 400 mg potency direct compression formulation. The applied force values for 400 mg potency direct compression formulation are at

TABLE 4

Comparison of Physical Properties of 400 mg Tablets Obtained from Direct Compression and Wet Granulated Formulations

Formulation Type					
Direct Compression			Wet Granulated		
Breaking Strength Kps ±SD	Disint. Time min' sec"	Diss. % Label Claim in Mins. 10,20,30	Breaking Strength Kps ±SD	Disint. Time min' sec"	Diss. % Label Claim in Mins. 10,20,30
11.88 ±0.33	1' 4" to 1' 20"	97,104,102	11.80 ±0.57	3' 5" to 3' 35"	101,102,102
12.45 ±0.31	1' 15" to 1' 48"	103,103,100	13.28 ±0.30	3' 45" to 4' 10"	96,101,102
14.28 ±0.35	2' 10" to 2' 55"	99,101,100	16.18 ±0.35	5' 30" to 6' 12"	90,100,113
17.28 ±0.78	4' 30" to 5' 33"	97,98,96	17.20 ±0.20	6' 20" to 6' 55"	92,98,103
18.6 ±0.39	5' 48" to 7' 30"	94,95,100	19.15 ±0.44	7' 40" to 9' 38"	83,100,102

least 50% smaller when compared to 200 mg potency wet granulated formulation with comparable breaking strengths. Although this comparison is rather qualitative, it confirms the superior compactibility of the direct compression formulation.

Figures 1 and 2 show the relationship between forces (applied or transmitted in KN) vs. breaking strength (in kps) for 200 mg and 400 mg potency tablets respectively. Both these figures show

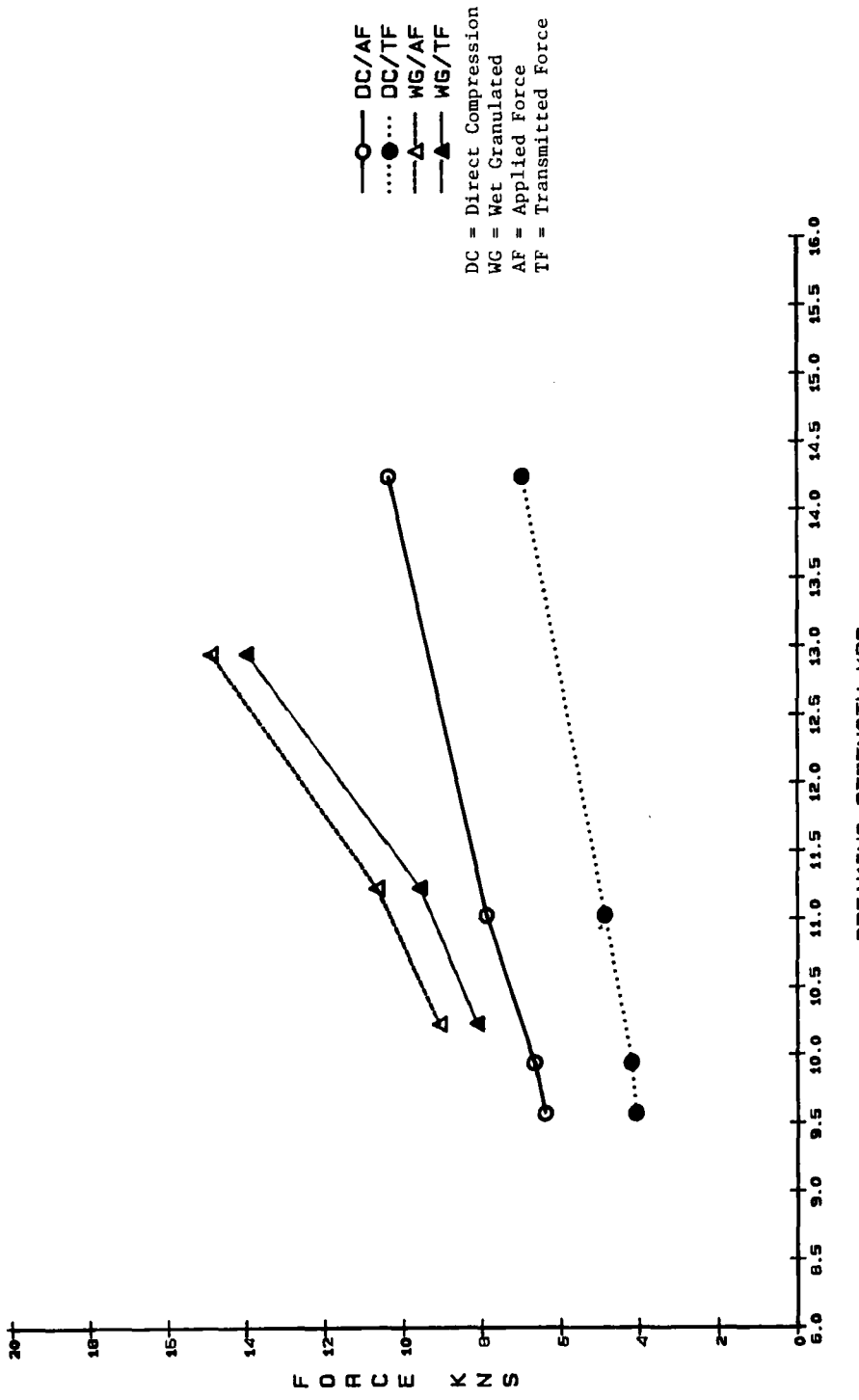

FIGURE 1

FORCE VS BREAKING STRENGTH FOR 200 MG TABLETS

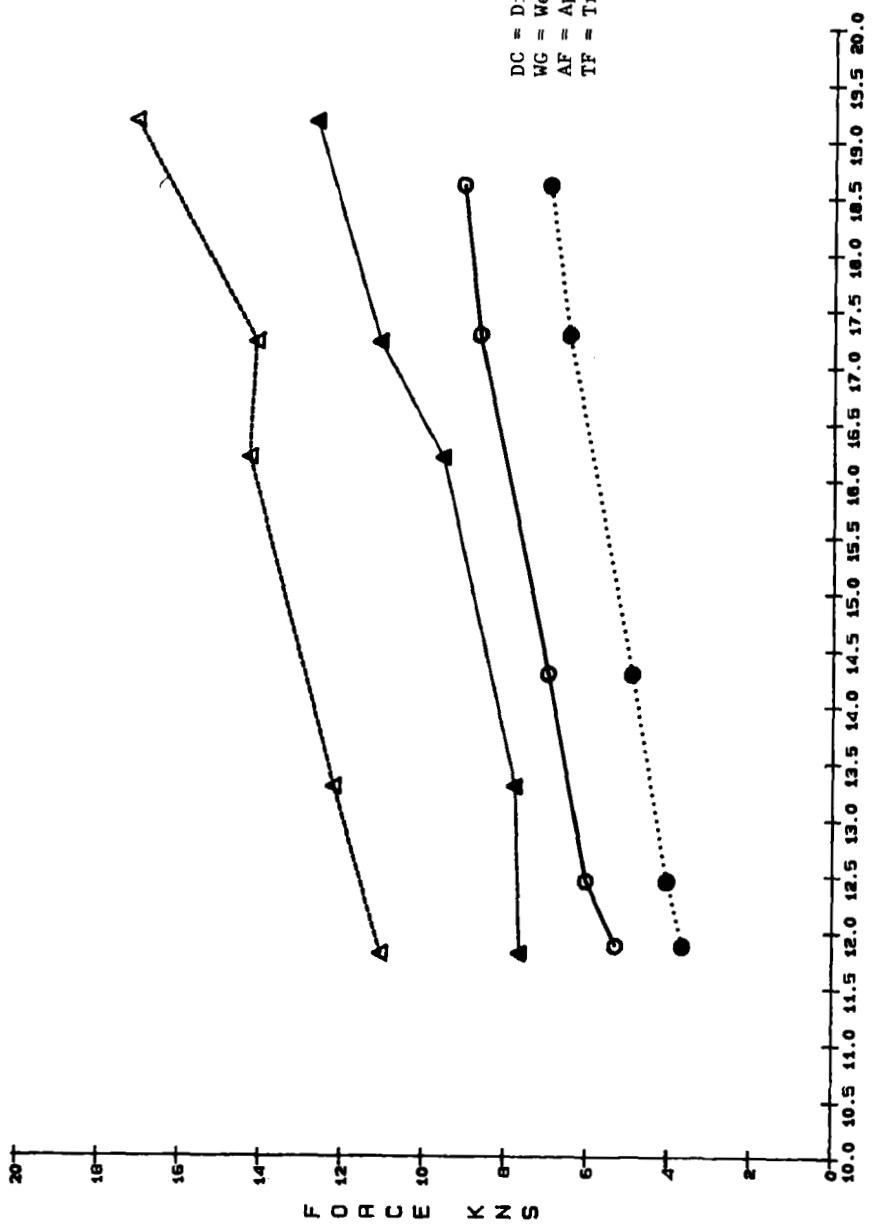

FIGURE 2

FORCE VS BREAKING STRENGTH FOR 400 MG TABLETS

superiority of the direct compression formulation for both the potencies. Tables 2 and 4 clearly show that the direct compression formulation is relatively insensitive to breaking strength values, whereas the wet granulated formulation is more sensitive, and the adverse effect of increasing breaking strength is reflected in slower initial dissolution rates. This relative insensitivity to breaking strength is one of the most desirable attributes of the direct compression formulation.

CONCLUSIONS

The compactibility characteristics of the direct compression formulation of norfloxacin are shown to be superior to that of the wet granulated formulation. In terms of disintegration and dissolution properties, the direct compression formulation is also less sensitive to changes in breaking strengths. From a more subjective point of view, the smaller tablet size made possible through the use of the direct compression formulation is more appealing, thus, should effect better patient compliance.

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